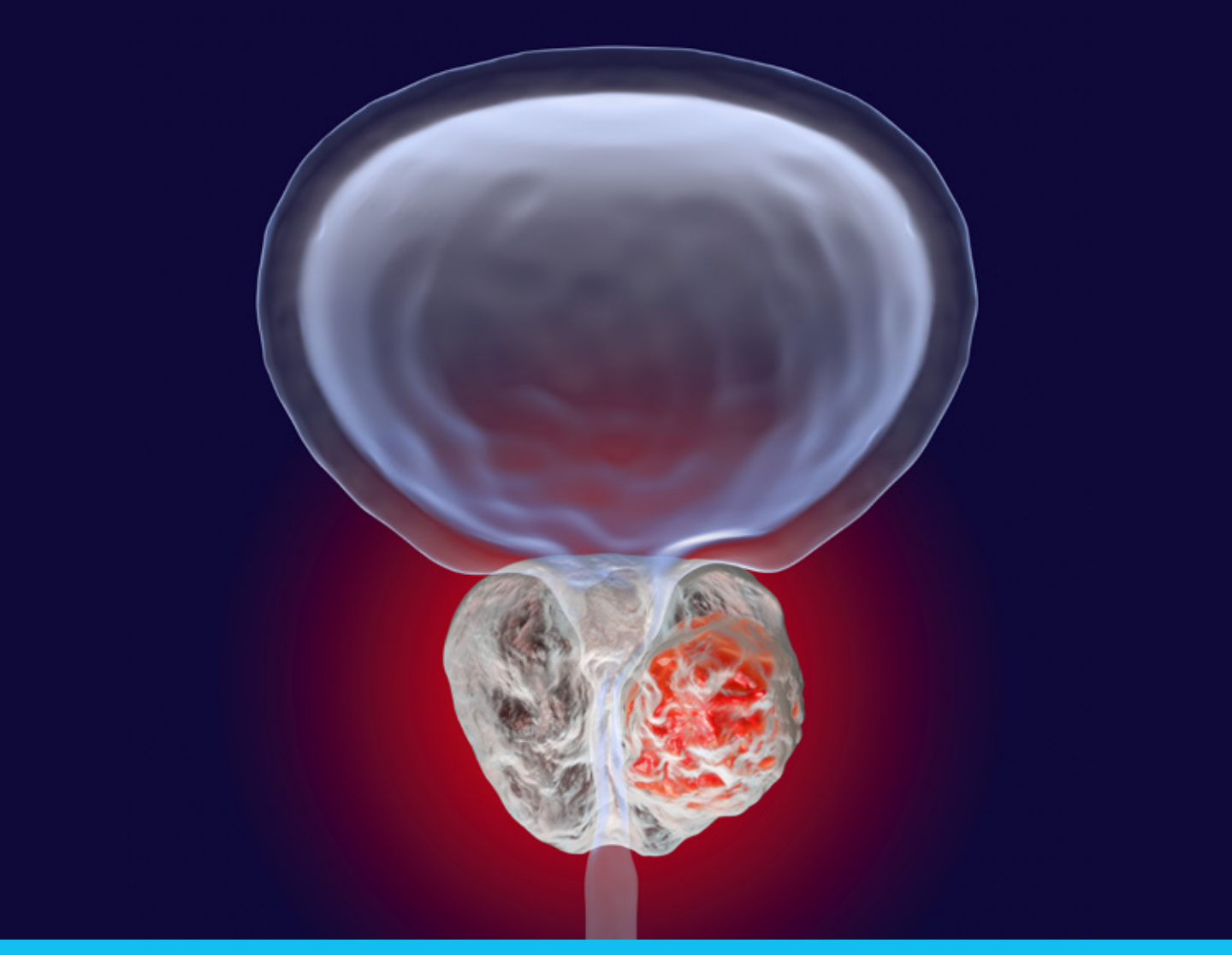


3RD WUOF/SIU ICUD ON LOCALIZED PROSTATE CANCER

Editors: Scott Eggener, Mack Roach 3rd, and Laurence Klotz

Managing Editor: Laurence Klotz

October 2024

International Consultation on Urological Diseases (ICUD)

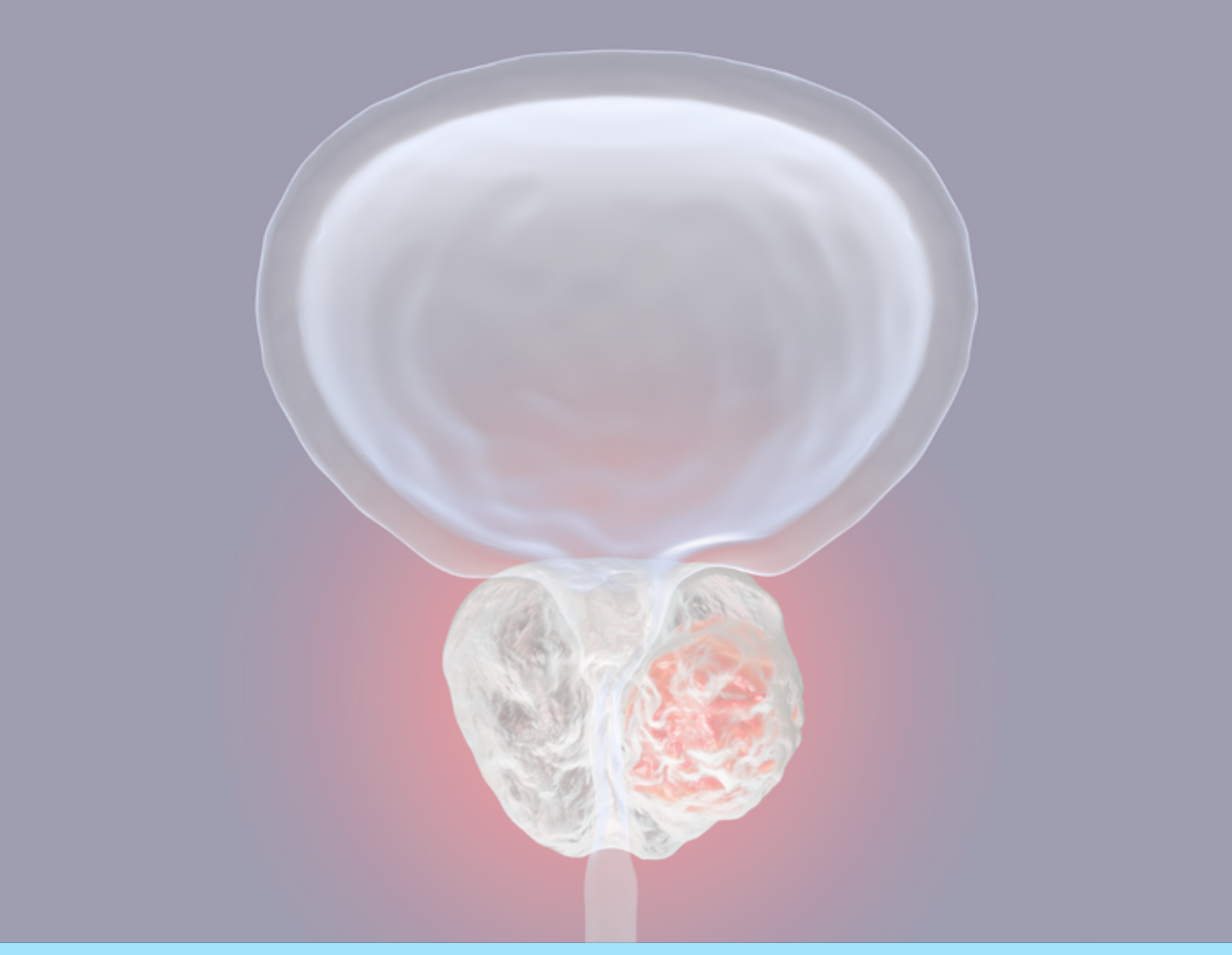
Société Internationale d'Urologie

World Urologic Oncology Federation (WUOF)

International Consultation
on Urological Diseases (ICUD)

Société Internationale
d'Urologie

World Urologic Oncology
Federation (WUOF)



3RD WUOF/SIU ICUD ON LOCALIZED PROSTATE CANCER

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3rd WUOF/SIU ICUD on Localized Prostate Cancer
October 2024

Editors
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ISBN: 978-1-06881-360-3

International Consultation on Urological Diseases (ICUD)
Société Internationale d'Urologie
World Urologic Oncology Federation (WUOF)

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Preface

ICUD, the World Urologic Oncology Federation, and the Société Internationale d'Urologie

Established in 1980, the International Consultation on Urologic Diseases (ICUD), has, for 44 years provided comprehensive, book-length overviews of major topics in urology. These have, in many cases, defined the state of the art of the topic and serve as important, internationally recognized references. The ICUD books are widely distributed and relied upon for their high-quality information and broad perspectives on disease management. A unique aspect of the ICUD is the tradition of international collaboration and discussion. The explicit goal is to gather input from diverse experts worldwide, recognizing that differences in economics, culture, politics, demographics, and healthcare delivery influence practice patterns and approaches to clinical problems. The list of ICUDs is presented in the section titled "Past ICUD Consultations." This monograph on localized prostate cancer is particularly significant, as the very first ICUD focused on prostate cancer, and several subsequent consultations have continued to explore various aspects of this disease.

Each ICUD book represents a substantial collegial and collaborative effort, involving scores of individuals as editors, chapter (or committee) chairs, and committee members. The structure of the ICUD has evolved considerably. The initiative began as a voluntary collaboration of international and national urological associations. The World Health Organization (WHO) and the Union for International Cancer Control (UICC) also provided support. The ICUD was formally established as a scientific, international, non-profit NGO under Belgian law on June 28, 1994, to facilitate collaboration on an "organization-to-organization" basis with the WHO and UICC.

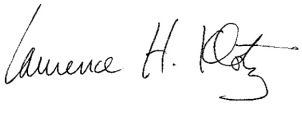
The principal aim of the ICUD is to promote improvement in the management of urologic diseases worldwide by producing evidence-based recommendations. The approach is to assemble experts in urology and related fields to develop chapters based on analysis of the available literature with an evidence-based approach. The recommendations must be amenable to adoption worldwide, considering wide variations of resources and cultural influences among countries. While the recommendations are not intended to be used as guidelines, historically many ICUD recommendations have been incorporated into national guidelines. The ICUD was for led many years by Prof Saad Khoury (Paris, France) and then by Prof Paul Abrams (Bristol, UK). Eventually the SIU became involved, initially as a collaborating partner, and subsequently took over the management of the initiative.

The World Urologic Oncology Federation (WUOF), an independent federation affiliated with the SIU, is the umbrella group for the 20 societies of urologic oncology around the world. It was a perfect fit as the organizational partner for oncology topics. In 2018, the WUOF assumed the responsibility for the oncology component of the ICUDs. The first WUOF-sponsored ICUD book was entitled "Molecular Biomarkers in Urologic Oncology" and released in November 2020, and the second ICUD on "Kidney Cancer" was released in October 2022. This is the 3rd textbook published under the current structure. All three of these comprehensive textbooks are freely available as a downloadable PDF on the WUOF website.

The ICUD differs from national guidelines in important ways. Most obviously, it represents an international perspective, drawing input from diverse regions worldwide. The ICUD process has evolved as well. Historically, groups of experts responsible for specific chapters would meet face to face, often on multiple occasions and for several days at a time, to hammer out consensus and resolve disagreements. This approach was very resource-intensive. It is no longer practical, or necessary. The advent of virtual meetings has facilitated the ability to collaborate across oceans and continents. This has resulted in extensive consultation and collaboration among members of the chapter committees, unconstrained by resource limitations. The result is the high quality of the chapters in this textbook. This edition will be published in digital form, which enables production of a quality document that is provided free of charge. It is freely available online, at www.wuof.org, and on the SIU website.

This latest textbook represents input on the state of the art of prostate cancer from scores of international experts. Industry sponsorship was critical to the success of this initiative, and we are grateful for their support. This textbook on localized prostate cancer is a significant achievement, and a testament to the talent and dedication of three editors—Scott Eggener, Mack Roach 3rd, and Laurence Klotz—as well as the chapter chairs and committees. We believe it will improve the understanding of key issues in prostate cancer by clinicians worldwide, and will enhance the management of patients and result in better outcomes and improved quality of life.

Producing a textbook like this also requires a production team with diverse skills and talents. The team, led by Areti Malapetsas of Medit Global, was superb. Ms. Malapetsas expertly managed the book production and was the senior medical copyeditor. The other members included Christian Bello and Christine Albino, contributing as copyeditors and proofreaders, and Falasteen Alfranji, serving as graphic designer. We are also grateful for the outstanding efforts of Ms. Patty Djan, who managed the ICUD sponsorship program. The quality of this book is a testament to their enthusiasm and expertise.



Laurence Klotz, CM, MD, FRCSC
Managing Editor, ICUD for Oncology

Evidence-Based Medicine Overview of the Main Steps for Developing and Grading Guideline Recommendations

P. Abrams, S. Khoury, A. Grant

Introduction

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). For more than 10 years, consultations have been organized on BPH, prostate cancer, urinary stone disease, nosocomial infections, erectile dysfunction, and urinary incontinence. These consultations have looked at published evidence and produced recommendations at four levels: highly recommended, recommended, optional, and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence-Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001, www.cebm.net).

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the consultations organized by ICUD. It is highly desirable that the recommendations made by the consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly "mapped" onto the Oxford system.

1. First Step

Define the specific questions or statements that the recommendations are supposed to address.

2. Second Step

Analyze and rate (level of evidence) the relevant papers published in the literature.

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer-reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer-reviewed journals in the relevant field but not yet published.
- Abstracts published in peer-reviewed journals should be identified. If of sufficient interest, the author(s) should be asked for full details of methodology and results. The relevant committee members can then "peer review" the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue—it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.
- Papers published in non-peer-reviewed supplements will not be included. An exhaustive list should be obtained through:

  I. The major databases covering the past 10 years (e.g., Medline, Embase, Cochrane Library, Biosis, Science Citation Index).

  II. The table of contents of the major journals of urology and other relevant journals, for the past 3 months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How are papers analyzed?

Papers published in peer-reviewed journals have differing quality and level of evidence. Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimize the possibility of bias and to maximize attribution.

It is influenced by:

The type of study, whose hierarchy is outlined below:

- Systematic reviews and meta-analysis of randomized controlled trials
- Randomized controlled trials
- Non-randomized cohort studies
- Case-control studies
- Case series
- Expert opinion

How well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increases the risk of bias or confounding factors, and thus reduces the study's reliability.

The use of **standard checklists** is recommended to ensure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the checklist is to give a quality rating for individual studies.

How well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted checklist. The CONSORT statement and the checklist are available at www.consort-statement.org.

2.3 How are papers rated?

Papers are rated following a level of evidence scale.

ICUD has modified the Oxford Centre for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (i.e.,therapy, diagnosis, differential diagnosis/symptom prevalence study) the Oxford Centre for Evidence-Based Medicine website: www.cebm.net.

3. Third Step: Synthesis of the Evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an **Evidence Table**.

4. Fourth Step: Considered Judgment (Integration of Individual Clinical Expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgment as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgment based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence-based medicine requires the integration of individual clinical expertise with the best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannized by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient. On the other hand, without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our "rules" for exercising judgment, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency, as well as applicability, generalizability, and clinical impact.

5. Fifth Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence, and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine. The levels of evidence shown below have again been modified in the light of previous consultations. There are now four levels of evidence instead of five.

The grades of recommendation have not been reduced and a "no recommendation possible" grade has been added.

6. Levels of Evidence and Grades of Recommendation for Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness, and cost-effectiveness. It is accepted that, at present, little data exists on cost-effectiveness for most interventions.

6.1 Levels of evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

Level of Evidence	Criteria

I	• Incorporates Oxford 1a, 1b
	• Usually involves:
	  • meta-analysis of trials (randomized controlled trials [RCTs]) or,
	  • a good-quality RCT or,
	  • "all or none" studies in which treatment is not an option (e.g., in vesico-vaginal fistula).

II	• Incorporates Oxford 2a, 2b, and 2c
	• Includes:
	  • ***low-quality RCT*** (e.g., > 80% follow-up),
	  • ***meta-analysis*** (with homogeneity) of ***good-quality prospective cohort studies***
	• May include a single group when individuals who develop the condition are compared with others from within the original cohort group.
	• There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.

III	• Incorporates Oxford 3a, 3b, and 4
	• Includes:
	  • ***good-quality retrospective case-control studies,*** where a group of patients who have a condition are matched appropriately (e.g., for age, sex, etc.) with control individuals who do not have the condition.
	  • ***good-quality case series,*** where a complete group of patients, all with the same condition, disease or therapeutic intervention, are described without a comparison control group.

IV	• Incorporates Oxford 4
	• Includes ***expert opinion***, where the opinion is based not on evidence but on "first principles" (e.g., physiological or anatomical) or bench research.
	• The **Delphi process** can be used to give expert opinion greater authority:
	  • involves a series of questions posed to a panel,
	  • answers are collected into a series of "options",
	  • these "options" are serially ranked; if a 75% agreement is reached, then a Delphi consensus statement can be made.

6.2 Grades of recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence, the grades of evidence may apply either positively (procedure is recommended) or negatively (procedure is not recommended). Where there is disparity of evidence, for example, if there were three well-conducted RCTs indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgment as to the grade of recommendation given and the rationale explained.

Grade A recommendation usually depends on consistent level I evidence and often means that the recommendation is effectively mandatory and placed within a clinical-care pathway. However, there will be occasions where excellent evidence (level I) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous, or unethical. Grade A recommendation can follow from Level II evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level I evidence.

Grade B recommendation usually depends on consistent level 2/3 studies, or "majority evidence" from RCTs.

Grade C recommendation usually depends on level 4 studies or "majority evidence" from level 2/3 studies or Delphi processed expert opinion.

Grade D "No recommendation possible" would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group, it is clear that application of levels of evidence/ grades of recommendation for diagnostic techniques is much more complex than for interventions. The ICUD recommends that, as a minimum, any test should be subjected to three questions:

1. Does the test have good technical performance? For example, do three aliquots of the same urine sample give the same result when subjected to dipstick testing?
2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management? Does the use of the test improve outcome? For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

Conclusion

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost-effectiveness, and also factors such as patient preference.

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Level of Evidence	Criteria
I	Meta-analysis of RCTs or high-quality randomized controlled trial (RCT)
II	Low-quality RCT or good-quality prospective cohort study
III	Good-quality retrospective case-control study or cohort study
IV	Expert opinion

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Level of Evidence	Criteria
A	Usually consistent with level I evidence
B	Consistent level II or III evidence or "majority evidence" from randomized controlled trials (RCTs)
C	Level IV evidence or "majority evidence" from level II or III studies
D	No recommendation possible because of inadequate or conflicting evidence

Past ICUD Consultations

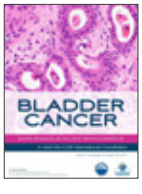
Below is a list of all past ICUD Consultations. To download a PDF of an ICUD, please visit the SIU-ICUD Joint Consultations page.

2022 – 2nd WUOF/SIU ICUD on Kidney Cancer
Montreal, Canada
Editors: Grant D. Stewart, Robert G. Uzzo, and Toni K. Choueiri

2020 – 1st ICUD-WUOF International Consultation on Molecular Biomarkers in Urologic Oncology
Montreal, Canada
Editors: Yair Lotan, Nathan Lawrentschuk, and Jack Schalken

2018 ICUD-SIU. Congenital Lifelong Urology: Caring for the Adolescent and Adult Patient with Congenital and Childhood GU Conditions
Seoul, South Korea
Editors: Dan Wood and Hadley M. Wood

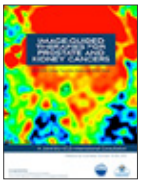
2017 ICUD-SIU. Bladder Cancer
Lisbon, Portugal
Editors: Peter Black and Paulo Gontero



2016 ICUD-ISC. 6th International Consultation on Incontinence
Tokyo, Japan
Chairs: Paul Abrams, Linda Cardozo, Adrian Wagg, and Alan Wein

2016 ICUD-SIU. Urological Management of the Spinal Cord Injured Patient
Buenos Aires, Argentina
Editors: Sean Elliott and Reynaldo Gómez

2015 ICUD-SIU. Image Guided Therapy in Urology
Melbourne, Australia
Editors: Rafael Sánchez-Salas and Mihir Desai



2014 ICUD-EAU. Minimally Invasive Surgery in Urology
Stockholm, Sweden
Chairs: Walter Artibani and Jens Rassweiler

2014 ICUD. Men's Health (facilitated by AUA)
Orlando, United States
Chairs: Ajay Nehra, Ridwan Shabsigh, and Graeme Jackson

2014 ICUD-SIU. Stone Disease
Glasgow, Scotland
Editors: Jean de la Rosette and John Denstedt

2014 ICUD-EAU. Medical Management of Urological Malignancy (MMUM)
Lisbon, Portugal
Chairs: Christian Stief and Christopher Evans

2013 ICUD-AUA. Topic Consultation on Anticoagulation in Urological Surgery
Chair: Stuart Wolf

2013 ICUD-SIU. Children's Congenital Anomalies
Vancouver, Canada
Editors: Catherine deVries and Rien Nijman

2013 ICUD-SIU. Upper Tract Urothelial Carcinoma
Vancouver, Canada
Editors: Shahrokh F. Shariat, Surena Matin, and Arnulf Stenzl

2012 ICUD-EAU. 5th International Consultation on Incontinence
Paris, France
Chairs: Paul Abrams, Linda Cardozo, and Alan Wein

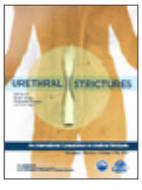
2012 ICUD-SIU. Male LUTS
Fukuoka, Japan
Chairs: Chris Chapple, Kevin McVary, and Claus Roehrborn

2011 – 2nd International Consultation on Bladder Cancer
Vienna, Austria
Chairs: Mark Soloway and Henk van der Poel

2011 – 4th International Consultation on Prostate Cancer
Berlin, Germany
Chairs: Manfred Wirth and Gerald Andriole

2010 – 1st ICUD-EAU International Consultation on Renal Cell Cancer
Barcelona, Spain
Chairs: Peter Mulders and Zya Kirkali

2010 – 1st ICUD-SIU International Consultation on Urethral Stricture
Marrakesh, Morocco
Chair: Gerry Jordan



2010 – 1st ICUD-SIU International Consultation on Obstetric Vesico-Vaginal Fistula
Marrakesh, Morocco
Chairs: Dirk de Ridder and Sherif Mourad

2009 – 3rd International Consultation on Sexual Medicine
Paris, France

2009 – 1st International Consultation on Genito-Urinary Infections
Stockholm, Sweden

2009 – 1st ICUD-SIU International Consultation on Testicular Cancer
Shanghai, China
Editors: Susanne Osanto and Jerome P. Richie

2008 – 4th International Consultation on Incontinence
Paris, France

2008 – 1st International Consultation on Penile Cancer
Santiago, Chile
Editors: Antonio Carlos L. Pompeo, Chris F. Heyns, and Paul Abrams

2007 – 2nd International Consultation on Stone Disease
Paris, France
Chairs: John Denstedt and Saad Khoury

2006 – 1st Consultation on Congenital Anomalies
Cape Town, South Africa

2005 – 6th International Consultation on New Developments in Prostate Cancer & Prostate Diseases
Paris, France

2004 – 1st International Consultation on Incontinence
Monte Carlo, Monaco

2004 – 1st International Consultation on Bladder Tumors
Honolulu, Hawaii
Editors: Mark Soloway, Adrienne Carmack, and Saad Khoury

2003 – 2nd International Consultation on Erectile and Sexual Dysfunctions
Paris, France

2002 – Consultation on Genitourinary Trauma
Stockholm, Sweden
Chair: Jack McAninch

2002 – 3rd International Consultation on Prostate Cancer New Treatment Modalities
Paris, France

2001 – 2nd International Consultation on Incontinence
Paris, France

2001 – 1st International Consultation on Stone Diseases
Paris, France

2000 – 5th International Consultation on Benign Prostatic Hyperplasia
Paris, France

2000 – 1st International Consultation on Nosocomial Infections in Urology
Paris, France

1999 – 2nd International Consultation on Prostate Cancer
Paris, France

1999 – 1st International Consultation on Erectile Dysfunction
Paris, France

1998 – 1st International Consultation on Incontinence
Monte Carlo, Monaco

1997 – 4th International Consultation on Benign Prostatic Hyperplasia
Paris, France

1996 – 1st Consultation on Prostate Cancer
Monte Carlo, Monaco

1995 – 3rd International Consultation on Benign Prostatic Hyperplasia
Monte Carlo, Monaco

1994 – 4th International Symposium on Recent Advances in Urological Cancer Diagnosis & Treatment
Paris, France

1993 – 2nd International Consultation on Benign Prostatic Hyperplasia
Paris, France

1991 – 1st International Consultation on Benign Prostatic Hyperplasia
Paris, France

1990 – 3rd International Symposium on Progress Urinary Tumors
Paris, France

1989 – 2nd International Symposium on Progress Urinary Tumors
Paris, France

1987 – 1st International Symposium on Progress Urinary Tumors
Paris, France

1986 – Prostate Cancer
Paris, France

1985 – Bladder Tumors
Paris, France

1984 – 1st International Symposium on Testicular Cancer
Paris, France

1983 – Kidney Tumors
Paris, France

1981 – Prostate Cancer
Paris, France

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Exact Imaging

Exact Imaging specializes in high-resolution micro-ultrasound systems for real-time imaging, primarily used for prostate cancer diagnosis and treatment.

Lantheus

Lantheus provides innovative diagnostic imaging agents and therapeutic products, focusing on precision healthcare, including solutions for cardiovascular and oncology applications.

2024 ICUD Consultation Committee Snapshot

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2024 ICUD Consultation Abbreviations

Abbreviation	Full Term	COMMITTEE #
3D	three-dimensional	6
4K	four-Kallikrein	6
5-ALA	5-aminolevulinic acid	10
5-ARI	5-alpha-reductase inhibitor	1,4,13
AJCC	American Joint Committee on Cancer	2,15
ABMGG	American Board of Medical Genetics and Genomics	5
ABMS	American Board of Medical Specialties	5
ACS	American Cancer Society	5
ACT	anticoagulant therapy	6
ADC	apparent diffusion coefficient	2,13,15
ADM	African descent men	5
ADT	androgen deprivation therapy	2,5,9,12,13,15,16
AFMS	anterior fibromuscular stroma	7
AI	artificial intelligence	9,10,11,13,14
AIP	atypical intraductal proliferation	2
AMACR	alpha-methylacyl-coenzyme A racemase	2
AMPK	AMP-activated protein kinase	4
APA	accessory pudendal artery	11
APFS	anterior pelvic fascia sparing	11
AR	augmented reality	10
ARO	German Cancer Society-Arbeitsgemeinschaft Radiologische Onkologie	16
ARPI	androgen receptor pathway inhibitor	15
ARSi	androgen receptor signalling inhibitor	5,15
ART	adjuvant radiation therapy	16
AS	active surveillance	2,4,5,7,8,9,13
ASA	acetylsalicylate	6
ASCO	American Society of Clinical Oncology	16
AUA	American Urological Association	3,5,6,9,10,14,15
AUC	area under the curve	2,5,15
AURKA	aurora kinase A	2

AUROC	Area Under the Receiver Operating Characteristic Curve	8
BAC	bacterial artificial chromosomes	5
BCR	biochemical recurrence	2,8,9,13,15,16
BCRFS	BCR-free survival	2
bDFS	biochemical disease-free survival	14
BFFS	biochemical failure-free survival	15
BMI	body mass index	4
BNED	biochemical no evidence of disease	12
BNP	bladder neck preservation	11
bPFS	biochemical progression-free survival	15,16
BPH	benign prostatic hyperplasia	2,7,9,13,15
BPLND	bilateral pelvic lymph node dissection	11
bRFS	biochemical relapse-free survival	15
BSU	bedside units	11
CAP	Cluster Randomized Trial of PSA Testing for Prostate Cancer	3
CAP	College of American Pathologists	2
CAPRA	Cancer of the Prostate Risk Assessment	2,9
CBCT	cone beam CT	12
CCL	cumulative cancer length	2
CCR	cell-cycle risk	9
CEUS	contrast-enhanced ultrasound	13,14
CI	confidence interval	5,6,13,15
CIPC	cancer involvement in positive cores	2
ciPCa	clinically insignificant prostate cancer	6,8
CIRT	carbon ion radiotherapy	12
cN+	clinically node positive	15
cN-	clinically node negative	15
CNS	central nervous system	12
cPFS	clinical progression-free survival	15
CRPC	castration-resistant prostate cancer	2
cs	clinically significant	13
CSM	cancer-specific mortality	2
csPCa	clinically significant prostate cancer	6,7,8,13
CSS	cancer-specific survival	15
CT	computed tomography	7,8,9,10,12,13,15
CTLA-4	cytotoxic T-lymphocyte associated protein 4	13

CTV	clinical target volume	12
CVD	cardiovascular disease	4
DA	detrusor apron	7
DAPT	dual antiplatelet therapy	6
DCE	dynamic contrast-enhanced imaging	7,13
DDR	DNA-damage repair	5
DE	docetaxel	15
DFS	disease-free survival	15,16
DHT	dihydrotestosterone	1,4
dMMR/MSI-H	MMR defects and/or microsatellite instability high	5
DRE	digital rectal examination	3,6,7,8,9,13
DSS	disease-specific survival	2
DVC	dorsal venous complex	7,11
DVH	dose-volume histogram	12
DW	diffusion-weighted	15
DWI	diffusion-weighted imaging	2,13
EAU	European Association of Urology	5,6,9,10,14,15
EAUiaiC	Intraoperative Adverse Incident Classification by the European Association of Urology	2
EBRT	external beam radiation therapy	9,15,16
eCC	electronic cancer checklist	2
ECE	extracapsular extension	8,15,16
ED	erectile dysfunction	6,13
EF	erectile function	6
EFS	event-free survival	15
EGFR	epidermal growth factor receptor	4
ELSI	ethical, legal, and social implications	5
ENI	elective nodal irradiation	15
EORTC	European Organization for Research and Treatment of Cancer	16
EPE	extraprostatic extension	2,7,8,10,16
EPI	ExoDx Prostate Intelliscore	9
EPIC	European Prospective Investigation into Cancer and Nutrition trial	4
EPIC	Expanded Prostate Cancer Index Composite	13,14
EPIC-26	Expanded Prostate Cancer Index Composite-26	12
EPID	electronic portal imaging	12

ePLND	extended pelvic lymph node dissection	15
ERSPC	European Randomized Study of Screening for Prostate Cancer trial	1,2,3,6
ESC	European Society of Cardiology	6
F-CTV	focal-clinical target volume	14
F-GTV	focal-gross tumour volume	14
F-PET	fluciclovine positron emission tomography	15
F-PTV	focal-planning target volume	14
FALCON	FocAL therapy CONsensus	14
FDA	US Food and Drug Administration	1,4,5,6,9,10,11,15
FDG	18F-fluorodeoxyglucose	15
FFPE	formalin fixed paraffin embedded	9
FFS	failure-free survival	13
FH	family history	5
FISH	fluorescence in situ hybridization	9
FLA	focal laser ablation	13,14
FT	focal therapy	13
G2	Gothenburg-2	3
GA	general anesthesia	6
GC	genomic classifier	9
GCC	genomic and clinical scores	9
GG	grade group	2,6,7,13
GI	gastrointestinal	12,15
GINA	Genetic Information Nondiscrimination Act of 2008	5
GLP-1	glucagon-like peptide 1	4
GP	Gleason pattern	2
GPS	Genomic Prostate Score	9
GRS	genetic risk score	5
GS	Gleason score	2,9,13,15,16
GTV	gross tumour volume	8
GU	genitourinary	12,15
GUPS	Genitourinary Pathology Society	2
GW-PRS	genome-wide polygenic risk scores	5
GWAS	genome-wide association studies	5
H&E	hematoxylin and eosin	2
HBED-CC	^{68}Ga and N, N'-bis-[2-hydroxy-5- (carboxyethyl) benzyl] ethylenediamine- N,N'-diacetic acid	15

HD-WPRT	high dose–whole pelvic radiotherapy	15
HDR	low-dose-rate	12,14
HEAT	HIFU Evaluation and Assessment of Treatment registry	13
HG	high grade	9
HGPIN	high-grade prostatic intraepithelial neoplasia	2
HIFU	high-intensity focused ultrasound	2,7,13,14
HIIT	high-intensity interval training	1
HINTS	Health Information National Trends Survey	5
HIT	Heidelberg Ion Treatment	12
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A	4
HMWK	high molecular weight keratins	2
HoLEP	Holmium laser enucleation of the prostate	14
HPV	human papillomavirus	1
HR	hazard ratio	2,3,4,15
HR	high-risk	15
HRR	homologous recombination repair	5
HSPCa	hormone-sensitive prostate cancer	15
HT	hormonal therapy	15
ICARUS	Intraoperative Complications Assessment and Reporting with Universal Standards	2
ICCR	International Collaboration on Cancer Reporting	2
ICE	International Cryotherapy Evaluation registry	13
ICG	indocyanine green	10
IDC	intraductal carcinoma	2
IFF	in-field failures	13
IGF	insulin growth factor	4
IHC	immunohistochemistry	9
IIEF/IIEF-13	International Index of Erectile Function	6,13
IMRT	intensity-modulated radiotherapy	12,13
INR	international normalized ratio	6
IO	immuno-oncology	13
IPSS	International Prostate Symptom Score	12,13
IQR	interquartile range	13
IRE	irreversible electroporation	13,14
ISUP	International Society of Urological Pathology	2,6,7,9,13,14,15

ISUP GG	International Society of Urological Pathology grade group	8
IVUS	intravascular ultrasound	7
LA	local anesthesia	6
LD	linkage disequilibrium	5
LDR	low-dose-rate	14,15
LIGAND	Lipitor and Biguanide to Androgen Delay Trial	4
LMWH	low-molecular weight heparin	6
LN	lymph node	15
LND	lymph node dissection	15
LNI	lymph node involvement	2,15
LNM	lymph node metastasis	15
LPLND	lateral pelvic lymph node dissection	15
LUTS	lower urinary tract symptoms	13
MAST	Metformin Active Surveillance Trial	4
MAX-PC	memorial anxiety scale for prostate cancer	4
mCRPC	metastatic castration-resistant prostate cancer	5
MFS	metastasis-free survival	2,15,16
mHSPC	metastatic hormone-sensitive prostate cancer	5
MiPS	Mi Prostate Score	9
miPSMA	molecular imaging prostate-specific membrane antigen	13
MMAI	multimodal artificial intelligence	12
MMR	mismatch repair	5
MP	multiport	11
mpMRI	multiparametric magnetic resonance imaging	6,7,8,9,13,14,15
MPS2	MyProstateScore 2	6
mpUS	multiparametric ultrasound	13
MRgFUS	MR-guided focused ultrasound	14
MRI	magnetic resonance imaging	2,3,5,6, 8,10,11,12, 13,15
MRI-US	magnetic resonance imaging-ultrasound	13
MRIgRT	MRI-guided radiotherapy	12
MSKCC	Memorial Sloan Kettering Cancer Center	8
MTD	maximum tumour diameter	2
mTOR	mammalian target of rapamycin	4
MUSIC	Michigan Urological Surgery Improvement Collaborative	15

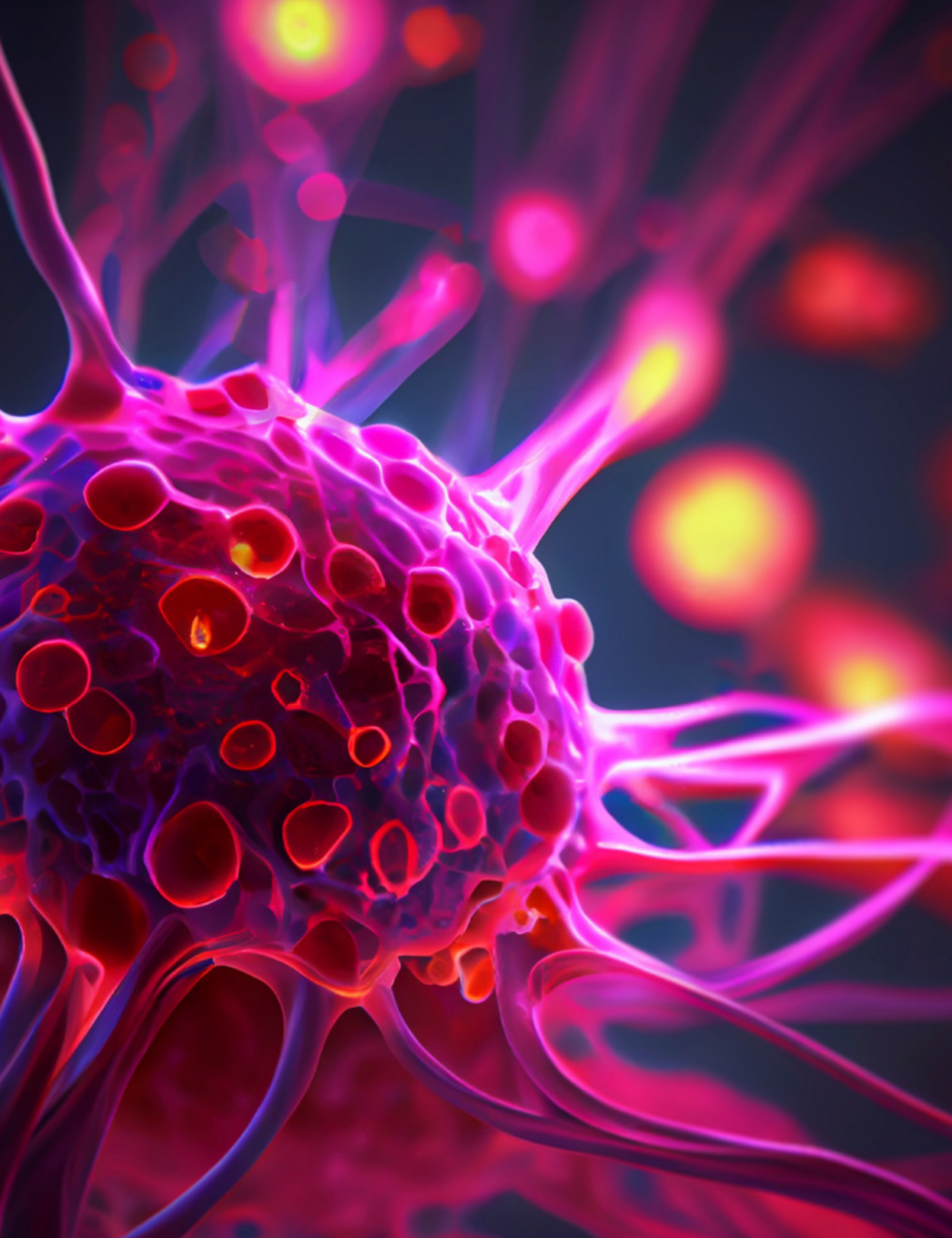
MUSIC-AS	MicroUS In Cancer—Active Surveillance	7
MVP	Million Veteran Program	5
N/M	lymph node/metastasis stage	13
NCCN	National Comprehensive Cancer Network	2,3,5,9,12,14,15
NCDB	National Cancer Database	15
NGS	next-generation sequencing	5,9
NHT	neoadjuvant hormonal therapy	15
NICE	National Institute for Clinical and Health Excellence	7
NND	number needed to diagnose	3
NPV	negative predictive/predicting value	7,8,9,13,15
NS	not significant	15
NVB	neurovascular bundle	11
OAB-q	Overactive Bladder Questionnaire	13
ODAC	Oncologic Drugs Advisory Committee	4
OFF	out-of-field failures	13
OLI-P	Effectiveness and Toxicity of Percutaneous High-dose Radiotherapy in Patients with OLIgometastases of Prostate Carcinoma trial	15
OM	overall mortality	2
OM	oligometastatic	15
OPT	organized prostate cancer testing	3
OR	odds ratio	1,5,9
ORIOLE	Observation vs. Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer	15
ORR	objective response rate	5
OS	overall survival	5,8,9,15,16
p2PSA	[-2]pro-PSA isoform	6
P2Y11	adenosine diphosphate signaling	6
PARPi	poly (ADP-ribose) polymerase inhibitor	5
PBCG	Prostate Biopsy Collaborative Group	3
PBRT	proton beam radiotherapy	12
PBRT	prostate-bed radiotherapy	15
PC	principal component	5
PCa	prostate cancer	1,6,7,8,9,10,13,15
PCA3	prostate cancer gene 3/ prostate cancer antigen 3	6/9
PCI	percutaneous coronary intervention	6

PCOR	Prostate Cancer Outcomes Registry	3
PCPT	Prostate Cancer Prevention Trial	3,4
PCPTRC	PCPT Risk Calculator	3,9
PCSS	prostate cancer–specific survival	15
PD-1	programmed cell death 1 receptor	5
PD-L1	programmed cell death 1 ligand 1	5
PDA	prostatic ductal adenocarcinoma	2
PDT	photodynamic therapy	13
PELICAN	Project to Eliminate Lethal Prostate Cancer	14
PET	positron emission tomography	8,13
PET-CHO	positron emission tomography [^{11}C]-labelled choline	15
PFS	progression-free survival	4,15
PFS-RARP	pelvic fascia sparing, or Retzius-sparing, robot-assisted radical prostatectomy	11
PGS	polygenic score	5
PHI	Prostate Health Index	3,6,9
PI-FAB	Prostate Imaging after Focal Ablation score	13
PI-RADS	Prostate Imaging–Reporting and Data System	2,3,6,8,13
PIN	prostatic intraepithelial neoplasia	2
PLCO	Prostate, Lung, Colorectal and Ovarian	1,3,6
PLND	pelvic lymph node dissection	15
pN+	pathologically node positive	15
PNI	perineural invasion	2
PORT	prostate-only radiotherapy	15
PPV	positive predictive value	5,7,8,9,13,15
PR	posterior reconstruction	11
PRECISE	Prostate Cancer Radiological Estimation of Change in Sequential Evaluation	13
PRECISION	Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not? trial	7
PRI-MUS	Prostate Risk Identification using MicroUS	7
PRS	polygenic risk score	4,5
PRS-CS	polygenic prediction via continuous shrinkage	5
PSA	prostate-specific antigen	1,2,3,4,5,6,7,8,9, 10,11,13,14,15,16
PSAFS	PSA-free survival	15
PSA50	prostate-specific antigen reduction ≥ 50%	5

PSAD	PSA density	9
PSAP	prostatic-specific acid phosphatase	2
PSAv	prostate-specific antigen velocity	13
PSM	positive surgical margin	2,10,11
PSMA	prostate-specific membrane antigen	5,8,13
PSMA PET	prostate-specific membrane antigen positron emission tomography	3,7,8,9,10,12,14,15,16
PSS	periurethral suspension stitch	11
PTEN	phosphatase and tensin homolog	2,9
PTV	planning target volume	12
PZ	peripheral zone	13
QoL	quality of life	4,12,13
RARP	robotic-assisted radical prostatectomy	10,11,13
RAS	robot-assisted surgery	11
RBE	relative biological effectiveness	12
RC 3	Rotterdam risk calculator number 3	RC
RCT	randomized controlled trial	4,6,7,9,13,15,16
REDEEM	Reduction by Dutasteride of Clinical Progression Events in Expectant Management trial	4
REDUCE	REduction by DUtasteride of prostate cancer Events trial	4,5
RFS	relapse-free survival	15
ROI	region of interest	13
ROSI	Remotely Operated Suction Irrigation system	11
RP	radical prostatectomy	2,6,9,11,13,15,16
rPFS	radiographic progression-free survival	5
RPM	rare pathogenic mutation	5
RR	rate ratio	3
RR	relative risk	1,4
RRP	radical retropubic prostatectomy	11,12
RT	radiotherapy	2,10,12,13
RTOG	Radiation Therapy Oncology Group	15,16
RTR	renal transplant recipient	11
S-RARP	standard robotic radical prostatectomy	11
SABR	stereotactic ablative radiation therapy	15
SABR-COMET	Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases trial	15

SAPT	single-agent antiplatelet therapy	6
SBRT	stereotactic body radiotherapy	8,12
SD	standard deviation	6
SDD	same-day discharge	10
SEER	Surveillance, Epidemiology, and End Results	1,9,15
SEPERA	Side-specific Extra-Prostatic Extension Risk Assessment tool	11
SePLND	super-extended pelvic lymph node dissection	15
SIB	simultaneous integrated boost	15
SIB-IMRT	intensity-modulated radiation therapy with simultaneous integrated boost	15
SLNB	sentinel lymph nodal biopsy	15
SNP	single-nucleotide polymorphism	1,3,5
SOC	standard of care	15
SP	single port	10,11
SPCG	Scandinavian Prostate Cancer Group	15
SP-RARP	Single-Port Robotic Assisted Radical Prostatectomy	11
SpaceOAR	absorbable hydrogel rectal spacers	10
SPARC	Single-Port Advanced Research Consortium	11
SRE	summary risk estimate	1
sRP	salvage radical prostatectomy	13
SRT	salvage radiotherapy	8,13,16
SSA	Sub-Saharan Africa	5
STAMPEDE	Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy trial	15
STHLM3	Stockholm3	9
STOMP	Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence trial	15
SUI	stress urinary incontinence	10
SUO	Society of Urological Oncology	3
SUV	standardized uptake values	8
SUVmax	maximum standardized uptake values	8
SVI	seminal vesicle invasion	2,8,15,16
SWOG	Southwest Oncology Group	16
T1WI	T1-weighted imaging	7,13
T2WI	T2-weighted imaging	7,13

TARGET	Technology-Enhanced Acceleration of Germline Evaluation for Therapy trial	5
TARGET	Transatlantic Recommendations for Prostate Gland Evaluation with Magnetic Resonance Imaging After Focal Therapy	13
TBR	tumour-to-background ratios	8
TLR	Toll-like receptor	13
TNM	tumour-node-metastasis staging system	1,7,8
TP-Bx	transperineal prostate biopsies	6
TR-Bx	transrectal prostate biopsies	6
TRUS	transrectal ultrasound	6,7,8,10,12,13
TTV	total tumour volume	2
TULSA	transurethral ultrasound ablation	13,14
TUR	transurethral resection	2
TURP	transurethral resection of the prostate	9,13,14
TV-RARP	transvesical single-port robotic-assisted radical prostatectomy	11
Tx	treatment	15
UICC	Union for International Cancer Control	2
UIR	unfavourable intermediate risk	12
ULN	upper limit of normal	15
UKB	UK Biobank	5
uPSA	ultrasensitive PSA	16
US	ultrasound	13
USPIO	ultrasmall superparamagnetic iron oxide	15
USPSTF	United States Preventive Services Task Force	1,3,5
VAS	visual analogue scale	6
VEGF1	vascular endothelial growth factor 1	14
VMAT	volumetric-modulated arc therapy	15
VTP	vascular-targeted photodynamic therapy	13
WBBS	whole-body bone scan	8,10
WHO	World Health Organization	2,3
WP	work packages	3
WP	whole pelvis	15
WPRT	whole pelvic radiotherapy	15
WW	watching waiting	9
yr	year	15



COMMITTEE 1

Epidemiology of Prostate Cancer

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Funding: The author's work was supported in part by funding from the National Institutes of Health/National Cancer Institute (P30-CA008748) and from CAPES Foundation (CAPES-PRINT – 88887.835383/2023-00).

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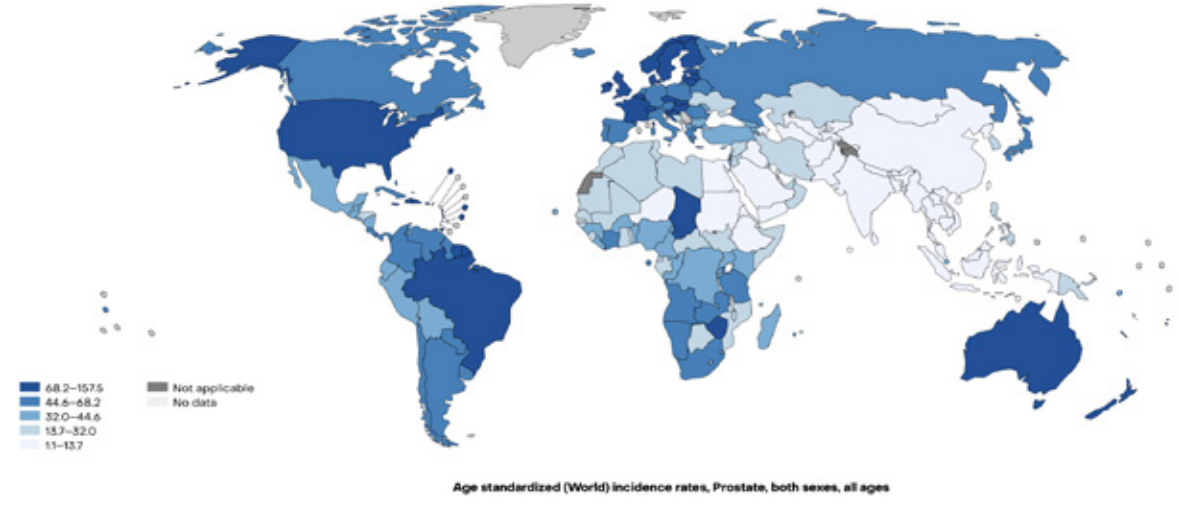
Prevalence, Incidence, and Mortality

Overview

In terms of cancer incidence, prostate cancer (PCa) is the most common cancer among men in 118 countries worldwide followed by lung cancer in 33 countries.[1] There were more than 1.4 million new cases in 2022 and the prevalence of prostate cancer is expected to surpass 5 million in 2027. However, the 2022 age-standardized incidence rates vary among continents (**FIGURE 1**), being higher in Northern America (73.5 cases per 100,000 men) and Oceania (72.2 cases per 100,000 men) and lower in Asia (12.6 cases per 100,000 men) (**FIGURE 2, TABLE 1**).[1,2]

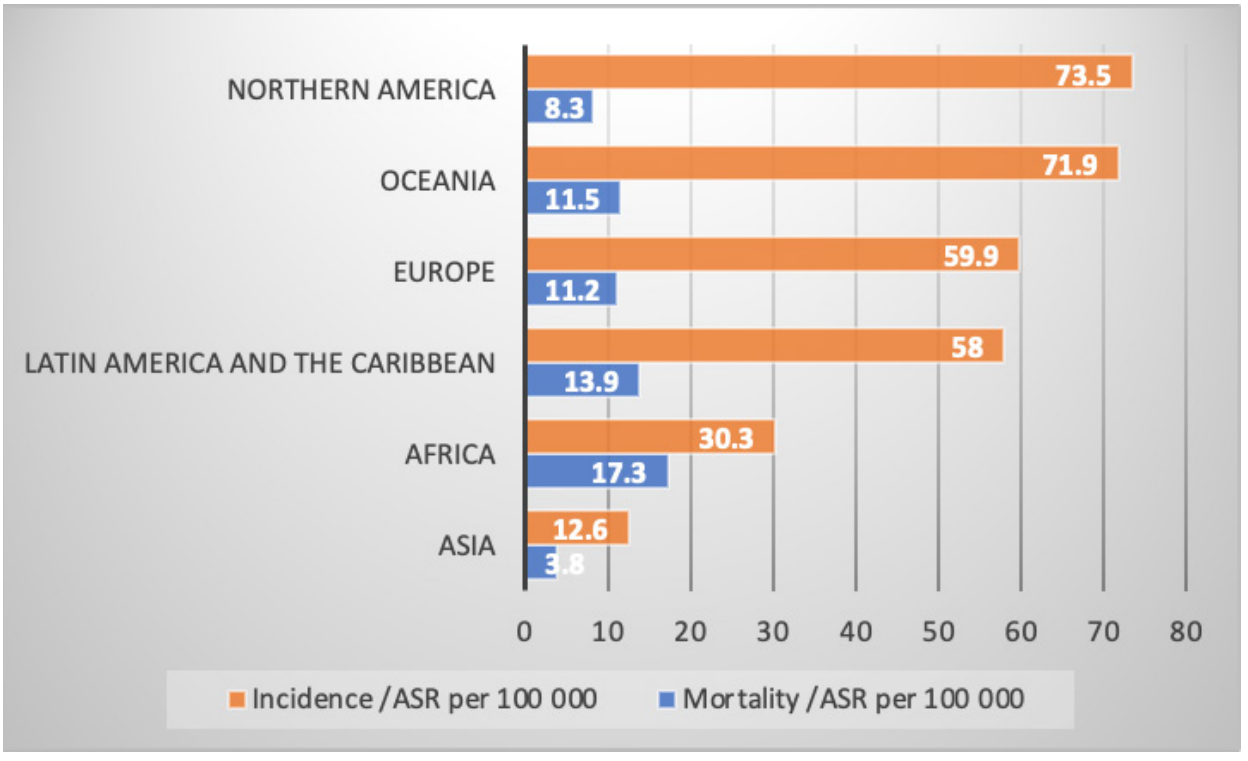
In 2022, PCa was the fifth leading cause of death from cancer in men worldwide, with a wide variation across the globe (**FIGURE 3**). It is the main cause of death from cancer in men in 52 of 185 countries worldwide and the leading cause of death from cancer in Africa (17.3 per 100,000 men) and Latin America and the Caribbean (13.9 per 100,000 men), while it is the seventh cause of mortality from cancer in Asia (3.7 per 100,000 men) (**FIGURE 2, TABLE 1**).[1,2]

FIGURE 1 Age-standardized prostate cancer incidence (WHO).



Abbreviation: ASR, age-standardized rate; WHO, World Health Organization.
Source: *Ferlay J, Laversanne M, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Tomorrow (version 1.1). Lyon, France: International Agency for Research on Cancer. Accessed April 30, 2024. https://gco.iarc.fr/tomorrow.*[2]

FIGURE 2 Age-standardized prostate cancer incidence and mortality per 100,000 among continents, in 2022.



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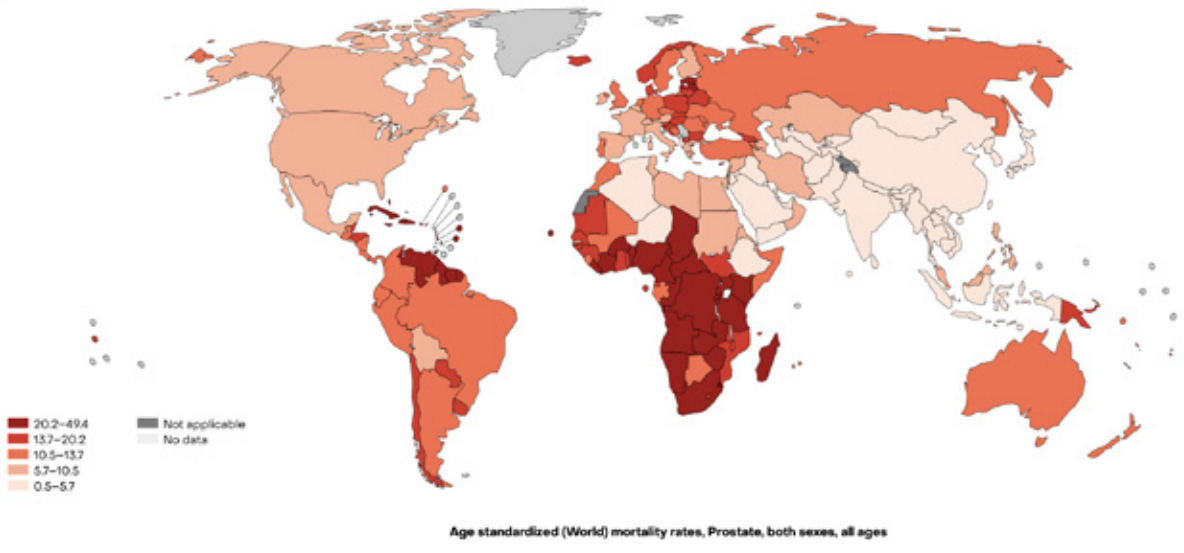
Geographical variation

There is a substantial geographic variability in PCa incidence and mortality rates, which can be attributed to variation in genetic susceptibility, life expectancy, PCa screening, access to medical care, available infrastructure in healthcare systems, and lifestyle factors.[3,4] Early detection of PCa is not standardized worldwide and there are differing recommendations among government agencies and specialty societies (see Chapter 3). The screening policies are derived mainly from studies from North America and Europe, which also provide most of the epidemiological data. PCa incidence rates among countries within the same continent can vary up to about 200 per 100,000 men. Moreover, epidemiological data are heavily influenced by record-keeping and registry completeness, which can be less complete in low- and middle-income countries and may underestimate the burden of PCa.[5,6]

Socioeconomic status is also associated with PCa incidence rates and inversely associated with PCa mortality rates.[7] The quality of care for PCa has increased globally over the past decades, but there remains a gap between high and low sociodemographic index regions. Furthermore, patient education, healthcare system infrastructure, screening policies, and availability of guidelines influence PCa quality of care and thereby both the incidence and mortality of the disease.[8]

FIGURE 3 Age-standardized prostate cancer mortality (WHO).



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Northern America

Northern America has the highest incidence of PCa of all continents, in part due to a high frequency of screening and early diagnosis and high quality of cancer registry data, and PCa mortality rates are among the lowest in the world (8.3 per 100,000 men), following Asia (3.8 per 100,000 men).[1] In the United States, the highest incidence is observed in the North and in some regions of the Southeast. Following a decrease in incidence rates in early 2010s related to changing screening recommendations, rates have increased in recent years. Incidence rates for advanced disease have increased by 4–6% per year over the past 5 years, leading to a slowdown in the decline in PCa mortality rates in the same period, following guideline recommendations against prostate-specific antigen (PSA) screening.[9,10] Moreover, in the United States, the risk of being diagnosed with PCa is 2-fold higher in Black or African-American men who are also more likely to die from PCa than non-black men.[11]

Latin America and the Caribbean

In Latin America and the Caribbean, PCa is the most common cancer in men (58 per 100,000 men) and the most common cause of cancer death (13.9 per 100,000 men). One in 14 men will develop PCa in their lifetime but the incidence rates vary among countries and the risk in some countries is among the highest in the world, such as those observed in Guadeloupe and Martinique, 19% (1 in 5 men) and 16.6% (1 in 6 men), respectively.[1] There are disparities within healthcare systems, especially between public and private systems that affect PCa outcomes, with the population with private coverage having the same early diagnosis rates as developed countries.[12] Moreover, a Brazilian study associated the level of education with PCa screening and demonstrated lower screening rates among illiterate men who were diagnosed in more advanced stages.[13] In Uruguay, which is classified as a high-income country in Latin America, PCa incidence rates have been stable since 2004 and a decrease in PCa mortality has been observed due to improvements in healthcare.[14] Despite that, the high cost of new treatments, unequal access to new technologies, and lack of continuing medical education are among the factors that explain the second-highest PCa mortality rates in the world in Latin America and the Caribbean, after Africa.[12]

Europe

In Europe, the average risk of being diagnosed with PCa before age of 75 years is 7.9% (1 in 13 men). Some of the highest PCa incidence rates in the world are found in Northern Europe, particularly in Sweden (82.8 per 100,000 men).[1] Geographic variability in background risk in different countries, the prevalence of risk factors, and differences in diagnostic practice, screening programs, and the effective delivery of national cancer control plans may be possible determinants of the variation.[15] An increase in PCa mortality rates has been seen in Western Europe and the Nordic countries, where PCa mortality rates trend toward stability or decline, as observed in Sweden and Norway.[16]

Africa

Africa is the continent with the second-lowest PCa incidence rates (30.3 per 100,000 men) but with the highest PCa mortality rates (17.3 per 100,000 men) in the world. Chad has the highest incidence rates (70.3 per 100,000 men), followed by Côte d'Ivoire (48.4 per 100,000 men), and South Africa (46.7 per 100,000 men).[1] Furthermore, PCa cases have increased by 60% from 2002 to 2018; and while Northern and Southern Africa have a high prevalence, the highest PCa mortality is found in Eastern, Western, and Central Africa. Ethnicity, population origin, and limited access to PSA testing and effective treatment play a relevant role in the numbers of PCa in Africa. Moreover, the continent faces some challenges, as it has a high percentage of advanced disease at diagnosis, not least in young men with more aggressive disease, which could be related to genetic and environmental factors and limited access to care.[16,17] Sub-Saharan countries with a high sociodemographic index have a quality-of-care index below the global average.[8]

Oceania

In Oceania, PCa is the most common cancer in men (71.9 per 100,000 men), but the continent is second highest in PCa mortality (11.5 per 100,000 men).[1] A New Zealand study reported fluctuating PCa incidence over the past 20

years and a decline in PCa mortality rates.[18] An Australian study observed that age-standardized incidence rates for localized PCa follow the trends in PSA screening rates, with a decrease in PCa incidence rates observed after 2008 and a decrease in PCa mortality rates.[19] As seen in other parts of the world, differences in treatment choices were identified between men diagnosed in private and public health services, which could not be explained by disease severity.[20] One study predicts that incidence rates of all cancers and their associated PCa mortality rates in men will decline in Australia in the next few decades, although there is expected to be an increase in the number of new cases, reinforcing the need for screening strategies and control of risk factors.[19]

Asia

Asia is the largest continent of the world and contains over 60% of the world's population, which explains its impact on the number of cancer cases, accounting for 30.3% of new PCa cases and 18.3% of new deaths from the disease worldwide despite it having the lowest PCa incidence (12.6 per 100,000 men) and PCa mortality in the world (3.8 per 100,000 men).[1] Asia comprises many different countries and has a high variation in PCa incidence and mortality rates, which reflects the lack of screening programs in some countries and the diversity in healthcare systems. PCa is the fifth most common cancer in Asian men and the seventh cause of mortality from cancer, but it is the leading cancer in men in Japan, Lebanon, Kuwait, and Israel. Yet, PCa mortality decreased in Japan and Israel from 2007 to 2016, likely explained by early diagnosis. In contrast, PCa mortality increased in Thailand and Uzbekistan during the same period.[21]

TABLE 1 Estimated PCa Incidence and Mortality for the World's Continents in 2022

	Numbers of countries	Cumulative risk (%) of PCa	PCa incidence ASR per 100,000	PCa cumulative risk (%) for death from PCa	PCa mortality ASR per 100,000
Africa	54	3.7 (1 in 27 men)	30.3	1.7	17.3
Asia	47	1.4 (1 in 71 men)	12.6	0.29	3.8
Europe	40	7.9 (1 in 13 men)	59.9	1.0	11.2
Latin America and the Caribbean	32	7.1 (1 in 14 men)	58	1.1	13.9
Northern America	2	9.5 (1 in 11 men)	73.5	0.69	8.3
Oceania	10	9.1 (1 in 11 men)	71.9	0.83	11.5

Abbreviation: ASR, age-standardized rate; PCa, prostate cancer.
Source: *Ferlay J, Laversanne M, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Tomorrow (version 1.1). Lyon, France: International Agency for Research on Cancer. Accessed April 30, 2024. https://gco.iarc.fr/tomorrow.*[2]

Trends over time

Trends in PCa cancer incidence rates over time reflect patterns related to an increase in life expectancy, and changes in use of screening and early detection. Because life expectancy and use of diagnostic test for detecting prostate cancer at an early stage are rising in most parts of the world, particularly in low- and middle-income countries, both the incidence and the prevalence of prostate cancer will dramatically increase; the incidence is estimated to double over the next 20 years.[22]

In 1986, PSA test was granted US Food and Drug Administration (FDA) approval. By 1992, approximately a quarter of the men in their fifties in the United States had undergo at least one test, leading to a rapid increase in PCa incidence.[23] However, after the US Preventive Services Task Force (USPSTF) made recommendations in 2012 against PSA-based screening,[24] the decrease in PSA screening in United States and Canada was followed by an increased incidence of advanced PCa.[23] In 2018, USPSTF updated its statement and recommended PCa screening for men between 55–69 years after discussion of the potential benefits and harms.[25] It was demonstrated by Nowroozi *et al.* in a study that quantified PCa quality of care, that the quality-of-care index increased whenever PCa screening was implemented.[8]

Culp *et al.* demonstrated a trend in stabilizing or declining PCa incidence rates over the past 5 years, mainly in highly developed countries located in North America, Oceania, and Northern Europe, which could be related to a more cautious use of PSA testing and more awareness to avoid overdiagnosis; and also a decrease in PCa mortality due to improvements in PCa treatments.[3,15] In the United States, a comprehensive analysis of Surveillance, Epidemiology, and End Results (SEER) data demonstrated that the incidence rates of advanced-stage PCa increased in all racial and ethnic groups from 2015 to 2019. Nevertheless, the decline in PCa mortality has leveled off in the United States in the same period, in part due to an increase in incidence rates of distant-stage disease following recommendations against screening.[9] In Europe, while PCa incidence rates are increasing in Eastern Europe, they are stable in Northern and Southern European countries during the recent period; and PCa mortality rates have stabilized in most of the countries.[3]

The CONCORD study is a global program to provide survival data. The last update, CONCORD-3, included patients diagnosed from 2000 to 2014 and with regards to PCa comprised data from 290 registries in 62 countries. It demonstrated an age-standardized 5-year survival of 70–100% for men with prostate cancer and an increase over the 20-year period prior to the study, driven by early diagnosis and improvements in treatment.[26]

Cancer stage and survival

Prostate cancer survival is influenced by different factors including age, race, comorbidity, and stage. PCa in older men is associated with adverse pathological features and more advanced disease.[27,28] Rates of 5-year survival are higher for White men when compared to Black or Hispanic men.[29] Stage at the time of diagnosis is influenced by government policies and screening recommendations. From 2011 to 2017, an increase in advanced PCa incidence was observed in the United States, followed by a similar trend in localized PCa diagnosis.[30] There are different risk classification systems for PCa, based on PSA, Gleason score, and clinical stage. An increasing PSA level is

associated with advanced TNM stage (tumour-node-metastasis staging system) and worse outcomes.[31] Survival of advanced PCa has improved over the past years, which might reflect improvements in clinical management; however, while PCa diagnosed and treated at localized stages has a 97% 5-year cancer-specific survival, in the metastatic setting, only one-third of the patients are alive at 5 years after diagnosis.[29]

Risk Factors for Prostate Cancer

Little is known about PCa etiology, the understanding of which would be paramount for prevention measures. Age, race, family history, and certain germline mutations are the few well-established risk factors for PCa, with environmental factors also contributing to PCa development.[4]

Nonmodifiable risk factors

Age

Prostate cancer incidence is known to increase with age and there is an association between advanced age and greater PCa aggressiveness.[32,33] The median age of PCa diagnosis has decreased with the widespread use of PSA-based screening, and studies have shown a greater reduction in PCa mortality when PSA testing starts at earlier ages (e.g., before 55 years instead of after).[34] Moreover, the burden differs between African Americans and patients with positive family history, who are affected at younger ages.[34,35]

Family history as a risk factor for prostate cancer

The first report on familial aggregation of prostate cancer was published in 1956.[36] Since then, a great number of epidemiological studies have consistently shown that brothers and sons of men with prostate cancer are more likely to be diagnosed with prostate cancer than men without a family history of the disease. The results of 22 cohort and case-controlled studies published up until 2002 were summarized in a systematic review and meta-analysis.[37] The risk for prostate cancer increased with the number of affected relatives and with decreasing age at diagnosis of these relatives.[37] The pooled relative risk (RR) for a prostate cancer diagnosis in first-degree relatives of men with prostate cancer was 2.5 (95% confidence interval [CI], 2.2–2.8). The relative risk in men whose father or brother was diagnosed before age 60 years was 4.3 (95% CI, 2.9–6.3). In men with two affected relatives the relative risk was 3.5 (95% CI, 2.6–4.8).[37] Having an affected brother increased the risk more than having an affected father.[37] The latter finding may be explained by X-linked and recessive inheritance, although shared environmental factors and detection bias may contribute.

More recent research has found that a family history of high-grade or metastatic disease increases the risk for high-grade and metastatic cancer more than a family history of low-grade, nonmetastatic disease.[38,39] Nonetheless, in a nationwide Swedish study a family history of low-risk prostate cancer in a brother increased the probability of high-risk disease by age 75 years to 8.0% (95% CI, 7.0–9.1%) from the average population risk of 5.2%.[38]

The reported relative and absolute risk increase for men with a family history of prostate cancer may be inflated by detection bias, as men with a positive family history may be more likely than other men to obtain diagnostic measures for detecting early prostate cancer. Such detection bias was documented in a study that found significantly higher incidence of T1c tumours (typically diagnosed after PSA testing in men without clinical signs of prostate cancer) in brothers of men with prostate cancer the first year after the diagnosis of the index case than in subsequent years (standardized incidence ratio 4.3 compared with 2.8 to 3.3).[40]

Not as many studies have investigated the association between family history and the risk of dying from prostate cancer. In a nationwide register study, the hazard ratio for death from prostate cancer was 1.6 for men with a father diagnosed with a nonfatal prostate cancer and 2.0 for men whose father had died from prostate cancer.[41] The "true" risk increase may be greater than this, as frequent PSA testing and subsequent curative treatment of localized cancer among men with a family history most likely reduces their risk of dying from the disease.

Familial aggregation of disease may be caused by not only genetic heritability but also shared environmental factors. For PCa, the former is more important than the latter. Indeed, two twin studies suggest that PCa is more genetically heritable than any other common cancer.[42,43] Further evidence that shared environmental factors are of less importance comes from a study that found an increased risk for PCa in adopted men whose biological father was diagnosed with PCa but not in adopted men whose nonbiological father was diagnosed with PCa.[44]

PCa heritability is to some extent linked to breast cancer heritability. A systematic review and meta-analysis of 18 studies showed that having a sister or mother with breast cancer increased the risk for prostate cancer 1.3-fold.[45] Besides the association with breast cancer, no other cancer type has been shown to have a clinically relevant familiar association with prostate cancer.

Most epidemiological studies of family history as a risk factor for PCa come from Europe and North America, and few have investigated the interaction with ethnicity or geography. A study from North America reported a somewhat lower prevalence of familial prostate cancer in Asian-Americans than in Blacks and Whites, although a positive family history was associated with a 2- to 3-fold higher prostate cancer risk in each of these three ethnic groups.[46] In a study from North Carolina, United States, of 1,225 men who had a prostate biopsy, family history was on multivariable analysis associated with high-grade cancer in Black (odds ratio [OR], 1.9, 95% CI, 1.0–3.3) but not in non-Black men.[47] One nationwide case-controlled study of men in Barbados found an odds ratio of 3.0 (95% CI, 2.2–4.2) for PCa in men with an affected father or brother compared with men without.[48] A smaller study from South Korea reported a multivariate odds ratio of 6.3 (95% CI, 2.8–14) for detecting Gleason grade group ≥ 2 cancer in men with a family history of prostate cancer versus men without.[49]

Clinical consequences of family history

Many clinical guidelines recommend regular PSA testing for men with a brother or father diagnosed with prostate cancer initiated some years earlier than for men in general. In the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial, men who had a family history of PCa had a significantly higher risk of dying from PCa if they were allocated to the nonscreening arm compared with the screening arm (hazard ratio [HR], 1.9).[50]

In contrast, two analyses from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial did not show different outcomes for men with a family history of PCa.[51,52] It is possible that men with a strong family history of PCa already had obtained screening and were therefore not invited to the ERCPC trial; if so, the trial underestimated the effect of screening in this subgroup.

A multicentre study of over 15,000 men who had a prostate biopsy found that, after adjusting for clinical factors, the relative risk of detecting high-grade cancer was 1.4 for men with a brother or father with PCa, 1.2 for men with a second-degree relative with PCa, and 1.2 for men with first-degree relative with breast cancer.[53] Family history was more strongly associated with detection of high-grade cancer in younger than in older men. The association between family history and detection of high-grade may be stronger in Black American men.[47] It may also be stronger in Eastern Asia.[49]

A systematic review of nine North American, one European, and one Asian study, with a total of nearly 40,000 patients, concluded that a family history of PCa does not increase the risk for biochemical recurrence or death from PCa after surgery or radiotherapy for localized PCa.[54]

Another systematic review of six North American and European studies investigating the clinical consequences of family history in men who opted for active surveillance of localized PCa included 2,400 patients.[55] Family history was associated with PCa progression among African-American men in one of the six studies,[56] but on a group level, men with a family history of PCa did not have more aggressive PCa than men with a negative family history.[55] With a possible exception for African-American men, family history does therefore not seem to be an important factor when determining eligibility for active surveillance.[55] These results do, however, not exclude that some rare germline mutations are associated with more rapid progression to incurable disease and studies are ongoing.

Genetic predisposition as an underlying cause of familial aggregation

The dominant cause of familial aggregation of prostate cancer is genetically inherited susceptibility.[42–44] Genetic variants conferring autosomal dominant susceptibility to PCa, as well as genetic risk scores based on analysis of hundreds of single nucleotide polymorphisms (SNPs), are described in Chapter 5.

Other

Baldness

Baldness has been associated with PCa risk, as there are common underlying risk factors, such as age and hormones. Meta-analyses published so far found no association between baldness and PCa risk;[57–59] however, He *et al.* found an increased risk for PCa when vertex pattern is presented (RR, 1.24; 95% CI, 1.05–1.46).[57] Moreover, Papa *et al.* evaluated the association between aggressive PCa and early-onset baldness and demonstrated an increased risk for advanced PCa with androgenetic alopecia at age 20 years (OR, 1.51; 95% CI, 1.07–2.12).[60]

Height

Height has been suggested as a factor related to PCa risk through different mechanisms, such as nutritional status, androgen, and insulin-like growth factor-1. In one study, taller height was associated with a 22% increased risk for high-grade PCa (OR, 1.22; 95% CI, 1.01–1.48).[61]

Modifiable

Diet

Dietary factors have been studied for possible associations with PCa risk. Studies have demonstrated an inverse association between high intake of fruits, vegetables, and nuts, and low-intake of meat and risk for PCa.[62,63] Carotenoids, for instance, have some proposed mechanisms that could reduce PCa development, such as an antitumour activity by inhibition of androgen receptor, suppression of telomerase activity, anti-inflammatory and antioxidant effect, and inhibition of angiogenesis, among others. The current literature, comprising experimental and epidemiological studies, remains inconclusive on the protective role of carotenoids and PCa incidence.[64] Furthermore, a network meta-analysis that investigated the effect of 10 antioxidants including vitamins, folic acid, selenium, beta-carotene, and green tea catechins demonstrated that the latter significantly reduced the risk for PCa, followed by vitamin D, vitamin B6, and folic acid.[65] Also, fibres are considered to have anti-inflammatory properties through an antioxidant activity, but no association has been found between fibre intake and PCa risk.[66] On the other hand, a proinflammatory diet, such as Western dietary pattern rich in processed food and sugar, has underlying mechanisms that potentially play a role in cancer development, and a recent meta-analysis found that a proinflammatory diet increases risk for PCa,[67] corroborating the findings of a previous study.[68] Liu *et al.* evaluated a postdiagnosis plant-based dietary patterns of 2,062 men and found a significant association between higher plant-based diet index and reduced risk for PCa progression in patients with Gleason >6.[69] Moreover, there is evidence that high intake of protein would be involved with PCa development, particularly dairy protein.[70] Dose-response studies associated a higher risk for PCa with high intakes of dairy products.[71,72] Red and processed meat have harmful compounds produced in high-temperature or prolonged cooking that have been reported to be carcinogenic. While two meta-analyses did not find an association between red or processed meat and an increased incidence of PCa,[73,74] Nouri-Majd *et al.* analyzed only prospective studies, comprising 25 studies and 1,900,910 individuals and found that high-processed meat consumption was marginally associated with an increased risk of developing PCa (RR, 1.06; 95% CI, 1.01–1.10) and advanced PCa (RR, 1.17; 95% CI, 1.09–1.26), but the association between red meat and PCa risk was not significant (RR, 1.05; 95% CI, 0.98–1.12).[75]

Physical activity

Physical activity is associated with a risk reduction for certain cancer types, although there is no strong evidence with regards to PCa. In a phase 2 trial, high-intensity interval training (HIIT) was evaluated among men undergoing active surveillance for prostate cancer. The findings indicated that HIIT significantly enhances cardiorespiratory fitness and may inhibit the biochemical progression of prostate cancer.[76] Benke *et al.* demonstrated a significant reduction in PCa risk with long-term physical activity, but it was nonsignificant in a leave-one out analysis.[77] In addition, physical activity after PCa diagnosis was related to a 31% reduction

in PCa mortality.[77] Despite the absence of data demonstrating a clear association, physical activity should be encouraged for its positive effect on general health, through different postulated mechanisms, such as modulation of immune responses, reduction of oxidant stress, and reduction of overweight and obesity.[78] Current physical activity guidelines recommend at least three sessions of exercise per week of aerobic and resistance exercises but highlight the need for a better understanding regarding associations with PCa risk.[79]

Alcohol

Alcohol is a carcinogen that has been associated with several cancers, including esophagus, larynx, breast, stomach, and liver, with a dose-response effect.[80] With regards to PCa, the evidence is inconclusive. Although several studies found no association between alcohol consumption and PCa risk,[81,82] a meta-analysis found a significant dose-response relationship, even with low-volume consumption (OR, 1.08; 95% CI, 1.04–1.12), but stronger with higher volumes.[83] A recent published meta-analysis by D'Ecclesiis *et al.* focusing on evaluating the effects of alcohol consumption on PCa mortality revealed no association overall (summary risk estimate [SRE], 0.97; 95% CI, 0.92–1.03).[84] However, when one of the studies that was responsible for the heterogeneity of the results was excluded from the pooled analysis, a direct association was found between alcohol intake and fatal PCa (SRE, 1.33; 95% CI, 1.12–1.58).[84] Regardless of contrasting results, the evidence suggests a direct link between alcohol intake and the development of PCa.[84]

Smoking

Burning cigarettes have at least 70 carcinogens and smoking is a known risk factor for a variety of cancers, including genitourinary cancers such as kidney and bladder cancers. However, its association with PCa is still controversial, with a previous meta-analysis demonstrating an increased risk for PCa among former smokers (RR, 1.09; 95% CI, 1.02–1.16), but not among current smokers (OR, 1.04; 95% CI, 0.87–1.24).[86] On the other hand, Islami *et al.* pooled data from 51 articles and Jochems *et al.* pooled data from 5 Swedish cohorts and both observed an inverse association between smoking and incident PCa, despite current smoking being associated with an increased risk for PCa death.[87,88] Moreover, two recent meta-analyses had the same findings, suggesting an inverse association with PCa incidence[89,90] and a higher risk for PCa death (RR, 1.42; 95% CI, 1.20–1.68),[89] and both associated the results to a poor adherence to PCa screening among smokers.

Medications and vitamins (5-ARIs, statins, vitamin D, vitamin E)

5-ARIs

5-alpha-reductase inhibitors (5-ARIs) are medications that inhibit the conversion of testosterone to dihydrotestosterone (DHT) and are commonly used in benign prostatic hyperplasia and suggested as potential chemopreventive agents for PCa. A meta-analysis comprising 23 studies found a decreased risk for overall PCa in 5-ARI users (RR, 0.77; 95% CI, 0.67–0.88) but an increased risk for high-grade PCa (RR, 1.19; 95% CI, 1.01–1.40).[91] Knijnik *et al.* confirmed in another meta-analysis the finding of a reduction of 26% in PCa diagnosis (RR, 0.74; 95% CI, 0.59–0.97) but did not demonstrate an increase in high-grade PCa.[92] None of the meta-analyses found an association with PCa mortality. None of the 5-ARIs are approved as chemoprevention.

Statins

Statins are lipid-regulating agents that decrease total cholesterol, low-density lipoprotein, and triglycerides. Studies have associated high cholesterol with an increase incidence of high-risk PCa and, since cholesterol is the precursor of androgen, this may be mediated by androgen signalling pathways,[93] but the effect of statin usage on the overall risk for PCa is yet unclear. A meta-analysis from Bonovas *et al.* could not demonstrate a suggested protective association with PCa (RR, 1.06; 95% CI, 0.93–1.20).[94] In contrast, two other meta-analyses observed a lower risk for PCa overall (RR, 0.93; 95% CI, 0.87–0.99) and advanced PCa (RR, 0.86; 95% CI, 0.73–0.91).[95,96] The most recent pooled analysis of 41 studies did not associate statin usage with PCa incidence (RR, 0.87; 95% CI, 0.82–1.08). However, when higher doses and longer time of use were considered, statins were associated with lower risk for PCa.[93]

Vitamin D

Vitamin D deficiency has been suggested to be associated with an increased risk for cancer and supplementation of vitamin D has been associated with a decrease in PCa risk in experimental models.[97] Furthermore, both deficiency and insufficiency have been associated with adverse pathology following radical prostatectomy.[98,99]

Vitamin E

Vitamin E is a fat-soluble micronutrient with antioxidant effects that was identified as a potential chemopreventive agent. To date, the data supporting its role in PCa is conflicting. A meta-analysis demonstrated no association between vitamin E intake and PCa incidence or mortality, even after sensitivity analysis considering only randomized controlled trials, performed due to the high heterogeneity among the studies.[100] However, Alkhenizan and Hafez associated vitamin E supplementation with reduction in incidence of PCa in a pooled analysis (RR, 0.85; 95% CI, 0.73–0.96), but not with cancer incidence and mortality of other cancers (RR, 0.99; 95% CI, 0.96–1.03).[101] The most recent meta-analysis on this subject evaluated the effect of dietary and supplemental vitamin E intake on PCa and found nonsignificant results, except for a reduction in PCa risk in studies in Europe in a subgroup analysis.[102]

Other (sexual activity, circumcision, infections, inflammation)

Sexual activity

Sexual behaviour is a potential modifiable risk factor for PCa and studies focused on frequency of sexual activity supported that more frequent ejaculation (more than 20 per month) could prevent PCa, which would be related to a decrease in carcinogenic secretions in prostatic tissue.[103] In addition, Papa *et al.* found an inverse association between PCa risk and ejaculatory frequency only in the fourth decade of life (RR, 0.83; 95% CI, 0.72–0.96).[104] However, a systematic review showed there is limited evidence that associates sexual activity with PCa risk. The evidence against an association between PCa development and vasectomy is now strong.[78]

Circumcision

Circumcision has well-established benefits, including decreased risk of penile cancer and cervical cancer in sexual partners, and risk reduction for sexually transmitted disease.[105] A meta-analysis by Morris *et al.* showed a lower PCa risk in men who underwent circumcision (OR, 0.87; 95% CI, 0.76–1.00).[106]

Infections

Human papillomavirus (HPV) is associated with several types of cancers, but its involvement in the development of PCa is uncertain. The most recent meta-analysis pooled data from 27 case-controlled studies and demonstrated higher rates of HPV infection on PCa tissue and a higher risk for PCa by HPV infection when PCa tissue was compared with normal prostate tissue (OR, 3.07; 95% CI, 1.80–5.21) or when benign prostate hyperplasia tissue was used as control (OR, 1.94; 95% CI, 1.43–2.63).[107] Moghoofei *et al.* also found a pathogenetic link between HPV infection and increased risk for PCa, more frequently associated with HPV type 16 (OR, 1.60; 95% CI, 1.23–2.08).[108]

Inflammation

The link between inflammation of the prostate and PCa is not yet clear, with some studies showing an increased risk for PCa in men with a history of prostatitis.[109,110] However, Langston *et al.* concluded that these findings might be related to detection bias due to increased PCa screening in men with prostatitis.[111]

Conclusion

Prostate cancer ranks as the most common cancer in men in 118 of 185 countries worldwide, with over 1.4 million new cases reported in 2022 and an anticipated prevalence exceeding 5 million within the next 5 years. Incidence rates vary significantly across continents, with the highest rates observed in Northern America, the Caribbean, and Oceania, and the lowest in Asia. PCa stands as the fifth leading cause of cancer-related deaths among men globally, with substantial regional differences, notably higher mortality rates in Africa, Latin America, and the Caribbean. The geographic variability in PCa incidence can be attributed to a combination of genetic predisposition, screening practices, healthcare accessibility, and lifestyle factors. Socioeconomic status plays a role, with lower socioeconomic groups exhibiting underestimated rates of PCa. Notably, Black men in the United States face a 2-fold risk for prostate cancer diagnosis and death compared to other racial groups.[112] Established nonmodifiable risk factors include familial history, age, and race, while modifiable factors comprise diet, physical activity, alcohol consumption, and smoking habits. Certain medications such as 5-alpha-reductase inhibitors demonstrate potential in reducing PCa risk, while others, such as statins and dietary supplements might play a role. Furthermore, lifestyle factors, including physical and sexual activity, which have been studied for their influence on PCa risk, have yielded varied results. Ongoing research endeavours are imperative for a more comprehensive understanding of PCa risk factors and the development of effective preventive strategies on a global scale.

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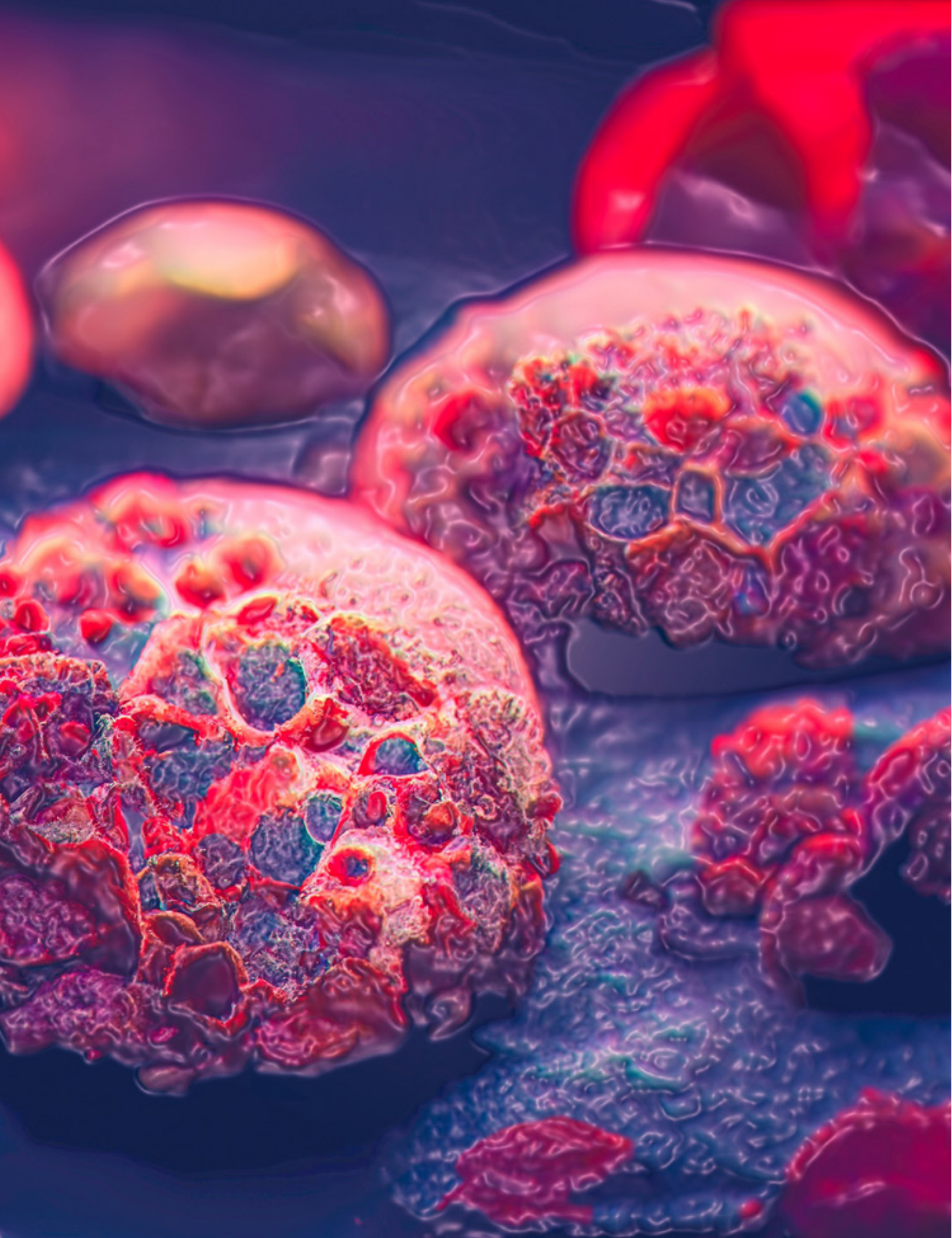

COMMITTEE 2

Localized Prostate Cancer: Pathological Factors That Influence Outcome and Management

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Table of Contents

Introduction

Pathological factors are among the major determinants that guide clinical decisions for localized prostate cancer.[1–3] Traditional factors in needle biopsy such as grade, number of positive cores, and tumour extent (percentage) have long been used for risk stratifications and preoperative prognostic tools or nomograms.[4–6] These variables are also monitored in patients during active surveillance (AS) for potential reclassification.[1,7,8] After radical prostatectomy (RP), adverse factors such as positive surgical margin (PSM), extraprostatic extension (EPE), seminal vesical invasion (SVI), or lymph node involvement (LNI) are used in postoperative prognostic tools for further management decision.[5,6,9,10] Because of the importance of pathological factors, standardized cancer reporting checklists such as the International Collaboration on Cancer Reporting (ICCR) datasets (http://www.iccr-cancer.org) and the College of American Pathologists (CAP) cancer protocols (http://www.cap.org) are being recommended or required for use by pathologists for consistency in reporting.[11–16]

In recent years, there has been an upsurge in studies looking at the usefulness of nuanced histological factors in prostate cancer to enhance prognostication. Refinements are made in deriving and recording of pathological factors including in magnetic resonance imaging (MRI)-targeted needle biopsy. New recommendations were made on prostate cancer grading and its derivatives in the 2014 and 2019 International Society of Urological Pathology (ISUP) consensus conferences and the 2019 Genitourinary Pathology Society (GUPS) white paper.[17–20] Many of these recommendations were codified in the 2022 World Health Organization (WHO) classification.[21] Some of the newer factors have made their way into the latest clinical guidelines, especially for lower-risk prostate cancer patients' categories. For example, the recent DETECTIVE study for localized prostate cancer added tumour length in mm, intraductal carcinoma (IDC), and cribriform pattern for use in the patient's eligibility criteria.[22] Herein, we summarize the significant updates and latest important studies on pathological factors in prostate needle biopsy and RP. **Our aim is to provide information on established, novel, and emerging pathological factors that can advise future guidelines on localized prostate cancer.**

Acinar Adenocarcinoma

The vast majority (≥ 95%) of prostate cancers are acinar adenocarcinoma.[21] Most of these tumours are detected as low-grade localized tumours in asymptomatic older adult men due to elevated serum prostate-specific antigen (PSA) levels. Over the past two decades, baseline biopsies for the diagnosis of adenocarcinoma have evolved from sextant to extended 12-site systematic sampling, and recently with the addition of MRI-targeted biopsy that has implications in detection and reporting of pathological factors.[23] Many tumours are also incidentally encountered in autopsies, transurethral resections (TURs) for benign prostatic hyperplasia (BPH), or in cystoprostatectomies for bladder cancers indicative of its largely indolent behaviour.[24–26] Between 56% to 87% of prostate cancers are multifocal, with many being clinically insignificant tumours.[27,28] Gene fusion of androgen-driven ETS transcription factors, such as *TMPRSS2*:*ERG*, is the most common molecular alteration, detected in about 50%

of prostate cancer.[29] *Speckle-type POZ protein* (*SPOP*) is another commonly mutated gene seen in 6% to 15% of localized and metastatic prostate cancers.[30]

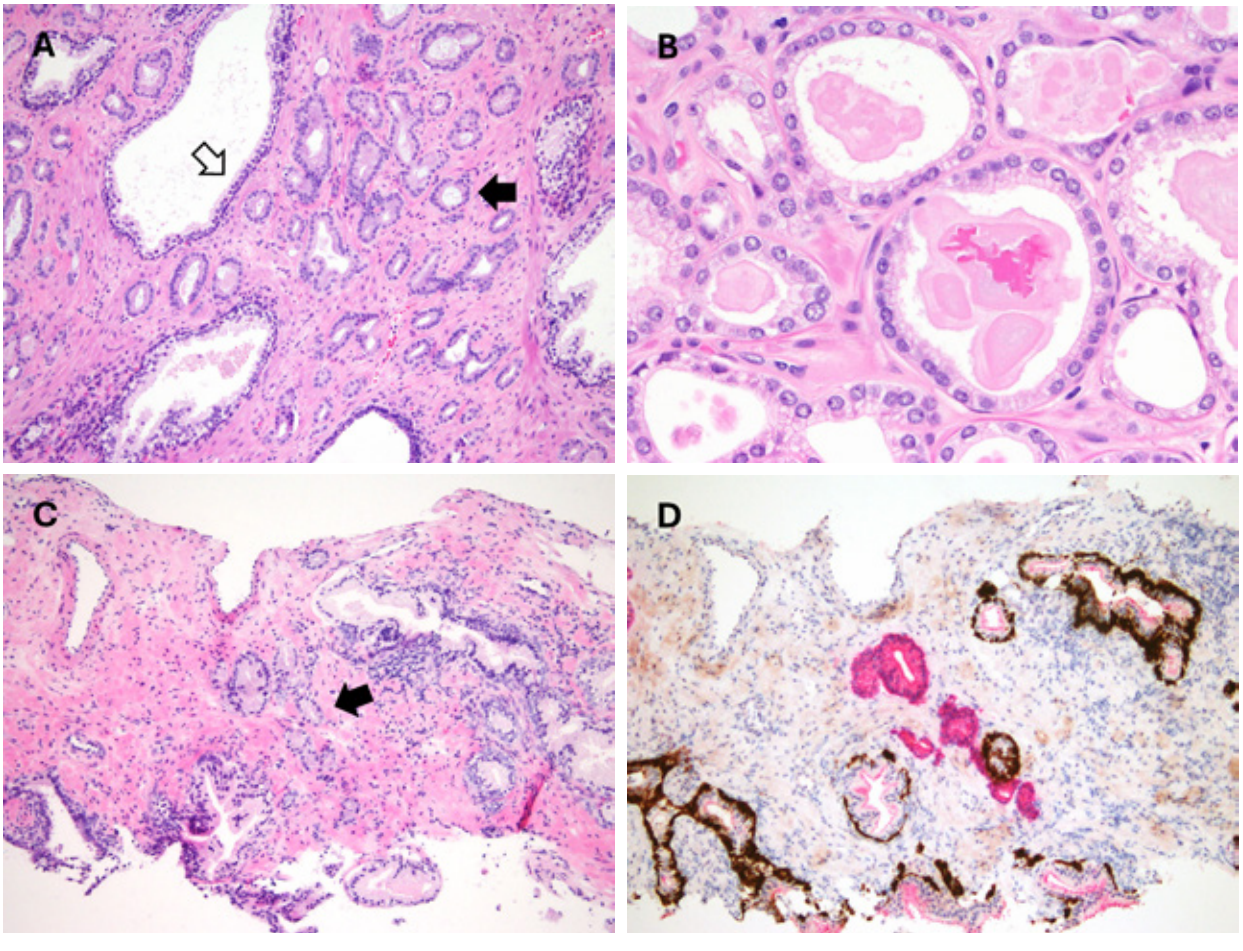
Acinar adenocarcinoma exhibits a range of histologic patterns that correlate with its degree of differentiation.[21,31] **This unique spectrum of histologic patterns in prostate cancer forms the basis for the Gleason grading system**.[32,33] The most differentiated pattern is a discrete well-formed gland that architecturally resembles benign prostatic glands. Deviations in architecture and luminal contents such as the presence of amorphous secretions, mucin, or crystalloids are helpful on screening magnification. On closer inspection, the presence of nuclear enlargement and nucleolomegaly with single or multiple nucleoli help facilitate the diagnosis. Cancer glands fundamentally lack basal cells and challenging lesions can be confirmed as cancer by their lack of immunohistochemical staining for basal cell markers such as high molecular weight keratins (HMWKs) and p63 (**FIGURE 1**).[34] Cancer glands also overexpress alpha-methylacyl-coenzyme A racemase (AMACR) and it is now routine for pathologists to use a dual chromogen immunohistochemical stain cocktail that combines AMACR and basal cell markers to distinguish carcinoma from benign glands in challenging cases.[34] **The well-formed carcinoma gland represents the contemporary Gleason pattern (GP) 3. Tumours that are purely GP 3 are overwhelmingly organ confined with limited capacity for EPE, and if resected, have virtually no risk for metastasis**.[35–39]

The patterns of acinar adenocarcinoma become complex or less organized as they lose differentiation and correspond to GP 4 and GP 5. The presence and increasing proportion of higher-grade patterns increase the risk for local aggressiveness and metastasis. Acinar adenocarcinoma expresses PSA and prostatic-specific acid phosphatase (PSAP) and these immunohistochemical stains may be used as ancillary markers to distinguish prostate adenocarcinoma from other organ carcinomas, especially at metastatic sites. Expression of the new marker NKX3.1 is better preserved in poorly differentiated prostate cancer and this marker is now commonly used in routine practice.[40–42] Inactivation of *phosphatase and tensin homolog on chromosome 10 (PTEN)* correlates with higher-grade patterns and loss of PTEN expression correlates with increased risk for locally advanced disease.[43] A subset of acinar carcinomas may become highly aggressive, usually after hormonal treatment, with transformation into lethal castration-resistant prostate cancer (CRPC) or carcinomas with neuroendocrine features.[44,45] About 50% of CRPCs show loss of PTEN expression compared to about 20% of primary prostate cancers.[46] Up to 20% of metastatic acinar adenocarcinomas harbour germline or somatic alteration in DNA repair genes such as *BRCA1*, *BRCA2, ATM, PALB2,* or *CHEK2* that can also be detected with higher frequencies in familial or hereditary tumours.[47,48]

A minority of acinar adenocarcinomas have unusual histologic features, some of which are recognized as formal subtypes of acinar adenocarcinoma in the WHO classification (discussed below) and others are considered just morphological patterns of conventional acinar adenocarcinoma.[21] These uncommon histologies are often accompanied by acinar adenocarcinoma and can be diagnostically deceptive by mimicking benign processes in the prostate. **The unusual adenocarcinoma patterns are diagnosed mostly as low-grade localized**

tumours, whereas adenocarcinoma subtypes such as signet-ring cell-like, sarcomatoid, and pleomorphic giant cell are aggressive and often present as locally advanced or metastatic tumours (**TABLE 1**). Cancer registries in the United States recorded 0.38% to 3.3% of prostate cancers as unusual histologies or subtypes of acinar adenocarcinoma.[49,50]

FIGURE 1 (A) Carcinoma glands (dark arrow) are smaller and have no basal cells in contrast to benign glands (open arrow). (B) Carcinoma glands with typical luminal contents. (C and D) A focus of carcinoma (arrow) in biopsy overexpressing AMACR (red) and lacking basal cell marker expression (brown).



Abbreviation: AMACR, alpha-methylacyl-coenzyme A racemase.

TABLE 1 2022 World Health Organization Classification of Carcinomas of the Prostate Gland

Carcinoma types	Increases risk*	Likelihood of extent at diagnosis
Adenocarcinoma of the prostate		
Acinar (usual) adenocarcinoma	No	Localized > non-localized
Acinar adenocarcinoma subtypes		
Signet-ring cell-like acinar adenocarcinoma	Yes	Non-localized > localized
Pleomorphic giant cell acinar adenocarcinoma	Yes	Non-localized > localized
Sarcomatoid acinar adenocarcinoma	Yes	Non-localized > localized
Prostatic intraepithelial neoplasia-like carcinoma	No	Localized > non-localized (EPE in 46.1%)
Unusual histologic patterns of acinar adenocarcinoma		
Atrophic pattern adenocarcinoma	No	Localized > non-localized
Adenocarcinoma with aberrant p63 positivity	No	Localized > non-localized
Pseudohyperplastic adenocarcinoma	No	Localized > non-localized
Microcystic adenocarcinoma	No	Localized > non-localized
Foamy gland adenocarcinoma	No	Localized > non-localized (≥pT3 in 46%)
Mucinous adenocarcinoma	No	Localized > non-localized
Intraductal carcinoma†	Yes	Non-localized > localized
Ductal adenocarcinoma	Yes	Non-localized > localized
Adenocarcinoma with neuroendocrine differentiation	Yes	Non-localized > localized
Squamous carcinoma of the prostate		
Adenosquamous carcinoma	Yes	Non-localized > localized
Squamous cell carcinoma	Yes	Non-localized > localized
Adenoid cystic (basal cell) carcinoma	Yes	Non-localized > localized

*Risk for adverse pathology at RP, metastasis, and poorer outcome.
†Includes the vast majority of intraductal carcinoma with concomitant invasive adenocarcinoma.
Abbreviation: EPE, extraprostatic extension; RP, radical prostatectomy.

Modified Gleason Grading

Grade group

The Gleason grading system has been applied for prostate cancer prognostication for more than half a century.[32,33,51] **While the original Gleason grading approach of combining two grades or GPs to derive a score (GS) has remained, the current application of Gleason grading has evolved. The differences are in grading rules, pattern compositions, and most importantly, their prognostic associations.** Changes made over time were codified at the 2004, 2014, and 2019 ISUP consensus conferences and in the 2019 GUPS white paper.[17–20,52] The 2014 ISUP consensus recommendations were mainly left unchanged by the 2019

ISUP consensus and the 2019 GUPS white paper. The 2019 changes updated the GP definitions and grading rules and introduced reporting of quantitative grades and tumour growths (**TABLES 2** and **3**). **Although there are a few discrepancies, the 2019 ISUP consensus and 2019 GUPS white paper recommendations on the grading of prostate cancer are largely in agreement.**[53,54]

TABLE 2 2019 ISUP Consensus Recommendations on Grading of Prostate Carcinoma[17]

Grade quantification
1. Percent GP 4 should be reported in biopsy for score 3+4=7.
2. Percent GP 4 should be reported in biopsy for score 4+3=7.
3. For RP, any amount of GP 5 ≥ 5% should be included in the GS as the secondary pattern.
4. For RP, any amount of GP 4 ≥ 5% should be included in the GS as the secondary pattern.
5. For RP, any amount of GP 5 < 5% should be reported as "minor pattern," but not included in the score.
6. For RP, any amount of GP 4 < 5% should be reported as "minor pattern," but not included in the score.
7. For RP, consensus against any amount of GP 5 < 5% should be included in the score as the secondary pattern.
IDC and tumour growth pattern
1. Pure IDC should not be graded.
2. In cases with invasive carcinoma, IDC should be incorporated into the GS.
3. If IDC is incorporated into the GS, then its presence and significance should be commented on.
4. Cribriform GP 4 has worse prognosis than poorly formed or fused pattern 4.
5. Presence of invasive cribriform cancer should be commented on in GS 7 cases.
6. Presence of invasive cribriform cancer should be commented on in GS 8 cases.
Grade heterogeneity
1. In grading RP specimens with multifocal tumours, GSs of (a) largest, (b) highest-stage, and (c) highest-grade tumour should be reported separately if the above are not identical.
2. In RP specimens, irrespective of multifocality, a global GS should be sufficient for further patient management.
3. In systematic prostate biopsies, a GS should be assigned to each individual biopsy site.
4. In grading of targeted prostate biopsies, consensus against a separate GS assigned for each core.
5. In MRI-targeted biopsy samples, a global GS for each suspicious MRI lesion should be assigned.
6. Benign histologic findings in targeted biopsies of high-suspicion lesions (PI-RADS 4–5) that are negative for cancer should be reported.

Abbreviations: GP, Gleason pattern; GS, Gleason score; GUPS, Genitourinary Pathology Society; IDC, intraductal carcinoma; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging–Reporting and Data System; RP, radical prostatectomy.

A major departure from the traditional Gleason grading is the introduction of the Grade group (GG), also referred to as WHO/ISUP grade, ISUP grade, or ISUP GG.[19] GG is a compression of GSs into 5 clinically meaningful prognostic groups, namely GG 1 to GG 5. The GG is a culmination of series of events that led to continued grading refinements and evolving clinical practices, especially with the rapid expansion of the AS program for lower-risk prostate cancer patients. **First, there is a gradual disappearance of the questionable GP 1 and GP 2 in routine pathology practice.** Most experts now recognize that the originally described GP 1 and GP 2 in the pre-immunohistochemistry era were benign adenosis (atypical adenomatous

hyperplasia).[55] Reducing the diagnosis of low GPs was initiated at the 2005 ISUP consensus by the statements that "with extremely rare exception" diagnosis of GS 2 cancer should not be made in any specimen and that diagnosis of GS 3 or 4 cancer should be "rarely made, if ever" in biopsy.[52] Almost two decades later, there is practically a total abandonment of the interpretation of GP 1 and GP 2 in routine practice. The latest WHO blue book commented that GP 1 and GP 2 should no longer be diagnosed in biopsy and diagnosis should only be made very rarely in RP and TUR of prostate (TURP).[21] **More importantly, GS 6 already has a baseline favourable outcome and further stratifying the lowest grade tumours with lower scores (GS 2 to 5) provides no additional clinical meaning.**

Second, over the years there has been a gradual narrowing of GP 3 with a shift of adverse architectural patterns toward GP 4 (FIGURE 2). Most cribriform glands were upgraded to GP 4 at the 2005 ISUP consensus and eventually, all (including small) cribriform glands were upgraded to GP 4 at the 2014 ISUP consensus.[19,52] Furthermore, the glomeruloid gland, regardless of morphology, was unanimously agreed to be assigned as GP 4 at the 2014 ISUP consensus. The grade migration resulted in the contemporary GS 6 cancers being vastly localized tumours and if resected, they have minimal to no incidence of metastasis or death.[35–39] Eggener *et al*.[56] looking at 15-year prostate cancer-specific mortality (CSM), identified only 3 of > 9,500 organ-confined GS 6 prostate cancer patients to die of the disease. **Third, contemporary GS 7 cancers are much more heterogeneous with a differing behaviour between GS 3+4 and GS 4+3 cancers.**[57–59] There also has been an inflation of GS 7 because of grade migration, additionally enhanced in RP as many GS 6 patients stayed on AS, further supporting the division of large GS 7 group into two prognostic categories.[60] **Fourth, studies identified the optimal groupings of the different GSs to include splitting of GS 7 and lumping of GS 9 and 10**. Pierorazio *et al*.[61] showed PSA biochemical recurrence (BCR)-free survival (BCRFS) rates in GS 6, GS 3+4, GS 4+3, GS 8, and GS 9-10 cancers of 94.6%, 82.7%, 65.1%, 63.1%, and 34.5%, respectively, and this study became the basis for the GGs.

The new 5-tiered prognostic group consists of GGs 1 (GS 6), 2 (GS 3+4), 3 (GS 4+3), 4 (GS 8), and 5 (GS 9–10) was endorsed by the 2014 ISUP consensus conference. **Although it appears that GGs are conversions of GSs, GGs can be derived directly with each group having a specific definition (TABLE 4)**.[19] **The main advantage of GG reclassification is that GG 1 is now the baseline lowest grade in the spectrum instead of GS 6, which may facilitate AS counselling of patients who may falsely perceive their low-risk tumour as an intermediate risk because it's in the middle of a GS 2 to 10 scale.** Several studies have validated use of GG, including in patients treated with surgery and radiotherapy.[62–70] The GG was subsequently codified in the 2016 WHO classification,[71] which was carried over in the latest 2022 WHO classification,[21] and is currently used in clinical guidelines and pathology reporting protocols,[1–3,11–16] although with some differences in the terminologies used. **The current recommended practice is to routinely report the GG alongside the GS.** Although GG 4 appears to be heterogeneous with GSs 4+4, 3+5, and 5+3, data so far shows no difference in prognosis between these different GSs, supporting their grouping into a single prognostic group.[72,73]

TABLE 3 2019 GUPS Statements on Grading of Prostate Carcinoma[18]

Percent GP 4
1. Record percent GP 4 in needle biopsy specimens with GGs 2 and 3.
2. Preferred method of reporting percent GP 4: either ≤ 5% or ≤ 10% and 10% increments thereafter for GGs 2–3.
3. Report percent GP 4 in needle biopsies in other parts (jars) of lower grade in cases with at least one part showing GS 4+4=8 (GG 4).
Tertiary grade patterns
1. When a minor tertiary (3rd most common) GP 5 is found on biopsy or transurethral resection, it should be combined with the primary pattern to derive the overall GS.
2. Replace "tertiary grade pattern" in RP specimens with term "minor tertiary pattern 5."
3. Only use "minor tertiary pattern 5" in RP specimens with GGs 2 or 3 (GS 3+4=7 or 4+3=7).
4. Use 5% as the cutoff for what is allowed as minor tertiary pattern 5. If > 5% GP 5, then GP 5 is considered the secondary GP in the GS.
5. Minor tertiary pattern 5 is noted along with the GS, with the GG based on the GS.
Global versus highest GS and MRI-targeted biopsies
1. When multiple undesignated cores are taken from a single MRI-targeted lesion, an overall grade for that lesion is given as if all the involved cores were one long core.
2. If providing a global score, when different scores are found in the standard and the MRI-targeted biopsy, give a single global score (factoring both the systematic standard and the MRI-targeted positive cores).
Grade groups
1. "GGs" is recommended as the terminology for reporting in both needle biopsy and radical prostatectomy specimens.
2. Retain GS 3+5=8 as GG 4.
3. Retain GSs 4+5=9 along with GSs 5+4=9 and 5+5=10 in GG 5.
Cribriform glands
1. Report the presence or absence of cribriform glands in biopsy and RP specimens with GP 4 carcinoma.
Intraductal carcinoma
1. Report the presence of IDC in biopsy and RP specimens.
2. Use criteria based on dense cribriform glands and/or solid nests and/or marked pleomorphism/necrosis. Dense cribriform glands are defined as > 50% of the gland composed of epithelium relative to luminal spaces; where the ratio is approximately equal, it is prudent to be conservative and diagnose lesion as not meeting full criteria for IDC.
3. When IDC is identified on prostate biopsy without concomitant invasive adenocarcinoma, add a comment stating that IDC is usually associated with high-grade prostate cancer.
4. Perform IHC for basal cell markers when the biopsy shows GS 6 cancer and cribriform glands that include a differential diagnosis of IDC versus GP 4 cancer.
5. It is not necessary to perform basal cell IHC on needle biopsy and RP to identify IDC if the results of the stains would not change the overall highest GS/GG for the case.
6. Do not include IDC in determining the final GS on biopsy and/or RP.

Abbreviations: AS, active surveillance; GG, grade group; GP, Gleason pattern; GS, Gleason score; GUPS, Genitourinary Pathology Society; IDC, intraductal carcinoma of the prostate; IHC, immunohistochemistry; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; RP, radical prostatectomy.

TABLE 3 2019 GUPS Statements on Grading of Prostate Carcinoma[18] *(Cont'd)*

Molecular testing
1. Ki67 is not ready for use in clinical practice due to the high level of variability in scores among cohorts and difficulty in defining high-labelling index.
2. Additional studies of AS cohorts are needed to establish the utility of PTEN loss in this clinical setting.
3. Though clinical use has been high for many of the RNA-based assays, dedicated studies in AS are needed to substantiate the utility of these expensive tests in this setting.
Artificial intelligence and novel grading approaches
1. While there is active research and promise in this area, the findings are premature for recommendations of digital pathology/artificial intelligence in routine clinical application.
2. Novel grading approaches factoring in reactive stroma grade, percent GP 4, tertiary GP 5, and cribriform/intraductal carcinoma all have some advantages but are not ready for adoption in current practice.

Abbreviations: AS, active surveillance; GG, grade group; GP, Gleason pattern; GS, Gleason score; GUPS, Genitourinary Pathology Society; IDC, intraductal carcinoma of the prostate; IHC, immunohistochemistry; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; RP, radical prostatectomy.

FIGURE 2 Evolution of Gleason patterns. One major change is the upgrading of adverse patterns from Gleason pattern 3 to Gleason pattern 4 (red box). Original Gleason image[33] published with permission from Elsevier. ISUP 2005 Gleason image[52] and ISUP 2014 Gleason image[19] published with permission from Wolters Kluwer Health, Inc.

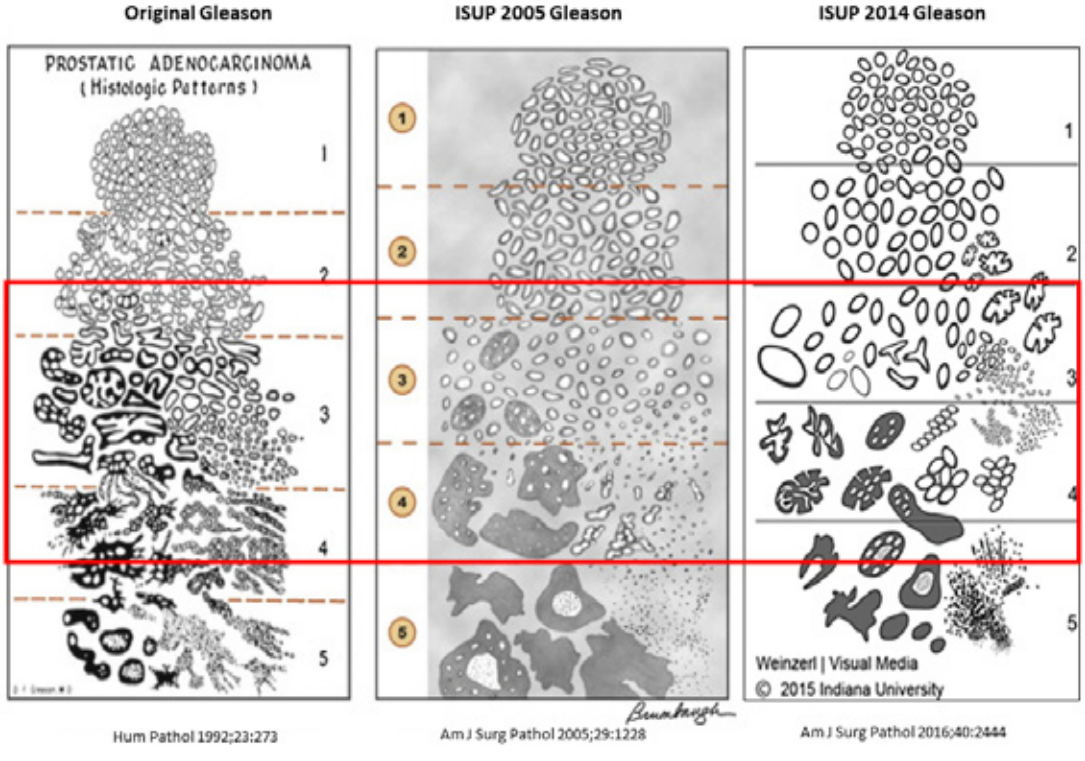


TABLE 4 Histologic Definition of Grade Group[19]

Grade group	Gleason score	Definition
1	6	Only individual, discrete, well-formed glands.
2	3+4=7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform/glomeruloid glands.
3	4+3=7	Predominantly poorly formed/fused/cribriform/glomeruloid glands with lesser component of well-formed glands.*
4	4+4=8, 3+5=8, 5+3=8	Only poorly formed/fused cribriform/glomeruloid glands, *or* Predominantly well-formed glands and lesser component lacking glands,† *or* Predominantly lacking glands with lesser component of well-formed glands.†
5	4+5=9, 5+4=9, 5+5=10	Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands.*

*For cases with > 95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of < 5% well-formed glands is not factored.
†Poorly formed/fused/cribriform glands can be more a minor component.

Morphology of contemporary Gleason patterns

Gleason pattern 3

The Gleason grading system is based almost purely on histologic architectures with the additional element of tumour necrosis for some of the GP 5 architectures.[17–19,21] Cytoplasmic or nuclear features, mitosis, or stromal reaction is not used in grading. The pattern composition of the current GPs is different from the original GPs, with the most significant change being in GP 3 (**TABLE 5**). **GP 3 is now composed of individual, discrete, well-formed glands.** Acceptable morphologic variations in GP 3 include small (microluminal or atrophic), large (pseudohyperplastic, microcystic, or prostatic intraepithelial neoplasia [PIN]-like), or falsely elaborate (tunneling or tangential section) glands (**FIGURE 3**). A branched well-formed gland is a recent addition at the 2014 ISUP consensus.[19]

Gleason pattern 4

The basic architectures of contemporary GP 4 include cribriform, glomeruloid, fused, and poorly formed glands (**FIGURE 4**).[17–19,21] A ductal pattern without necrosis is also considered GP 4. The most prevalent GP 4 in RP is cribriform (seen in 44% of cases), followed by poorly formed (40%), fused (38%), and glomeruloid (21%) glands in GS 7 cancers.[74] Among the GP 4 architectures, interobserver reproducibility is better with cribriform and glomeruloid glands compared with fused and poorly formed glands.[75] Some experts suggested that interobserver reproducibility for poorly formed glands can be improved by requiring a minimum number (> 5) of poorly formed glands seen in a cluster and not intermixed with well-formed glands.[76]

TABLE 5 Contemporary Architectures of Gleason Patterns 3, 4, and 5

Gleason pattern (or grade)	Gleason architectural patterns
3	Well-formed glands, branched well-formed glands.
4	Cribriform, glomeruloid, fused, poorly formed glands. Hypernephromatoid cancer no longer used.
5	Single cells, cords, solid sheet, small solid cylinders, solid medium-to-large nest with rosette-like spaces. Unequivocal comedonecrosis, even if focal.

FIGURE 3 Gleason pattern 3 with (A) round, (B) small (microacinar), (C) elongated, and (D) large or branching glands.

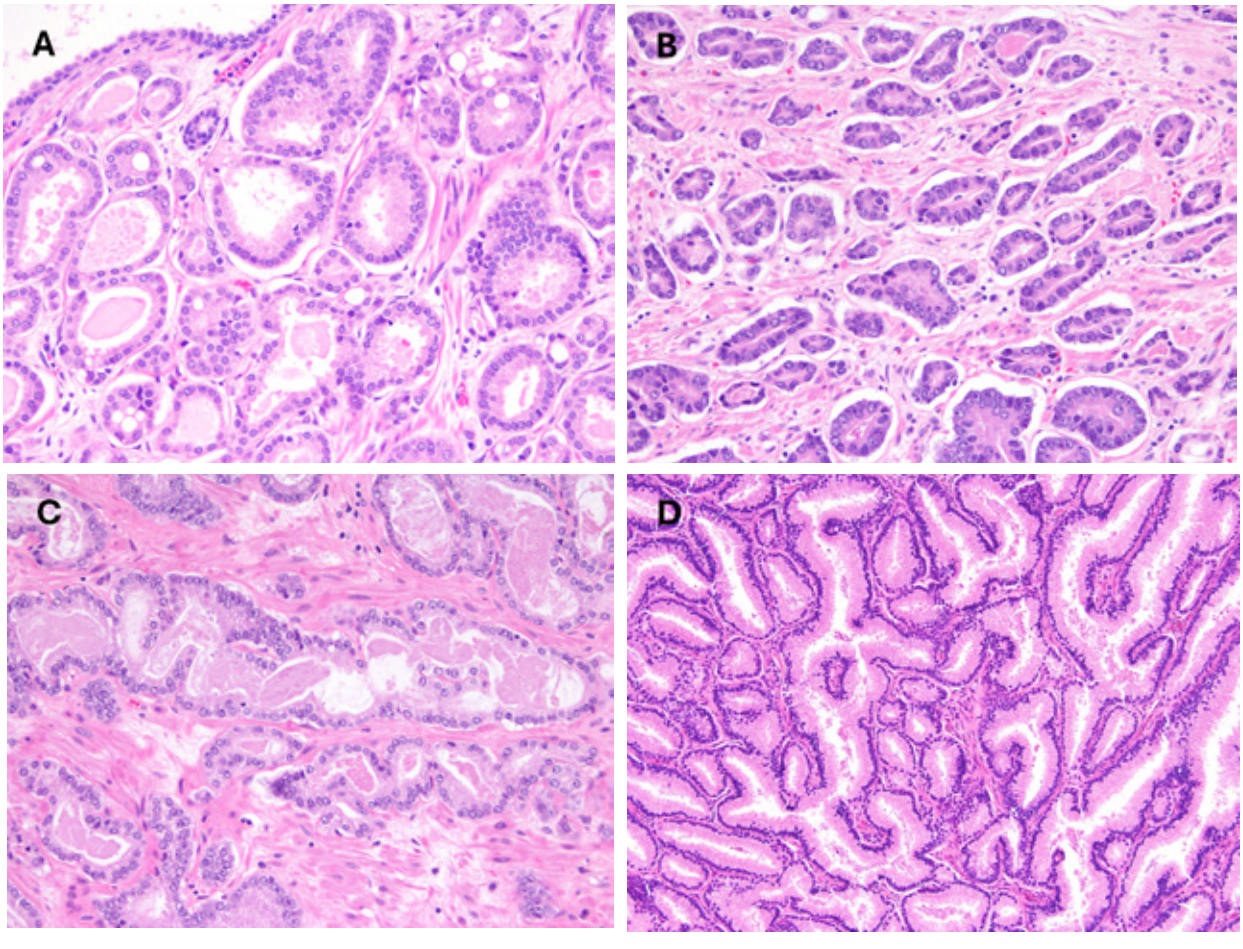
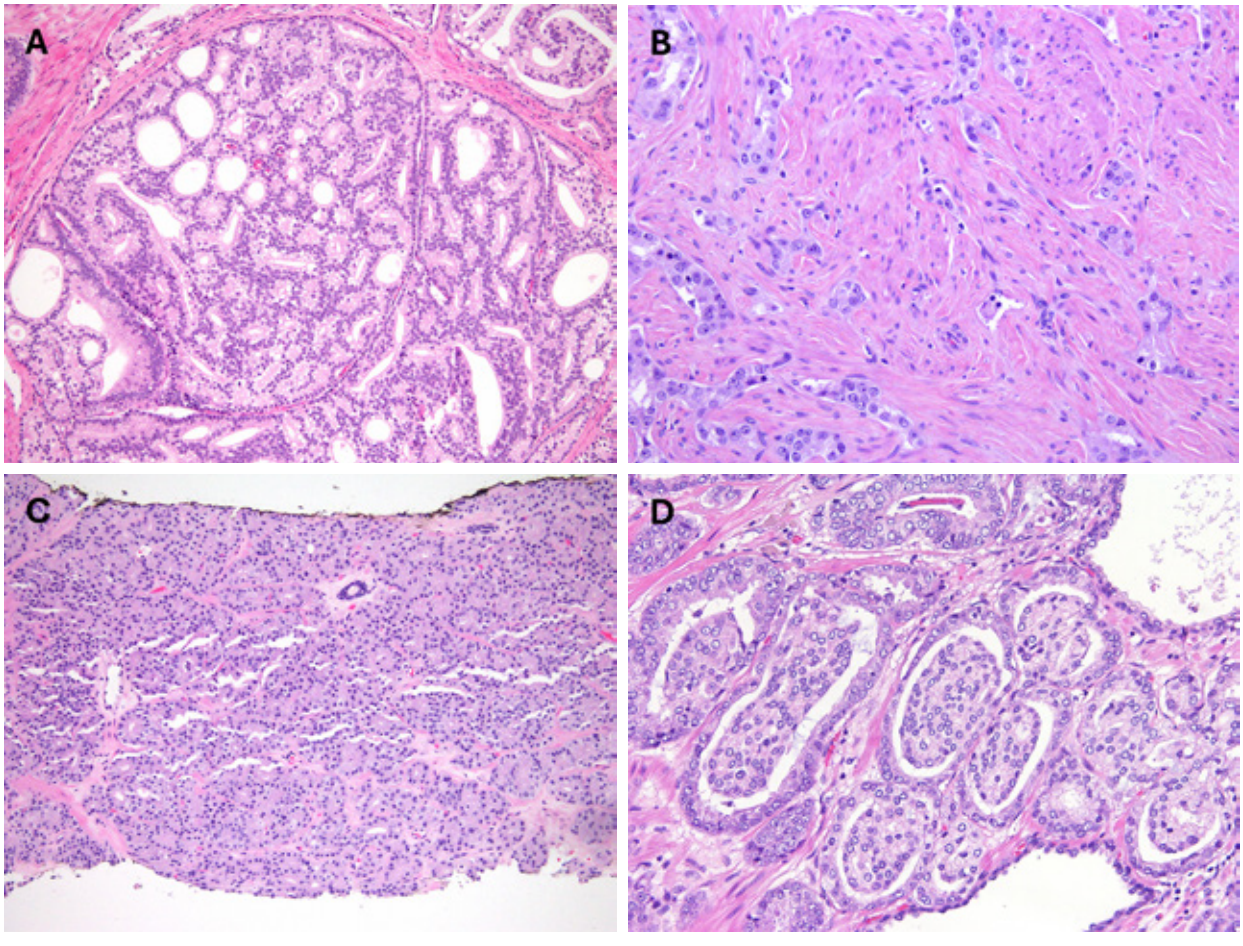


FIGURE 4 Gleason pattern 4 with (A) cribriform, (B) poorly formed, (C) fused, and (D) glomeruloid glands.



Among GP 4 architectures, cribriform pattern is associated with worse outcome and its presence or absence is now recommended to be reported in GS 7 and 8 prostate cancers (discussed below).[17,18,74,77–81] Because of the importance of consistency in diagnosis, there have been recent attempts to formally define cribriform pattern (**TABLE 6**).[82,83] ISUP drafted a definition of cribriform based on the opinions of expert genitourinary pathologists.[82] Concurrently, Shah *et al.*[83] conducted an interobserver reproducibility study among expert genitourinary pathologists and identified reproducible morphologic features for cribriform, and from these features, a definition was also proposed. There appears to be a strong correlation between the two definitions of cribriform glands. Using the ISUP criteria, an interobserver study among nine prostate pathology experts showed 90% consensus (2/3 agreement) reached in diagnosing cribriform carcinoma.[84] **Because of the association of cribriform to worse outcomes, some authors suggest designating cribriform as a separate prognostic group**.[81,85] The main differential diagnosis for cribriform is IDC, the latter distinguished by the presence of basal cell layers morphologically or immunohistochemically.

TABLE 6 Proposed Definitions for Cribriform Glands

Authors	Cribriform definition
van der Kwast *et al.* (ISUP)[82]	A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina easily visible at lower power (objective magnification 10X). There should be no intervening stroma or mucin separating individual or fused gland structures.
Shah *et al.*[83]	A dense sheet of tumour cells forming multiple lumens with transluminal bridging, imparting a "sieve-like" architecture, in which a majority of intraglandular cells are not in direct contact with stroma or mucin, and a clear luminal space along the periphery of gland accounts for < 50% of the glandular circumference.

Gleason pattern 5

GP 5 is the least differentiated pattern characterized by consolidation (solid sheet, small solid cylinders, solid medium-to-large nests with rosette-like spaces), dispersal (single cell, single file), or necrosis (comedonecrosis, cribriform with necrosis) of tumour cells (FIGURE 5).[17–19,21] The most prevalent GP 5 in biopsy are single cells and cords or single linear arrangement of individual cells, and the least prevalent are comedonecrosis, solid medium-to-large nests with rosette-like spaces and small solid cylinders.[86,87] The interobserver agreement among urologic pathologists for GP 5 in biopsy is fair, with highest reproducibility for comedonecrosis and least for solid nests.[88] Accuracy in interpretation in needle biopsy is enhanced if GP 5 is the primary (most prevalent) GP.[89]

FIGURE 5 Gleason pattern 5 with (A) single infiltrative cells, (B) cylinders, (C) solid, (D) solid with pseudorosettes, (E) comedonecrosis, and (F) cribriform glands with necrosis patterns.

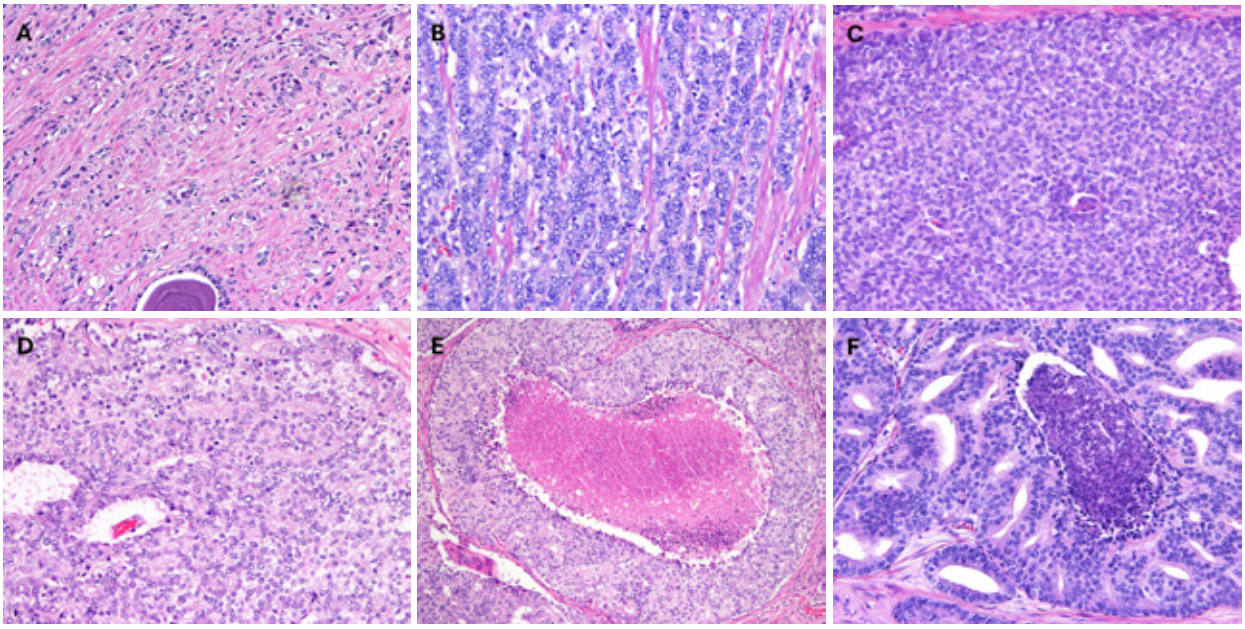
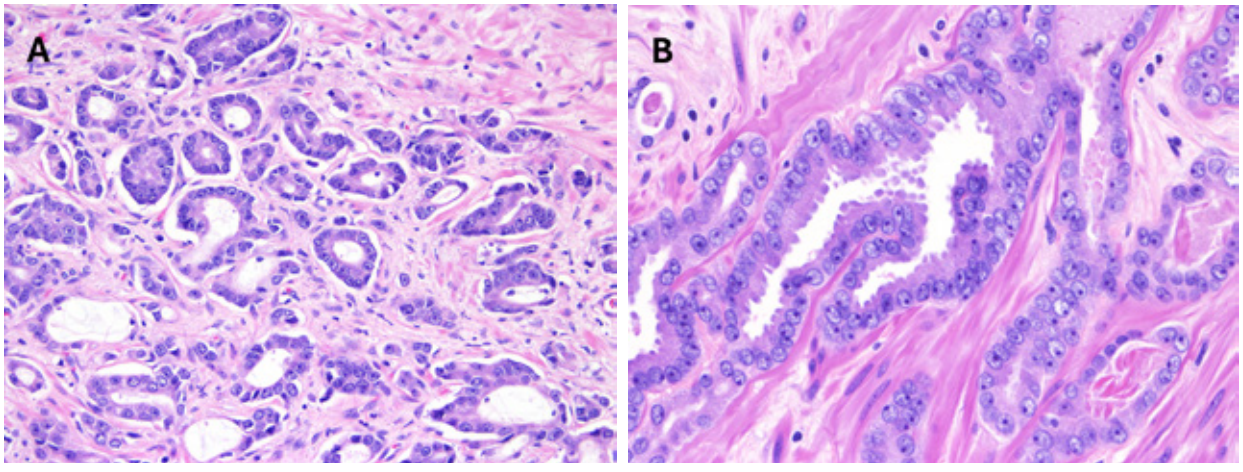


FIGURE 6 Carcinoma with (A) stromal desmoplasia (stromogenic cancer) and (B) pleomorphic nuclei.



Outside of the architectural patterns (GPs), there are studies suggesting that grading can be further improved by the addition of other histologic features such as reactive stroma (stromogenic cancer) and nuclear features (FIGURE 6), although this have not been routinely incorporated into reporting guidelines at this time.[85,90–94]

Current Gleason grading rules

Evolution of grading rules

The original concept devised by Dr. Donald F. Gleason in the 1960s of grouping several architectures into GPs and then combining GPs for a GS (sum of two addends referred to as *primary* GP and *secondary* GP) has remained.[32,33,51] However, additional modifications or exceptions to these rules were made in the past two decades.[17–19,52] **The series of modifications in grading through the years had shifted and enhanced the prognostic ability of the contemporary GS.** GS 6 now has a favourable outcome, GS 7 is expanded and heterogeneous, and GS 9–10 can be lumped and have the worst outcome. **Grading rules between needle biopsy and RP have variations as well. It is useful for clinicians to understand (at least) the basic rules of how GSs are derived since grade has a major impact on the management decision for localized prostate cancer** (**TABLE 7**).

In a recent study by van der Slot *et al.*,[95] interobserver agreement for GS was substantial (Krippendorff's α 0.626). However, discrepancies in challenging borderline patterns can go up to 41.4% even among expert genitourinary pathologists.[96] For example, when GP 4 is scattered among GP 3, there is a tendency to undergrade the tumour.[97] Communication regarding borderline cases between pathologists and clinicians is important.[98]

TABLE 7 Current Gleason Score Rules in Biopsy and RP Specimens

GP present	Biopsy	RP	Example scenarios
One	Double the GP as *primary* (first addend) and *secondary (*second addend) GPs.	Similar	100% GP 3 **GS 3+3=6**
Two	Primary GP is most prevalent. Secondary GP is less prevalent.	Similar	60% GP 3 40% GP 4 **GS 3+4=7**
	Exception: secondary GP not included in GS if of lower grade and minimal (≤ 5%).	Similar	95% GP 4 5% GP 3 **GS 4+4=8**
		Exception: secondary GP if of higher GP and minimal (≤ 5%) is not included in GS and is reported as *minor* GP (ISUP only)	95% GP 3 5% GP 4 Biopsy: **GS 3+4=7** RP: **GS 3+4=7 or GS 3+3=6, with minor GP 4** (ISUP only)
Three (GPs 3, 4 and 5)	Primary GP is most prevalent. Secondary GP is second most prevalent.	Similar	65% GP 4 25% GP 5 10% GP 3 **GS 4+5=9**
	Exception: If *tertiary* GP (least prevalent) is higher than secondary GP, it is included in GS as secondary GP.	Exception: If tertiary GP is higher than secondary GP and is > 5%, it is included in GS as secondary GP.	60% GP 4 30% GP 3 10% GP 5 Biopsy and RP: **GS 4+5=9**
		Exception: If tertiary GP is higher than secondary GP but is ≤ 5%, it is not included in GS and reported as *minor tertiary* GP.	60% GP 4 37% GP 3 3% GP 5 Biopsy: **GS 4+5=9** RP: **GS 4+3=7, with minor tertiary GP 5**

Abbreviations: GP, Gleason pattern; GS, Gleason score; ISUP, International Society of Urological Pathology.

Current Gleason grading rules in biopsy

Grading when one or two Gleason patterns are present

Grading is straightforward if there is only one or two GPs present in a biopsy (**TABLE 7**). **If there is one GP present, the GP will be doubled to obtain the GS. If two GPs are present, the more prevalent GP will be considered as the primary GP (first addend) and the less prevalent GP as the secondary GP (second addend). An exception to this rule in biopsy is when the secondary GP is minimal (≤ 5%) and of lower grade, then this secondary GP will not be included in the GS.** The minimal lower-grade secondary GP likely has no impact on prognosis and it's better to be discounted. On the other hand, if the

minimal pattern is of higher grade, it should be incorporated as the secondary grade. **Recent studies however suggest that GS 7 with minimal (≤ 5%) GP 4 in biopsy has similar pathologic parameters in RP and outcome compared to GS 6 tumours**.[99–102]

Grading when three Gleason patterns are present

Grading in biopsy becomes more intricate if all three contemporary GPs (3, 4, and 5) are present. **Similar rule for presence of two GPs is applied to three GPs with the exception that if the least prevalent GP (tertiary GP) is higher than the secondary GP, the tertiary GP will be considered the secondary GP**. Trpkov *et al.*[103] showed that GP 5 as tertiary GP in a biopsy case had outcome comparable with GP 5 as secondary pattern, but had better outcome compared to when GP 5 was the primary pattern. **In any given scenario (with one, two, or three GPs present) in biopsy or in RP, the most prevalent GP always remains as the primary GP and ONLY the secondary GP is adjusted**.

Indeterminate grade

There are occasionally tumour foci that are limited in amount (< 1 mm) in biopsy, for which rendering accurate grading is challenging. Two typical examples include: a) small foci with elements of GP 3 and 4 in which determining GS 3+4 versus GS 4+3 and a reproducible % GP4 is difficult; b) a tumour microfocus displaying only GP 4, which would be graded GS 8, in which other tumour-bearing cores from a similar region contain only GS 6. In both scenarios, grading the minute focus may inappropriately impact management, especially if that specimen part is the highest grade in a biopsy set. **In such cases, pathologists should either include a note to this effect along with the assigned grade OR consider assigning an "indeterminate grade" with an explanatory comment.**[11,13,17] Presence of indeterminate higher grade (GP 4 or GP 5) can be commented. Grading should also be avoided if the tumour is invading a nerve, as the process will complicate the gland architecture (e.g., pseudohyperplastic PNI).[104]

Current Gleason grading rules in radical prostatectomy

Grading when one or two Gleason patterns are present

The rule in RP is similar to that in biopsy if there are one or two GPs present (**TABLE 7**). An exception (only recommended by ISUP) is if secondary GP is higher but minimal (≤ 5%), it should not be incorporated in GS but will be reported with the GS as a "minor" GP.[17]

Grading when three Gleason patterns are present

In the presence of three GPs, the same rule in biopsy is applied in RP but with exceptions. If the third-most-common pattern (tertiary GP) is higher than the secondary GP, the tertiary GP will be used as the secondary GP like in biopsy, but only if the tertiary GP is > 5%. If there are three GPs present, the least predominant GP can technically range from 1% to 32%. Presence of GP 5 as the third-prevalent pattern is associated with adverse pathological features and worse outcome in GS 7 tumours, with some studies showing the significance at ≥ 5% cutoff.[105–110] Thus, to avoid omission of the high-grade GP, the tertiary GP 5 is incorporated as secondary GP in GS.

Minor tertiary pattern (≤ 5% cutoff)

Another exception in RP with three GPs present is if the higher tertiary GP is ≤ 5%, the tertiary GP is not included in the GS but will be reported with the GS as a "minor tertiary pattern." Even a small amount of GP 5 can increase the risk for BCR.[111] Presence of minimal (≤ 5%) GP 5 results to BCR rates intermediate between GS without a minor GP 5 and the next-higher GS, and is an independent predictor of BCR.[111–113] Integrating tertiary GP 5 into GGs has been suggested to improve the accuracy of patient outcome prediction after RP.[114]

Reporting of Grades

Reporting grade in biopsy

Reporting grade in systematic (multiple site) biopsy

At specimen level (or per-site) reporting, individual grade for every prostate cancer–positive specimen should be rendered.[11,13,115,116] In the study by Kunz *et al.*,[115] biopsies with GS 4+4 in one core and GP 3 in other cores had higher overall GS and more advanced stage in RP than biopsies with pure GS 4+3. In the study by Kunju *et al.*[116] on global GS (combining grades of positive specimens), worst GS, and GS of largest volume in biopsies with multiple positive specimens, the worst GS had the best correlation with RP GS. Clinically significant upgrading at RP was least for worst GS (4%) and highest for global GS (37%). These studies support the approach of reporting individual GS for every positive specimen to identify the highest GS.

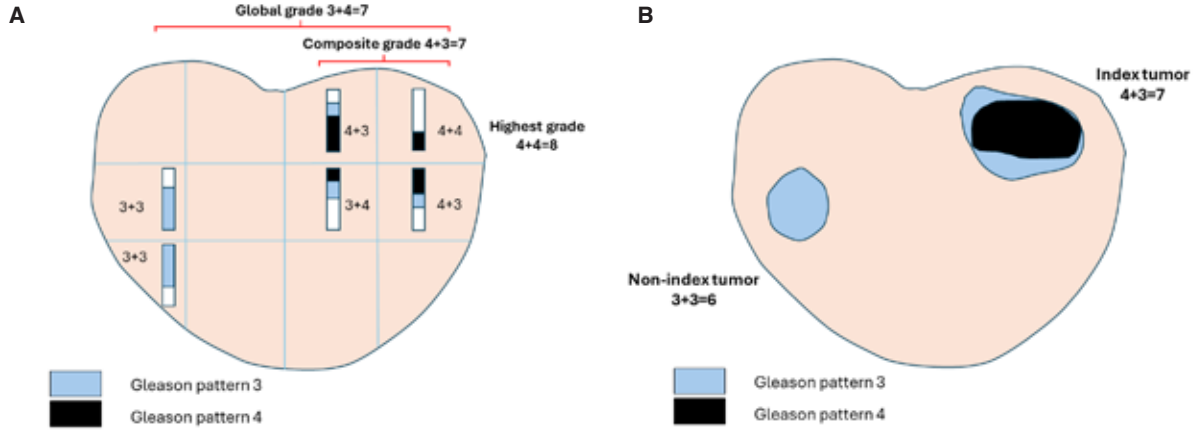
At case-level (or aggregate-sites) reporting, there are different approaches for reporting grade of a biopsy set with multiple positive specimens including by highest grade and global grade, with the highest grade more commonly used by clinicians for decision-making (**TABLE 8**).[14,16,117] A recent survey by Varma *et al.*[117] among clinicians in the UK revealed that 78% would prefer to use highest GS for clinical decision while only 12% would use global GS. Tolonen *et al.*[118] compared the worst GS and overall GS and showed that both are strong predictors of BCR, and no significant prognostic difference was shown between these two grades. Trpkov *et al.*[119] found that global GS, highest GS, and GS of largest volume cancer were similar with the final RP GS in 60.4%, 57%, and 54.3%, respectively. In biopsies without tertiary pattern, global GS and highest GS were identical on 92.4% biopsies. Athanazio *et al.*[120] found that global GS was concordant with the final GS in 59.3% of cases. Global GS was upgraded in 32.3% and downgraded in 8.3% of cases. Highest upgrade was in GS 6 (52.3%) and GS 9–10 (32.9%), attributed to missing GP 4 and GP 5 components in biopsies, respectively. Downgrading in final RP was highest with GS 8 (45.7%) that can be attributed to the dilutional effect of GP 3 component not detected in biopsy. Most clinical studies and clinical nomograms do not specify whether highest or global was used. Future studies should specify which reporting of grade was used to allow for better standardization and comparison of studies.

TABLE 8 Approaches in Reporting Grades at Case Level for Biopsies with Prostate Cancer

Grade	Definition
Highest or worst grade	Highest grade in any positive specimen in a biopsy set.
Global or overall grade	Grade derived by considering all positive specimens in a biopsy set.
Grade in largest volume cancer	Grade of the specimen with largest tumour volume in a biopsy set.
Composite grade	Assign grade to the entire biopsy set on the basis of positive cores from contiguous anatomic locations of the presumed dominant nodule. Tumour morphology in these separate cores is required to be similar to be included.

Arias-Stella *et al.*[121] introduced the composite grade that attempted to correlate the grade in biopsies with the grade of the presumed dominant nodule (**FIGURE 7**). In the study, composite GS showed better overall correlation with RP GS and was less likely to be downgraded compared to the highest GS. Although composite GS appears promising, validation studies are needed, as well as interobserver reproducibility studies, as selection of positive cores for inclusion into the composite grade may introduce subjectivity.

FIGURE 7 (A) Example of a biopsy set with different highest (GS 4), global (GS 3+4), and composite (GS 4+3) grade. (B) Corresponding RP shows index (GS 4+3) and non-index (GS 3+3) tumours.
Abbreviations: GS, Gleason score; RP, radical prostatectomy.



Reporting grade in targeted (with and without systematic) biopsy

A global grade should be reported for every MRI-targeted lesion as recommended by ISUP and GUPS.[17,18] Deng *et al.*[122] compared global grade, highest grade, and largest-volume grade in MRI-targeted biopsies and showed that global, highest, and largest-volume grades had substantial agreement with RP-targeted lesion grade. However, targeted lesion global grade yields slightly better agreement than either targeted highest or largest-volume grade. Subsequent study from the same group showed that when there was discrepancy between

targeted lesion global grade and highest grade, the global grade more accurately predicted the RP grade compared to highest grade, particularly in GS 3+4 (61%) and GS 4+3 (54%) lesions.[123] The study by Jabbour *et al.*[124] on MRI and systematic with Prostate Imaging–Reporting and Data System (PI-RADS) ≥ 3 lesions compared the use of highest grade in a biopsy core and global grade (for targeted biopsy with or without perilesional biopsies [10 mm of periphery of suspicious MRI lesion]) and showed that reporting a global grade improves the accuracy with final RP specimen.

In the study by Gaffney *et al.*,[125] targeted biopsy alone influenced the oncologic risk (adverse pathology) compared with systematic biopsy grade alone. Interestingly, if grades were discordant between the targeted and systematic biopsies, the risk was intermediate between the grades. The study findings cast doubt on the use of the highest grade. He *et al.*[126] assessed the targeted and systematic biopsies for (1) global grade, (2) most common grade, (3) highest grade, and (4) largest-volume/linear length cancer grade, and introduced the term "optimal grade," defined as the best agreement for the 2, 3, and 4 grades. In the study, the optimal grade had better agreement with RP grade than global grade.

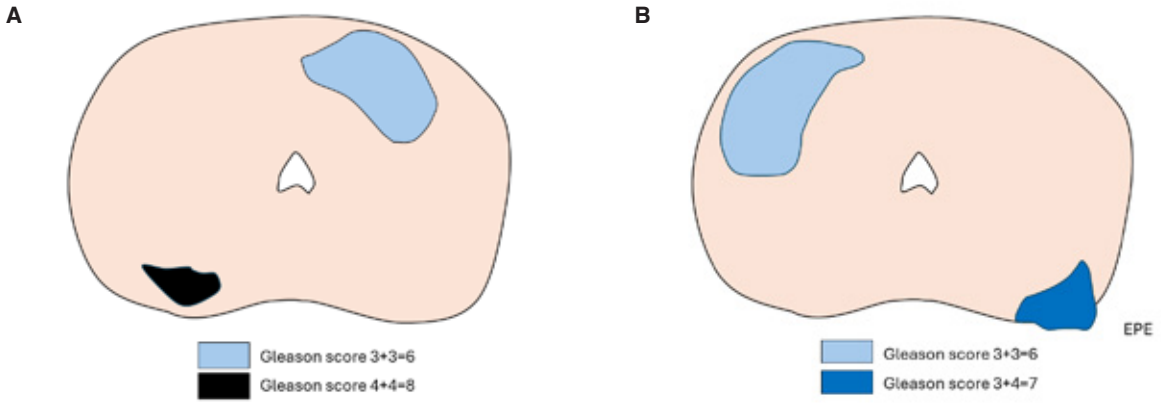
Reporting grade in radical prostatectomy

Prostate cancer is commonly multifocal, and in this situation, grade can be derived based on the largest tumour, highest-stage tumour, highest-grade tumour, and global (overall) grade. (TABLE 9) ISUP recommends that if GSs of the largest, highest-stage, and highest-grade lesions are not identical, then the different grades should be reported separately (FIGURE 8).[17] In the study by Matsumoto *et al.*,[127] when the largest lesion was GS 3+4 and with secondary lesion of GS 4+3 and GS 8–10, BCRFS rates for those with secondary lesion of GS 4+3 and GS 8–10 were 76% and 67%, respectively. But when the secondary lesion was GS 3+4, the BCRFS rate was 91%, which was significantly better than the other cohorts. The study by Best *et al.*[128] on localized prostate cancer that defined index grade as the highest grade of any tumour, compared the index grade with the global grade (referred in the study as composite grade) and showed that with discordant cases, the higher GS was associated with increased rates of BCR after RP rather than the global grade. **Thus, in RP with multifocal tumours and grade heterogeneity, grade is best determined by the highest grade instead of the grade of the largest lesion or by the global grade.** Several studies highlight the problem of using global grade, as it introduces spurious lowering of the grade by non-index tumours with GP 3 in prostate; many of these secondary lesions are clinically insignificant.[129–131] While ISUP recommends recording different grades if dissimilar in RP with multifocal tumours, ISUP also states that a global GS should be sufficient for further patient management.[17]

TABLE 9 Approaches in Reporting Grades in RP with Multifocal Tumours

Grade	Definition
Highest grade	Highest grade among the multiple tumour nodules.
Grade of largest tumour	Grade of largest among the multiple tumour nodules.
Grade of highest stage (pT) tumour	Grade of tumour nodule with extraprostatic extension or seminal vesicle extension.
Global grade	Aggregate grade of all the tumour nodules.

FIGURE 8 Examples of multifocal tumours in RP with grades different between the (A) larger and smaller higher-grade tumours and (B) larger and smaller higher-stage tumours. In these examples, the smaller tumours are considered the index tumour.
Abbreviation: RP, radical prostatectomy.



Prognostic Impact of the Different Gleason Pattern 4 and 5 Components

Effect of Gleason pattern 4 architectures

Effects of cribriform glands

Prognostic effect of cribriform glands

There is strong evidence that among GP 4 architectures, cribriform gland is significantly associated with adverse outcome. Presence of cribriform gland is associated with a greater risk for adverse pathology at RP, worse BCR, metastasis, and prostate cancer-specific mortality (CSM).[74,77–79,81] Cribriform gland is associated with increased risk for EPE, SVI, and PSM at RP.[77,78] In GS 7 cancers in RP, cribriform gland is an independent predictor of disease-specific survival (DSS) and metastasis-free survival (MFS).[79] In localized prostate cancers treated with RP, BCRFS is significantly poorer when cribriform glands are present.[80] In biopsy, Kweldam *et al.*[37] showed that cribriform architecture (invasive cribriform carcinoma and/or intraductal carcinoma [IDC]) was independently associated with worse DSS. **Both ISUP and GUPS recommend reporting the presence of cribriform gland in GS 7 and GS 8 prostate cancers in biopsy and RP.**[17,18]

Cribriform glands in intermediate-risk cancer

Patients with prostate cancer showing cribriform gland in needle biopsy should be considered suboptimal for AS. Using prostate biopsies from the European Randomized Study of Screening for Prostate Cancer (ERSPC), three studies by Kweldam *et al.*[132–134] showed that cribriform architecture (invasive cribriform and/or IDC) in GS 3+4 tumours was an independent predictor of BCR,[132] and that GS 3+4 without cribriform glands did not have a statistically different DSS than GS 6 cancers,[133] and similarly that GS 7 cancers without cribriform gland did not have a statistically different BCRFS after RP compared to GS 6 tumours.[134] Thus, it has been suggested that patients with GS 3+4 tumours without cribriform glands may be considered eligible for AS if they have acceptable PSA level and tumour volume. In a study by Roobol *et al.*,[135] ERSPC Rotterdam risk calculator number 3 (RC 3) can effectively distinguish men without prostate cancer from men with low risk (GS 6 or 3+4 without invasive cribriform and/or IDC) or high risk (3+4 with invasive cribriform and/or IDC and ≥ GS 4+3) tumours, which would potentially decrease unnecessary biopsies and overdiagnosis of potentially indolent cancers.

Cribriform glands in higher (≥ 8) Gleason score cancer

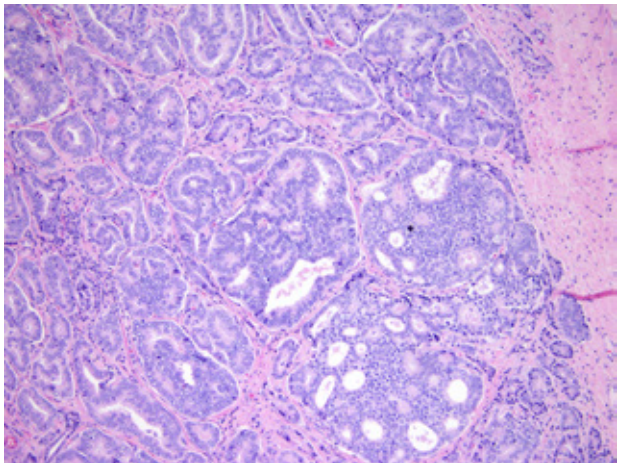
The presence of cribriform glands may have value in stratifying the outcome of GS 8 to 10 prostate cancer. Hollemans *et al.*[136] showed that among GS 8 tumours in RP, invasive cribriform carcinoma and/or IDC occurred more frequently in GS 4+4 than in GS 3+5 and GS 5+3 tumours and was shown to independently predict BCR and metastasis. Oufattole *et al.*[137] showed that in GS 9 and 10 cancers, presence of comedo/solid components in GP 5 was associated with a higher frequency of concurrent cribriform and/or IDC, and its presence was independently associated with higher risk for BCR after RP.[137]

Prognostic effect of size of cribriform glands

Several studies have explored the effect of the size of cribriform glands in stratifying outcome (FIGURE 9).[138–143] Because of the challenges in distinguishing invasive cribriform gland and IDC, these patterns were often combined in prior studies. The study by Chan *et al.*[138] using tissue microarray from the Canary retrospective RP study and stratifying RFS curves by cribriform gland size identified 0.25 mm as the optimal cutoff to identify aggressive disease. In another study by Greenland *et al.*[139] using the same 0.25-mm cutoff for large cribriform gland in GS 3+4 tumours in biopsy showed that large cribriform glands were associated with increased risk for adverse pathologic findings in RP.

Using a simpler definition for large cribriform, i.e., at least twice the size of adjacent benign glands for large cribriform gland, Hollemans *et al.*[141] showed that large cribriform glands in GS 3+4 cancer in RP was an independent predictor of BCRFS while small cribriform glands were not. Using the same definition, Rijstenberg *et al.*[143] however showed in prostate biopsies from ERSPC that large and small cribriform glands were both associated with worse MFS and DSS and that large cribriform glands did not have worse MFS or DSS compared to small cribriform glands. **Additional studies are needed to identify which definition for size of cribriform glands is most predictive and diagnostically reproducible, as well as whether this parameter retains significance once other common clinicopathological factors are accounted for.**

FIGURE 9 Large and small cribriform glands carcinoma.



Effects of other (non-cribriform) Gleason pattern 4 architectures

Glomeruloid gland is usually observed with other GP 4 architectures and was initially suggested to be an early stage of cribriform gland.[144] **Glomeruloid glands, including those with complex architecture, appear to be associated with better outcome when compared to cribriform glands and other GP 4 architectures in GS 7 tumours**. In the study Choy *et al.*,[74] GS 7 cancers in RP, glomeruloid gland was associated with better survival when compared to GS 7 cancers without this architecture. Greenland *et al.*[140] showed the risk of BCR for tumours with expansile cribriform gland was 4.4-fold greater than tumours with glomeruloid glands. Hollemans *et al.*[145] divided glomeruloid glands into simple and complex architectural growths and showed that in contrast to cribriform, simple or complex glomeruloid gland was not an independent predictor of BCRFS in GS 3+4 tumours.[145] **Distinction should be made between glomeruloid and cribriform glands, and glomeruloid glands are not classified as variant of cribriform glands.**

Study on prognostic effects of the other GP 4 patterns, such as poorly formed and fused glands, is limited. Choy *et al.*[74] in a study in RP of GS 7 tumours with GP 4 showed that unlike with cribriform gland, presence of poorly formed or fused glands was not associated with poorer BCRFS when compared to GS 7 without these architectures. Hollemans *et al.*[146] in a study of 192 GS 3+4 cancers without cribriform (other GP 4 architectures present) in RP showed that these tumours had more advanced disease and shorter BCRFS than GS 6 cancers. **Data suggests that among GP 4 architectures in GS 7 tumours, cribriform glands are associated with worse outcome and glomeruloid gland is associated with favourable outcome, while fused and poorly formed glands appear to be intermediate between these two patterns.**

Effect of Gleason pattern 5 architectures

Comedonecrosis may occur as a component of invasive or intraductal carcinoma.[147,148] Hansum *et al.*[149] showed that the presence of comedonecrosis pattern commonly coincided with the presence of cribriform glands. **Comedonecrosis pattern is suggested to be able to substratify the poor outcome of high-grade prostate cancer.**[87,149–152] Hansum *et al.*[149] showed that invasive comedonecrosis was an independent predictor of BCRFS and MFS after RP. Acosta *et al.*[151] showed that GP 5 with invasive comedonecrosis was associated with poor prognostic histologic features (SVI, larger volume, and trends toward LNI and PSM) and high rates of BCR after RP. Comedonecrosis pattern in prostate biopsy was shown to be predictive of high tumour volume in RP, and of prostate cancer death independent of GS.[152] Data is limited on the prognostic effects of the other GP 5 architectures individually in high-grade prostate cancer.[87]

Quantitative Grading

Extent of Gleason pattern 4

Extent of Gleason pattern 4 in biopsy

Percentage of Gleason pattern 4

Studies have shown a strong correlation of increasing percentage of GP 4 (% GP 4) with prostate cancer aggressiveness. Incremental increase in % GP 4 in GS 7 cancers in biopsy independently predicts adverse pathology in RP and BCR.[153] Quantifying % GP 4 in biopsy can also identify various intermediate-risk groups with the corresponding RP grade.[154] **It is recommended by ISUP and GUPS that % GP 4 should be reported in GS 7 cancers in biopsy.**[17,18] An advantage of reporting % GP4 is that it further substratifies GS 3+4 tumours, as prognosis of small % GP4 and high % GP 4 will be different while both are being reported under the same GS**. Information on % GP 4 is important in selecting patients for AS especially that favourable intermediate-risk patients are now being considered for AS.**

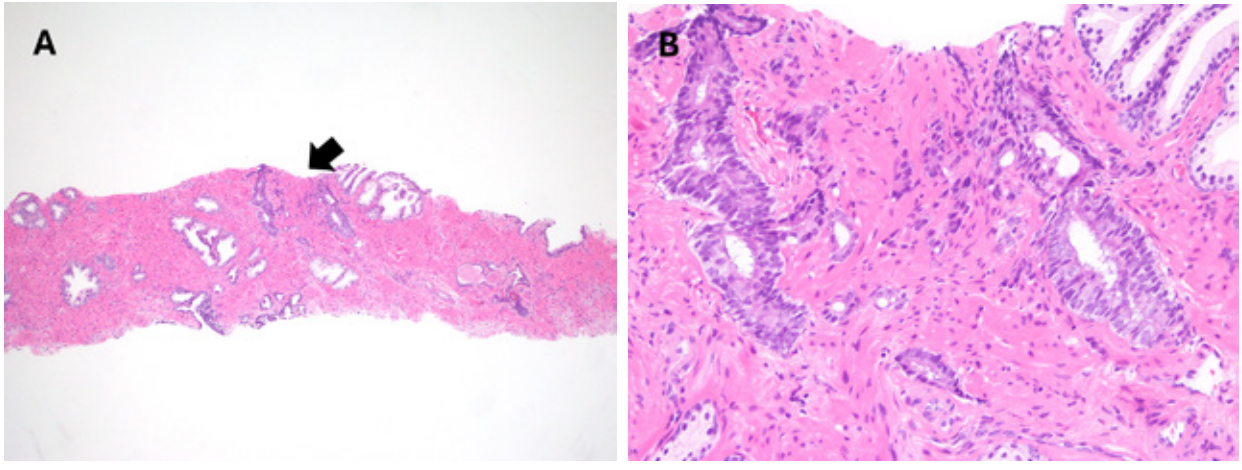
van der Slot *et al.*[155] showed that even without IDC and/or cribriform, % GP 4, together with prostate imaging reporting and data system (PI-RADS) 5 lesion, remained independently predictive of tumour upgrading. Perlis *et al.*[156] showed that correlation of % GP 4 with other factors, including PSA and tumour volume, enhanced the prediction of non-organ–confined disease. Kachanov *et al.*[157] showed that combination of targeted and systematic biopsies for % GP 4 also allowed for a more precise detection of lower % GP 4 in corresponding RP. In terms of reproducibility, van der Slot *et al.*[95] divided % GP 4 into four tiers (0–25%, 26–50%, 51–75%, and 76–100%) and showed moderate interobserver agreement among 6 pathologists.

Percentage of Gleason pattern 4 in a small cancer

The study by Sadimin *et al.*[158] showed that reproducibility in assessing % GP 4 in biopsy had substantial agreement if there was a significant amount of cancer (≥ 10%) in a biopsy core. If the tumour focus in a core was small

(< 10%), agreement in % GP 4 was only moderate. **One should consider not reporting % GP 4 in a small GS 7 cancer to avoid an inaccurate % GP 4** (**FIGURE 10**). It is also unclear whether incremental changes in % GP 4 in a small (≤ 1 mm) GS 7 tumour bear any prognostic significance.

FIGURE 10 (A) A biopsy with small focus of GS 3+4 cancer (arrow). (B) In this case, quantifying % GP 4 can introduce inaccuracy.



Abbreviations: GP; Gleason pattern; GS, Gleason score.

Small (≤ 5%) percentage of Gleason pattern 4

Several studies suggest that a minimal (≤ 5%) amount of GP 4 has no prognostic impact on GS 3+4 tumours. A small amount of GP 4 in biopsy with GS 3+4 tumours has no effect in adverse pathology at RP, BCR, and survival when compared to GS 6 tumours.[99–102] The study by Berney *et al.*[99] looked at prostate cancer death as endpoint and showed that patients with GS 3+4 cancers with < 5% GP 4 had similar survival to patients with GS 6 cancers. The study by Huang *et al.*[100] showed that GS, stage, tumour volume, and insignificant tumour rate in RP were similar for GS 3+4 with ≤ 5% GP4 and GS 6 tumours. Another study by Kato *et al.*[102] showed that a higher cutoff of ≤ 10% GP4 and without IDC for GS 3+4 cancers in biopsy also had similar recurrence rate to GS 6 cancers. **If other factors are acceptable, patients with GS 3+4 cancers and small % GP 4 in biopsy can be considered for AS.**

Length in mm of Gleason pattern 4

There are several other methods to report the extent of GP 4 in biopsy (**TABLE 10**). **The length in millimeter (mm) of GP 4 in GS 3+4 tumours in biopsies may have better predictive ability for adverse pathology in RP and BCR than % GP 4.**[159,160] The study by Dean *et al.*[159] applied 3 different quantitation methods for GP 4 in biopsies with GS 3+4 tumours and showed that maximum % GP 4 in any single core, overall % GP 4 (GP 4 mm/total cancer mm), and total length in mm of GP 4 across all cores were all significantly

associated with increased risk for adverse pathology in RP. The total length in mm of GP 4 across all cores provided the largest area under the curve (AUC) increase to predict adverse pathology features and the greatest net benefit for clinical decision-making. Another study from the same institution, using the same quantitation methods and adding mm GP 4 in the highest-volume core also showed that all 4 quantitation methods of GP 4 were associated with BCR after RP.[160]

TABLE 10 Different Approaches in Recording the Extent of Gleason Pattern 4 in Biopsy

Measure	Definition
Individual % GP 4	mm of GP 4 tissue/total mm of cancer in a core or site
Overall % GP 4	mm of GP 4 tissue (all cores)/total mm of cancer (all cores)
Maximum % GP 4	Single core with the greatest involvement by GP 4
Total length (mm) GP 4	Sum of the total length in mm of GP 4 across all cores
Length (mm) of GP in greatest core	Length in mm of GP 4 in core with highest GP 4

Extent of Gleason pattern 4 in radical prostatectomy

Percentage of Gleason pattern 4

The incremental increase in % GP4 in RP also corresponds to an increasing risk for BCR; however, its additive clinical value beyond common clinicopathologic factors needs to be confirmed.[74,154] Sauter *et al.*[154] demonstrated a continuous increase of risk for BCR with increasing % GP 4 fractions, and with small differences in outcome at clinically important thresholds (0% vs. 5% or 40% vs. 60% GP 4). Choy *et al.*[74] divided % GP 4 into 1–20%, 21–50%, 51–70%, and > 70% and showed a 5-year BCRFS of 84%, 74%, 66%, and 32%, respectively. Iakymenko *et al.*[161] showed that % GP 4 in RP was independently associated with adverse pathology including EPE and PSM.

Absolute amount of Gleason pattern 4

There were studies that used other metrics to measure the amount of GP 4 in RP. Deng *et al.*[162] quantified the amount GP 4 in RP using 3 methods that included a quantitative GS based on the proportion of tumour composed of GP 4 (%), a size-weighted score (g) that incorporated the overall quantity of GP 4, and a size index (mm) that incorporated the overall quantity of GP 4 based on the index lesion and showed that all 3 methods were significantly associated with BCR and were better predictors than GS. Andolfi *et al.*[163] reported that for each 1 cm^3 of GP 4 in RP there was an associated 6- to 8-fold higher serum PSA level in comparison to GP 3. Vickers *et al.*[164] used the same RP cohort from the study by Andolfi *et al.*[163] and combined it with biopsies from another study (Dean *et al.*[159]) and showed that quantifying the total length of GP 4 would improve GG assignment in localized prostate cancers. Interestingly, the absolute amount of GP 3 did not add meaningfully in the prediction that was determined solely by the absolute amount of GP 4. **Additional studies are needed to compare which, if any, measure of GP 4 (%, mm, or g) in RP is most predictive.**

Percentage of Gleason pattern 4/5 or 5

The importance of % GP 4/5 in predicting BCR and survival has long been recognized,[165,166] which has led to widespread acceptance of reporting tertiary GP 5 in GS 7 tumours. The study by Berney *et al.*[99] in needle biopsies of localized prostate cancer showed that the worst % GP 4/5 (% GP 4 /5 in worst positive core) and overall % GP 4/5 (global % GP 4/5) were both significant predictors of prostate cancer death and suggested that either approach can be used. For % GP 5 only, Yaxley *et al.*[167] showed that quantification of % GP 5 in high-grade (GS 4+5) prostate cancers did not correlate with BCR.

Intraductal Carcinoma and Atypical Intraductal Proliferation

Intraductal carcinoma

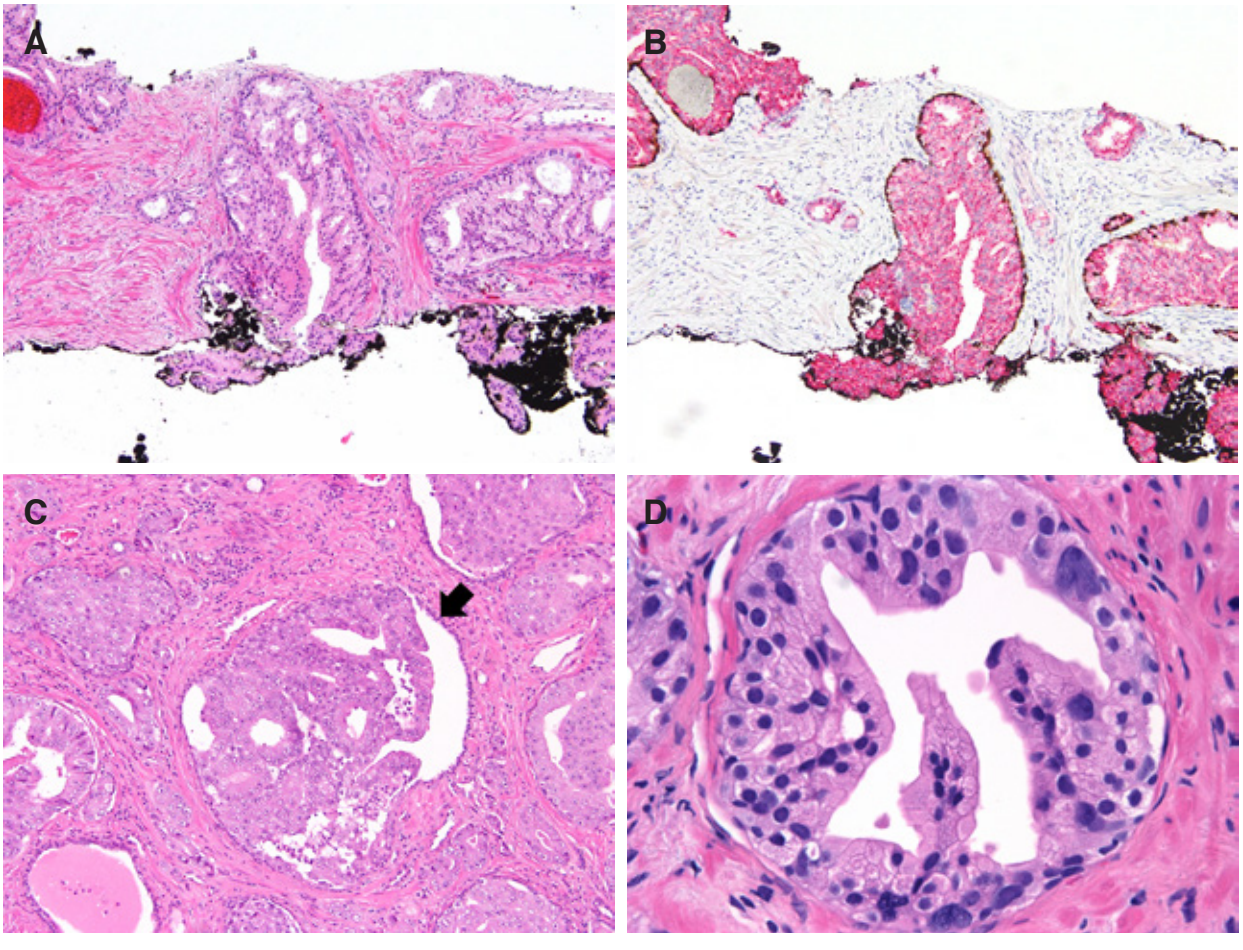
IDC is significantly associated with adverse outcomes for prostate cancer in needle biopsy and RP (FIGURE 11).[24,78,168–174] The meta-analysis by Miura *et al.*[168] showed that IDC in localized prostate cancer was associated with lower BCRFS and CSS. Likewise, in the multi-institutional study by Leung *et al.*,[80] IDC in localized cancers treated with RP had significantly poorer BCRFS than usual adenocarcinoma. Porter *et al.*[174] showed strong association between IDC prevalence and prostate cancer aggressiveness and revealed the increasing frequency of IDC from low-risk patients (2.1%) to moderate-risk (23.1%), high-risk (36.7%), and metastatic or recurrent disease-risk (56%) categories. A population-based study showed that IDC was associated with high-grade, higher-stage, PSMs, LNI, and worse-prostate CSM.[170] In biopsy, presence of IDC had been associated with high-grade and high-stage cancer in RP, distant metastasis at presentation, poorer CSS, and OS.[171,173] In patients treated with radiotherapy, IDC in biopsy with intermediate- or high-risk prostate cancer was shown to be an independent predictor of BCR and metastatic failure.[175] **Thus, IDC in biopsy with GS 3+4 prostate cancer should be considered suboptimal for AS. Both ISUP and GUPS recommend reporting the presence of IDC in biopsy and RP.**[17,18] For ISUP, reporting is recommended even if IDC is incorporated into grade.

Several criteria have been proposed for the diagnosis of IDC,[168,172,173,176] but the most applied definition is that by Guo and Epstein[173] (TABLE 11). A recent study questioned the ≥ 6X nuclear enlargement in Guo and Epstein's criteria.[177] Regardless, using the different definitions, IDC is significantly associated with lower BCRFS, CSS, and OS by Guo and Epstein[173] (pooled hazard ratio [HR], 1.86 for BCR-free survival; pooled HR, 2.6 for CSS; pooled HR, 1.61 for OS), McNeal and Yemoto[176] (pooled HR, 2.58 for OS), Cohen *et al.*[172] (pooled HR, 1.86 for BCR-free survival), 2016 WHO criteria[71] (pooled HR, 5.78 for CSS), and combination of these published criteria (pooled HR, 2.5 for BCR-free survival).[168]

TABLE 11 Definition of Intraductal Carcinoma of the Prostate by Guo and Epstein[173]

Malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells and:
Solid or dense cribriform pattern
or
Loose cribriform or micropapillary pattern with either: - Marked nuclear atypia: nuclear size 6 x normal or larger - Nonfocal comedonecrosis

FIGURE 11 (A) IDC in biopsy with (B) basal cell markers expression. (C) IDC with basal cells discernable in H&E (arrow). (D) Non-cribriform IDC with markedly pleomorphic nucleoli.



Abbreviations: H&E, hematoxylin and eosin; IDC, intraductal carcinoma.

Most IDC is considered an intraductal spread of cancer in the later phase of prostate carcinogenesis. For that reason, most IDC is identified with concurrent high-grade and advanced cancers. Loss of expression PTEN, which is strongly associated with advanced prostate cancer, is present in 84% of IDC, further supporting its advanced state.[178] Some authors suggest that IDC can also be a "precursor-like" lesion, especially those that occur in isolation or associated with adjoining microcarcinoma. Miyai *et al.*[179] showed that regular IDC had significantly higher GS, more frequent EPE and SVI, more advanced T stage, and lower 5-year BCR-free rate compared to precursor-like IDC.

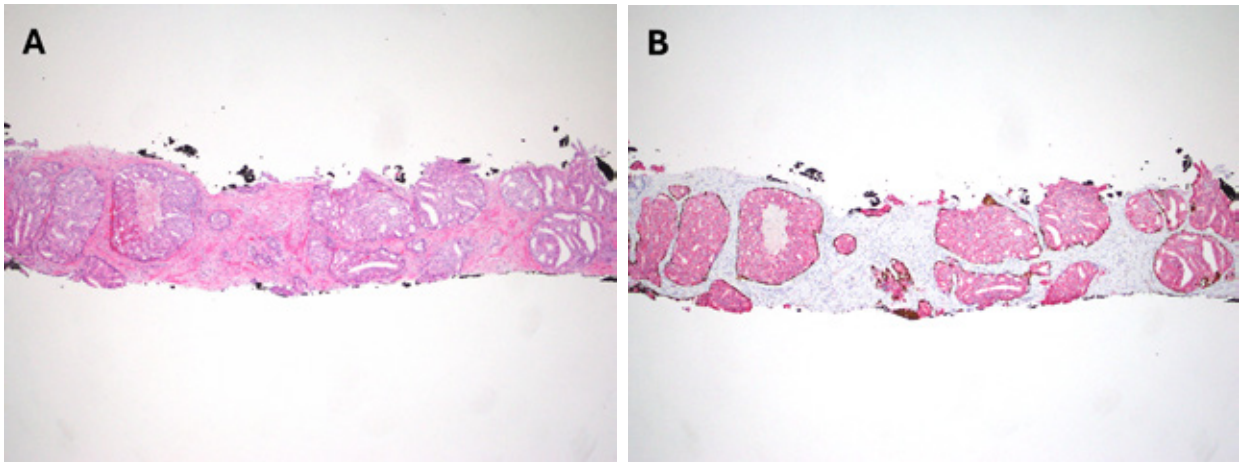
The main differential diagnoses for IDC are invasive cribriform (GP 4) and invasive comedonecrosis (GP 5) glands, which are also recognized as adverse histologic patterns. Distinction is made by the presence of basal cells in IDC that are usually recognizable on hematoxylin and eosin (H&E) stain. Occasionally, presence of basal cells can only be confirmed by immunohistochemical staining. The clinical significance of distinguishing IDC from invasive cribriform and comedonecrosis is unclear, and several recent studies and reporting guidelines are merging these adverse patterns (discussed below). **However, IDC must be distinguished from high-grade PIN (HGPIN).** HGPIN, the putative precursor of prostate cancer, when identified in isolation in biopsy is usually managed with observation, or repeat biopsy if there is high suspicion for cancer, unlike for IDC, which is a consideration for active treatment.[3] Distinction between PIN and IDC can often be made on morphological grounds. Unlike IDC, PIN has flat, tufted, or micropapillary patterns and overlap occurs when nuclear pleomorphism is more than what is expected for PIN.[180] Unlike IDC, PTEN expression is rarely, if ever, lost in PIN and can be helpful in these rare difficult cases.[178,181] **Lesions falling short of the morphologic criteria for IDC are labelled as atypical intraductal proliferation (AIP),** [182–185] further discussed below.

Isolated intraductal carcinoma

Rarely, IDC occurs without a concomitant invasive carcinoma in biopsy (FIGURE 12).[186] The study by Robinson and Epstein[186] identified 83 cases with isolated IDC in prostate biopsy and in the corresponding RP of 23 cases, 38% were pT3a and 13% pT3b. Of the cases, 14% experienced post-RP BCR and 5% had metastasis. **Thus, even if IDC is identified in isolation in biopsy, it suggested that therapy, similar to that used in non–low-risk invasive adenocarcinoma should be considered.** A repeat biopsy, with MRI to detect a lesion, is a prudent approach since most cases of IDC are associated with high-grade cancers that likely will be sampled in the follow-up biopsy.

There are extremely rare examples of IDC in a fully examined prostate purely confined within the ducts and without a concomitant invasive adenocarcinoma.[187,188] Despite being confined in the ducts, the tumour can extend into the seminal vesicles (pT3b).[187] There are also uncommon cases of IDC with concomitant few GS 6 glands.[189,190] Khani *et al.*[190] showed low expression of ERG (7%) and loss of PTEN expression in 53% of isolated IDC and IDC associated with GS 6 cancers but with intact PTEN expression in the concomitant GS 6 cancers, supporting that IDC is not an *in-situ* carcinoma of the low-grade carcinoma, but a molecularly unique *in-situ* carcinoma of unclear clinical significance.

FIGURE 12 (A) Pure IDC in biopsy (B) confirmed by PIN4 immunostaining.



Abbreviation: IDC, intraductal carcinoma.

Grading of intraductal carcinoma

There is divergence in the recent recommendations for grading of IDC. **Both ISUP and GUPS agree that isolated IDC should not be graded, and its presence should be reported.**[17,18] However, there is disagreement when IDC occurs with concomitant invasive carcinoma. ISUP recommends that IDC should be incorporated into grade, whereas GUPS recommends that IDC should not be incorporated into grade.[17,18] If IDC is graded, grading will be based on its conformity with the traditional GPs, for example, cribriform IDC [as GP 4], cribriform with necrosis IDC [as GP 5], comedonecrosis IDC [as GP5], or solid IDC [as GP 5]) patterns in IDC. GUPS further recommends that it is not necessary to perform immunohistochemistry for basal cells if the results of the stain will not change the highest GS.[18] This discrepancy in grading may not be an issue with higher-grade tumours since IDC is often accompanied by invasive high-grade carcinoma. However, this may become an issue for those uncommon IDCs with concomitant GS 6 cancers or for GS 7 cancers.[189] Rijstenberg *et al.*[191] showed that disparity in grading approaches by ISUP and GUPS only had minimal impact, with grade change affecting only 1.6% of prostate biopsy and 0.6% of RP specimens.

Combining intraductal carcinoma and cribriform gland (high-grade cribriform pattern)

Because of the challenge in separating IDC and invasive cribriform gland and their shared clinical significance, several studies and reporting checklists have merged these two adverse tumour growths into "IDC and/or cribriform" or as high-grade cribriform patterns[11,12,16,192,193] This may be beneficial in parts of the world where availability of immunohistochemical stains is limited. The presence of IDC and/or cribriform glands in biopsy is an independent predictor of BCR after RP and is associated with worse

BCRFS and DSS.[132–134] Seyrek *et al.*[194] showed that IDC and/or cribriform in GS 3+4 cancers in RP outperforms % GP 4 and minor tertiary GP 5 in predicting BCRFS. Hollemans *et al.*[136] showed that IDC and/or cribriform in RP with GS 8 prostate cancer was an independent parameter for BCRFS and MFS. Recently, Yu *et al.*[195] showed that addition of IDC and/or cribriform improved patient stratification for Cancer of the Prostate Risk Assessment (CAPRA) scores 3–5 and 6–10, and for National Comprehensive Cancer Network (NCCN) scores 4 and 5–6. Downes *et al.*[196] used a cohort of 1,326 prostate cancer patients from three tertiary institutions and validated the addition of IDC and/or cribriform into both CAPRA and NCCN scores including the subset of biopsy with GS 3+4 cancer. The study by Shah *et al.*[197] revealed that radiorecurrent prostate cancers were enriched with IDC and/or cribriform and defects in DNA damage and response and repair genes. Böttcher *et al.*[198] showed that IDC and/or cribriform is associated with increased genomic instability clustering to genetic regions involved in aggressive prostate cancer.

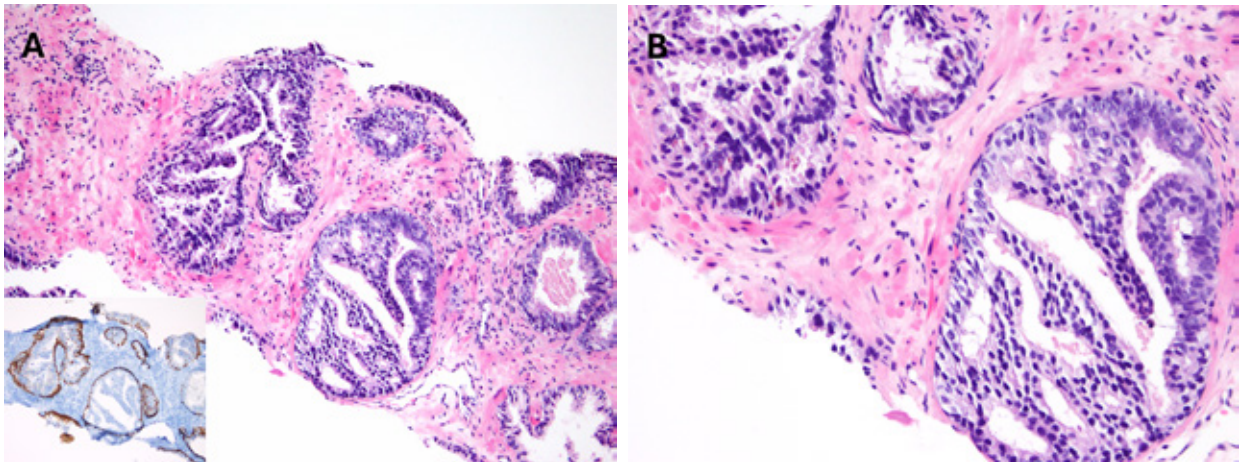
Intraductal carcinoma with comedonecrosis

There is a strong association of comedonecrosis (traditionally a GP 5 pattern) with IDC.[147,148] Fine *et al.*[147] revealed that 95% of 19 RP prostate cancers with comedonecrosis had the presence of basal cells by immunohistochemical staining. Of these cases, 63% were exclusively IDC and 32% were mixed IDC and invasive comedonecrosis. Madan *et al.*[148] showed that most tumours containing IDC with comedonecrosis were high stage and had higher LNI than tumours with invasive comedonecrosis. Wang *et al.*[199] showed that patients with IDC with comedonecrosis had worse histopathologic features in RP than patients with IDC without comedonecrosis, and that IDC with comedonecrosis independently predicted progression-free survival. Another study from the same group showed that IDC with necrosis was significantly associated with worse progression-free survival compared to invasive acinar adenocarcinoma with necrosis (GP 5).[200] Necrosis within IDC should be commented upon, especially if IDC with necrosis (GP 5) is not incorporated into grade.

Atypical intraductal proliferation

AIP shows architectural complexity and/or cytological atypia greater than that seen in HGPIN but falling short of the morphologic criteria for IDC (**FIGURE 13**).[183] Lesions that were formerly referred to as "cribriform HGPIN" are now classified as AIP (also referred to previously as atypical cribriform lesion).[18,201,202] **AIP in biopsy is potentially a marker of undersampled cancer including IDC and for adverse pathological features in RP**.[182–185] AIP alone is uncommon, with an estimated incidence of 1% in needle biopsy.[183] Several studies have demonstrated overlap in ERG expression and loss of PTEN staining between AIP and IDC.[182,184,203] Shah *et al.*[183] showed that AS candidate patients (GS 6 and GS 3+4) with AIP had adverse pathological features in most RPs including ≥ GS 4+3 (15%), IDC (77%), invasive cribriform (69%), pT3a (77%), or pT3b (8%). Miyai *et al.*[185] showed that tumours with AIP in RP had higher risk for BCR than tumours with high-grade PIN and lower risk than tumours with IDC. **The presence of AIP in biopsy, whether with low-risk prostate cancer or in isolation, should warrant repeat biopsy, including MRI targeting, to search for higher-grade cancer including IDC**.

FIGURE 13 (A and B) AIP in biopsy confirmed by presence of basal cell markers expression (inset).



Abbreviation: AIP, atypical intraductal proliferation.

Unusual Histologic Patterns of Acinar Adenocarcinoma

Atrophic adenocarcinoma resembles atrophic benign glands and may pose as a diagnostic challenge (**TABLE 1**) (**FIGURE 14**).[204–206] This tumour pattern was reported in 3% to 15.8% of consecutive RPs, usually admixed with non-atrophic adenocarcinoma, with the atrophic pattern comprising only the minority (16–27%) of the tumour.[204,205] **This tumour is mostly GS 6, identified in about 75% of organ-confined tumours, with the EPE often due to the concomitant non-atrophic higher-grade carcinoma**.[204] Cancer treated with radiation or hormonal therapy may also show atrophic changes, and these scenarios should be ruled out.[207–209]

p63, a basal cell–associated marker,[34] **is expressed in the nuclei of the rare adenocarcinoma with aberrant p63 expression** (**FIGURE 15**). The tumour cells exhibit ill-formed, multilayered, atrophic, or spindled cells, and basaloid nuclei.[210,211] Giannico *et al.*[211] showed admixture of this pattern with usual adenocarcinoma in 85.7% of cases, and p63-positive component comprised 65% of the tumour.[211] Because of its unusual histology, > 70% exhibit non-GP 3 architectures with about half showing GP 5 features. **Despite the frequent GP 4 and GP 5 histologies, adenocarcinoma with aberrant p63 positivity has favourable features at RP** (e.g., most are organ confined, low rates of PSM, negative lymph nodes). Due to the discordance in grade and presentations, experts suggested that this pattern should not be graded to avoid

potential overgrading.[211] This pattern also exhibits low cell cycle and Decipher prognostic score, keeping with its favourable pathologic features. Unlike usual acinar adenocarcinoma, this pattern lacks ERG rearrangement and ERG expression, and frequently expresses GSTP1, suggesting this tumour to be molecularly distinct.[212]

FIGURE 14 (A and B) Atrophic pattern adenocarcinoma.

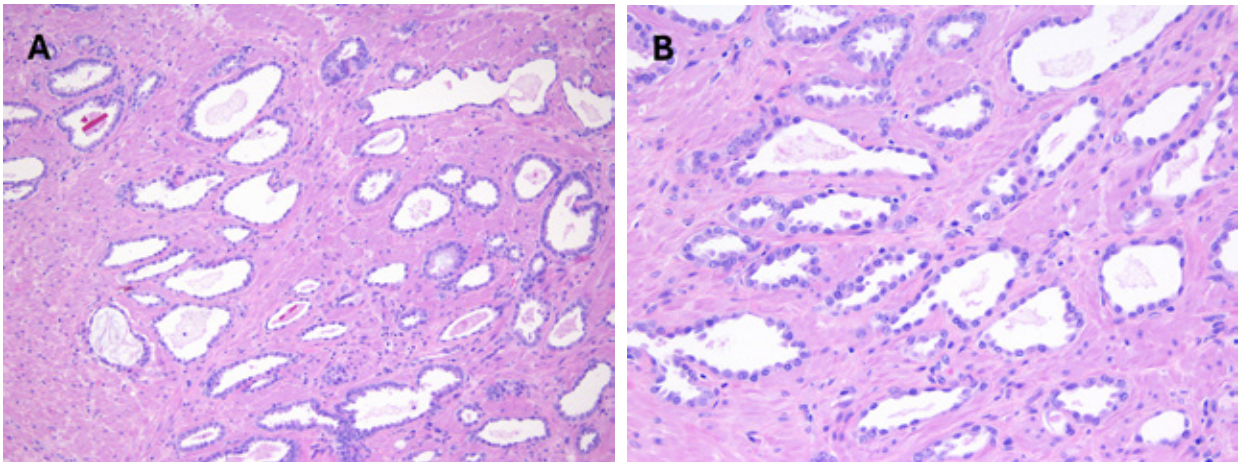
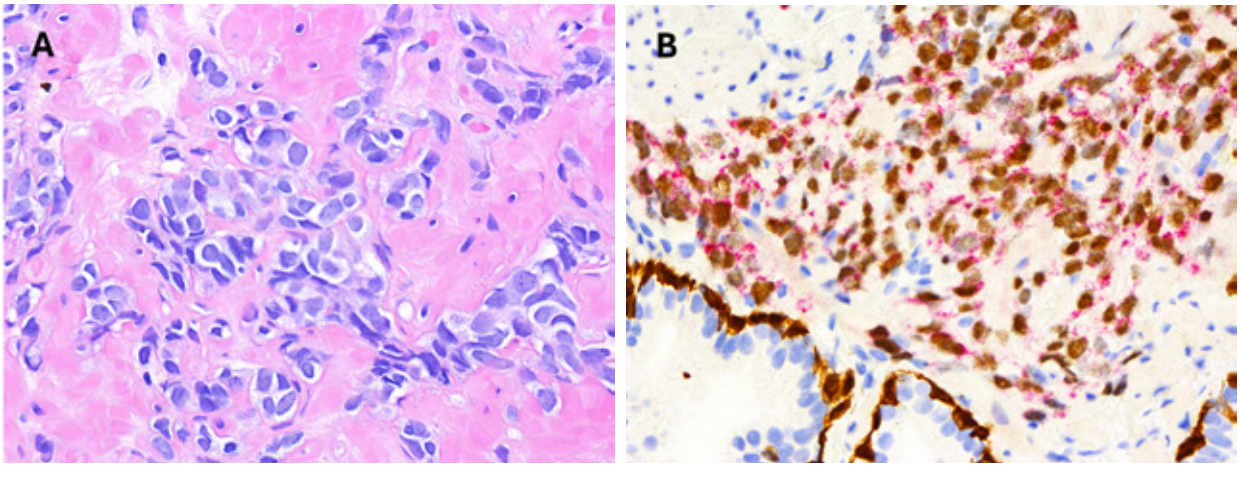


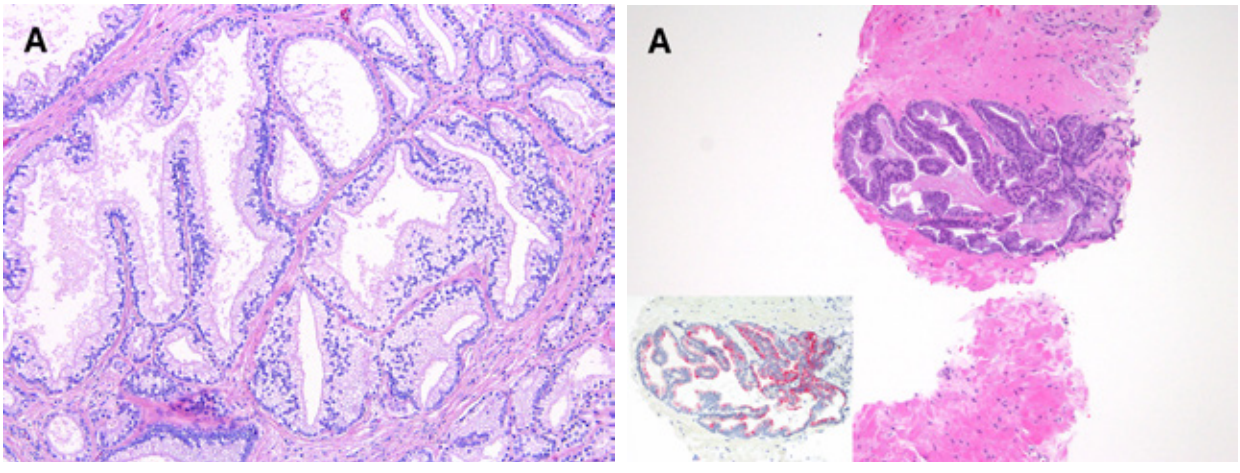
FIGURE 15 (A) Adenocarcinoma with aberrant p63 expression. (B) Tumour cells express p63 in nuclei (brown) and AMACR in cytoplasm (red).



Abbreviation: AMACR, alpha-methylacyl-coenzyme A racemase.

Pseudohyperplastic adenocarcinoma is another deceptive tumour pattern that mimics hyperplastic benign glands (**FIGURE 16**).[213–215] Humphrey *et al.*[213] detected this tumour pattern in 2% of consecutive needle biopsies and 22% of RP, usually with concomitant usual acinar adenocarcinoma.[213] **This tumour pattern is mostly GS 6 and organ confined, with the EPE largely due to the concomitant non-pseudohyperplastic adenocarcinoma.**[213,214] Interestingly, prostate cancers that harbour *HOXB13* G84E mutation, a gene associated with early onset hereditary prostate cancer, demonstrate dominant focus of pseudohyperplastic pattern in close to half of cases.[216]

FIGURE 16 (A) Pseudohyperplastic adenocarcinoma. (B) Biopsy with pseudohyperplastic carcinoma confirmed by PIN4 immunostaining (inset).



Microcystic adenocarcinoma is composed of cystically dilated glands with flat luminal cells that can mimic cystic atrophic benign glands (**FIGURE 17**).[217,218] Yaskiv *et al.*[217] detected this tumour pattern in 11.2% of RP, typically seen adjacent to usual adenocarcinoma. Microcystic pattern is graded as GS 6. In the same study, the associated usual adenocarcinoma is mostly GS 6 (64%) and when graded in aggregate, the most common GS is 7. **This tumour pattern is identified mostly in localized prostate cancer (66%), with this pattern less (< 2%) responsible for the EPE.**[217]

Foamy gland adenocarcinoma is another deceptive tumour pattern characterized by neoplastic cells that contain abundant xanthomatous or foamy cytoplasm (**FIGURE 18**).[219–223] This unusual pattern is detected in 17% to 22% of adenocarcinomas in needle biopsy, often mixed with usual adenocarcinoma.[220,222] Warrick *et al.*[220] graded 80% of foamy adenocarcinomas in needle biopsy as GS 6. Hudson *et al.*[224] identified this pattern in 14.5% to 23% of RP and the most common grade was GS 7 (63.8%). The tumours were mostly organ confined although ≥ pT3 is seen in 46% of cases, with margin positivity reported in 83% of cases.[224] **Foamy gland histology can also be present in high-grade adenocarcinoma with aggressive behaviour.**[219,225] Gao *et al.*[225] studied high-grade (GS 8–10) foamy gland adenocarcinoma and

showed 75% of patients had metastasis or died of cancer. However, recurrence rate and time to recurrence of foamy gland adenocarcinoma is similar compared to non-foamy gland adenocarcinoma, suggesting that aggressive behaviour is dependent on higher GS and not on foamy gland feature.[220,224]

FIGURE 17 (A and B) Microcystic adenocarcinoma.

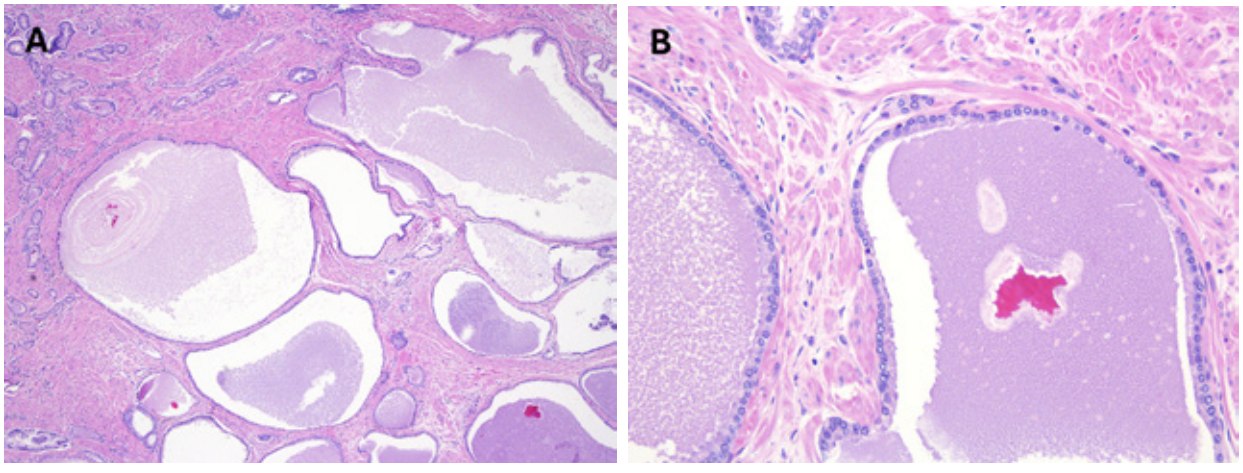
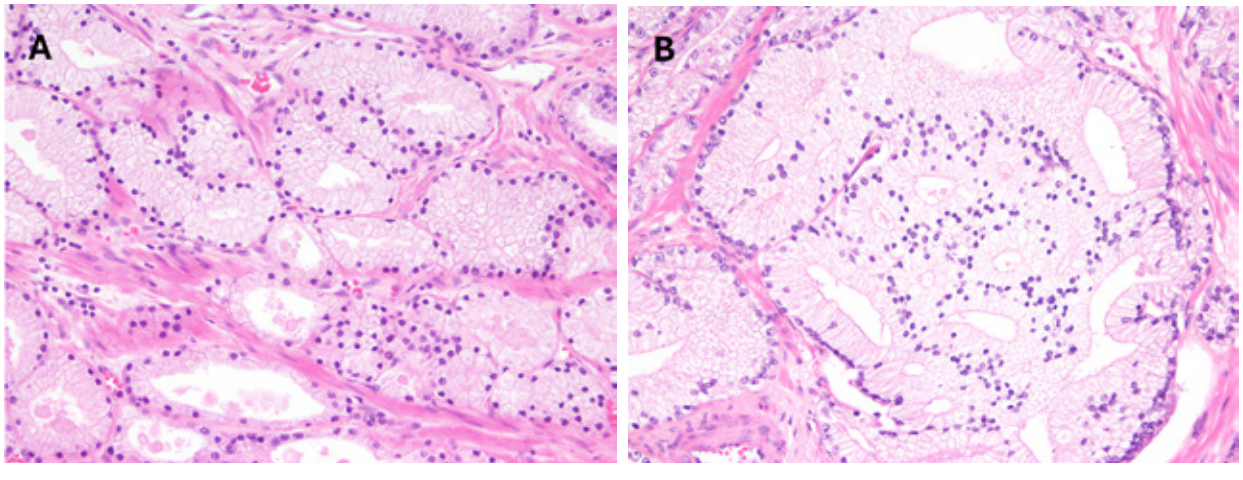


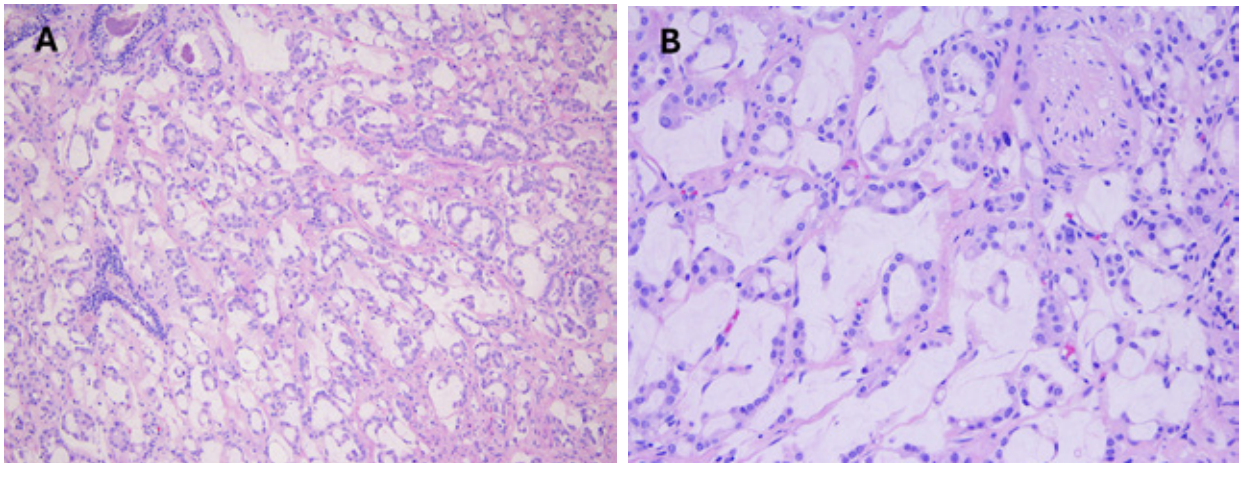
FIGURE 18 Foamy gland adenocarcinoma with (A) well-formed glands and (B) cribriform patterns.



Mucinous adenocarcinoma is characterized by neoplastic glands floating in pools of mucin (**FIGURE 19**).[226–228] Samaratunga *et al.*[227] identified mucinous adenocarcinoma in 2.2% of RP. This tumour pattern is often mixed with usual adenocarcinoma, and the mucinous component ranges from 25% to 90%, although others have reported the mucinous component to be as low as 5%.[227,228] Diagnosis requires at least 25%

mucinous component.[226,229] Thus, diagnosis of "adenocarcinoma with mucinous features" is rendered in needle biopsy where full examination of the tumour is not possible. However, the 25% cutoff is being questioned, as one large series showed no difference in EPE and BCR rates between tumours with ≤ 25% versus > 25% mucinous component.[227] The presence of mucinous "pools" may make grading challenging. The tumour tends to be GS 7 with high proportion of GS 4+3 tumours.[227,228] Registry data reported GS 7 in 57.9% of mucinous adenocarcinomas.[230] EPE was reported in 42.5% to 46.8% of mucinous adenocarcinomas, which can be extensive, with the mucinous component responsible for about half of EPE cases.[227,228] Registry data showed that mucinous adenocarcinoma tends to be localized in 69.7% of cases.[230] **When compared to usual adenocarcinoma, studies suggest mucinous adenocarcinoma has a similar outcome,**[227,230,231] **or even better outcome**.[49,228] Osunkoya *et al.*[228] showed a favourable 97.2% 5-year actuarial PSA progression-free risk for mucinous adenocarcinoma after RP compared to 85.4% for matched nonmucinous adenocarcinoma. A high proportion (86%) of these tumours show retained PTEN expression, which correlates with its non-aggressive behaviour.[232]

FIGURE 19 (A and B) Mucinous adenocarcinoma.

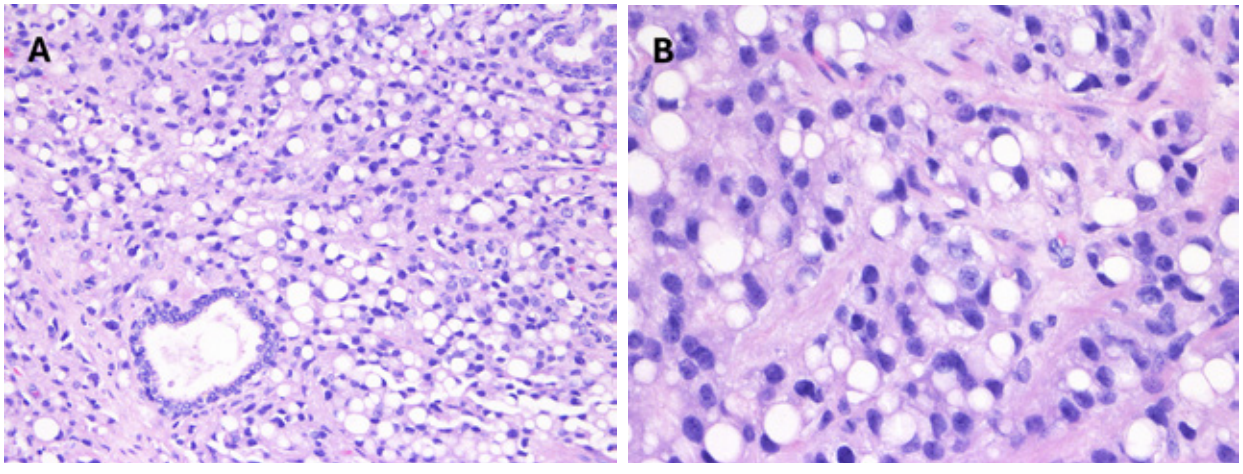


Subtypes of Acinar Adenocarcinoma

Signet-ring cell-like adenocarcinoma is a rare aggressive subtype characterized by tumour cells with intracytoplasmic vacuoles that compress the nuclei (**TABLE 1**) (**FIGURE 20**). Diagnosis requires the presence of at least 25% signet ring-like cells.[21] **This tumour usually presents with higher GS, often locally advanced, and with a poor prognosis.** In a review by Fujita *et al.*,[233] up to 78% of tumours were locally advanced or metastatic. Registry data indicates this tumour has worse CSS and OS compared to non-variant adenocarcinoma.[50] Metastasis was reported in 10.3% of cases, with an estimated 10-year OS of 56.8%, which is significantly worse than non-variant adenocarcinoma.[49] The differential diagnoses include other organ

signet ring-cell carcinomas, such as from the gastrointestinal tract and urinary bladder. Most tumours express PSA and are variably positive for mucin histochemical stain.[234,235]

FIGURE 20 (A and B) Signet-ring cell-like adenocarcinoma.



Sarcomatoid adenocarcinoma is an aggressive acinar adenocarcinoma subtype characterized by presence of high-grade dedifferentiated spindle cells (sarcomatoid carcinoma) or malignant heterologous elements (carcinosarcoma) (**FIGURE 21**)**.** In the study of 42 cases by Hansel *et al.*,[236] most (66%) tumours had prior diagnosis of adenocarcinoma (mean interval, 6.8 years). Few cases were also reported to develop after radiotherapy for conventional adenocarcinoma.[237] Most tumours at diagnosis have coexisting adenocarcinoma including unusual forms such as ductal, squamous, or small cell carcinoma.[236,238] **Most tumours present as locally advanced disease.** The tumour may lose expression of PSA and PSAP.[236,239] **Sarcomatoid carcinoma has a high risk for metastasis and worse outcome.**[236,238,239] The National Cancer Database (NCDB) reported metastatic disease in 33.3% and an estimated 10-year survival of only 14.6%.[49] A few examples of patients with localized disease survived 2 years after surgery and/or radiation with or without hormonal therapy.[238]

Pleomorphic giant cell carcinoma is an aggressive acinar adenocarcinoma subtype characterized by pleomorphic or anaplastic cells with single or multiple large bizarre-appearing nuclei (**FIGURE 22**).[240,241] Because of its poorly differentiated nature, expression of PSA is low, and the tumour cell can be negative for NKX3.1. Lotan *et al.*[242] recently showed that DNA damage repair gene (including *BRCA2*) alterations are frequent in this tumour. Admixed usual adenocarcinoma is common, and the grade is typically GS 9–10.[240] **Pleomorphic giant cell adenocarcinomas are typically high-stage tumours with a poor prognosis**.[240,241] In a series by Alharbi *et al.*[240] of 30 cases, 37% were dead of disease at a median of 8 months after diagnosis.

FIGURE 21 (A and B) Sarcomatoid adenocarcinoma showing high-grade spindle cells.

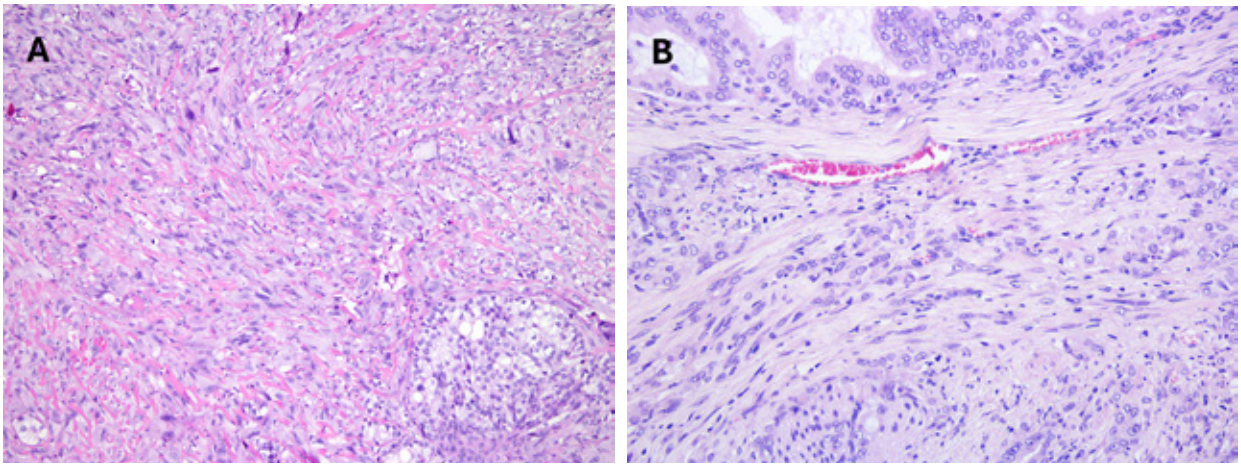
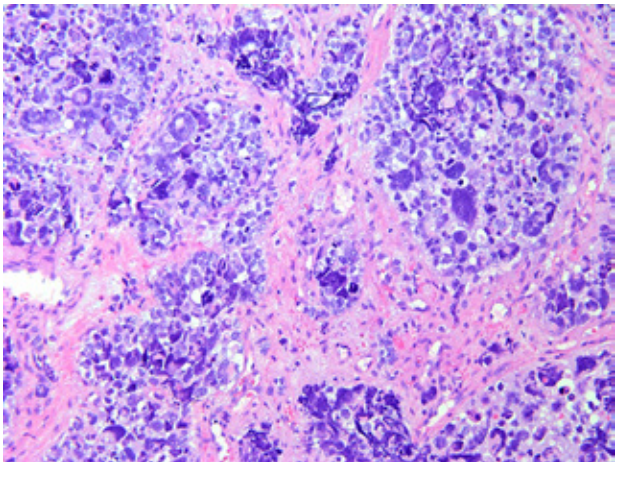


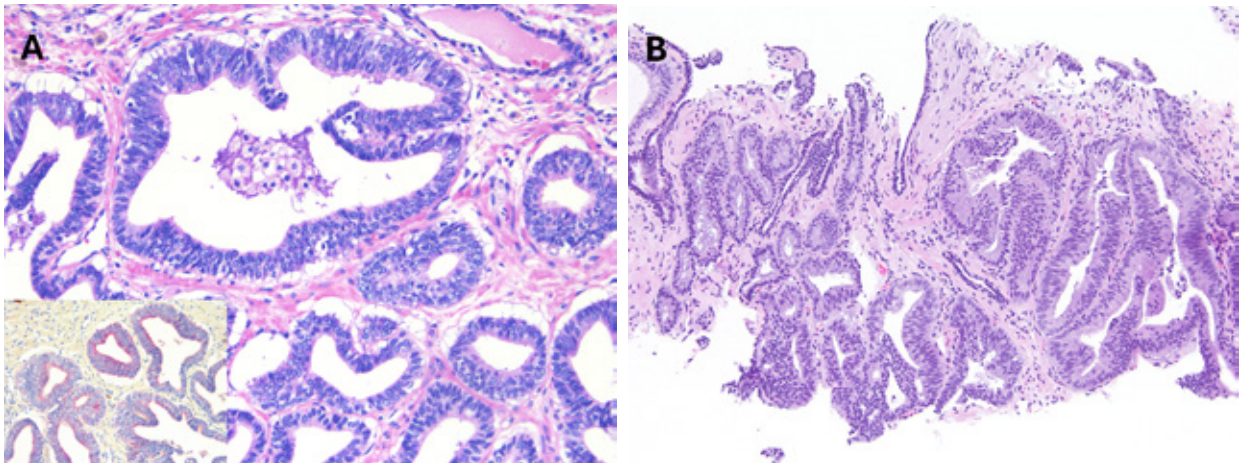
FIGURE 22 Pleomorphic giant cell adenocarcinoma.



PIN-like carcinoma is characterized by large, dilated glands lined by pseudostratified columnar cells and architecturally resembles flat, tufted, or micropapillary PIN (FIGURE 23).[243–245] Kaur *et al.*[246] described frequent activating RAS/RAF mutations in this tumour, a molecular profile different from ductal adenocarcinoma. Most tumours are associated with acinar adenocarcinoma, often seen as distinct from the PIN-like carcinoma focus. About 45% of tumours had the highest grade of GS 6. **Unlike other acinar carcinoma subtypes above, PIN-like carcinoma may not exhibit aggressive behaviour.** Only a few cases have been described in RP specimens, with 46.1% of tumours reported to have EPE, and the PIN-like carcinoma

component responsible in 83.3% of EPE.[243] The tumours are usually small in size and not in advanced stage, and show low rates of GS 7 or higher grades. It is suggested that classic PIN-like carcinoma should be graded as GP 3, and the micropapillary pattern should be graded as GP 4. However, the higher rate of EPE is incompatible for a GS 6 tumour.

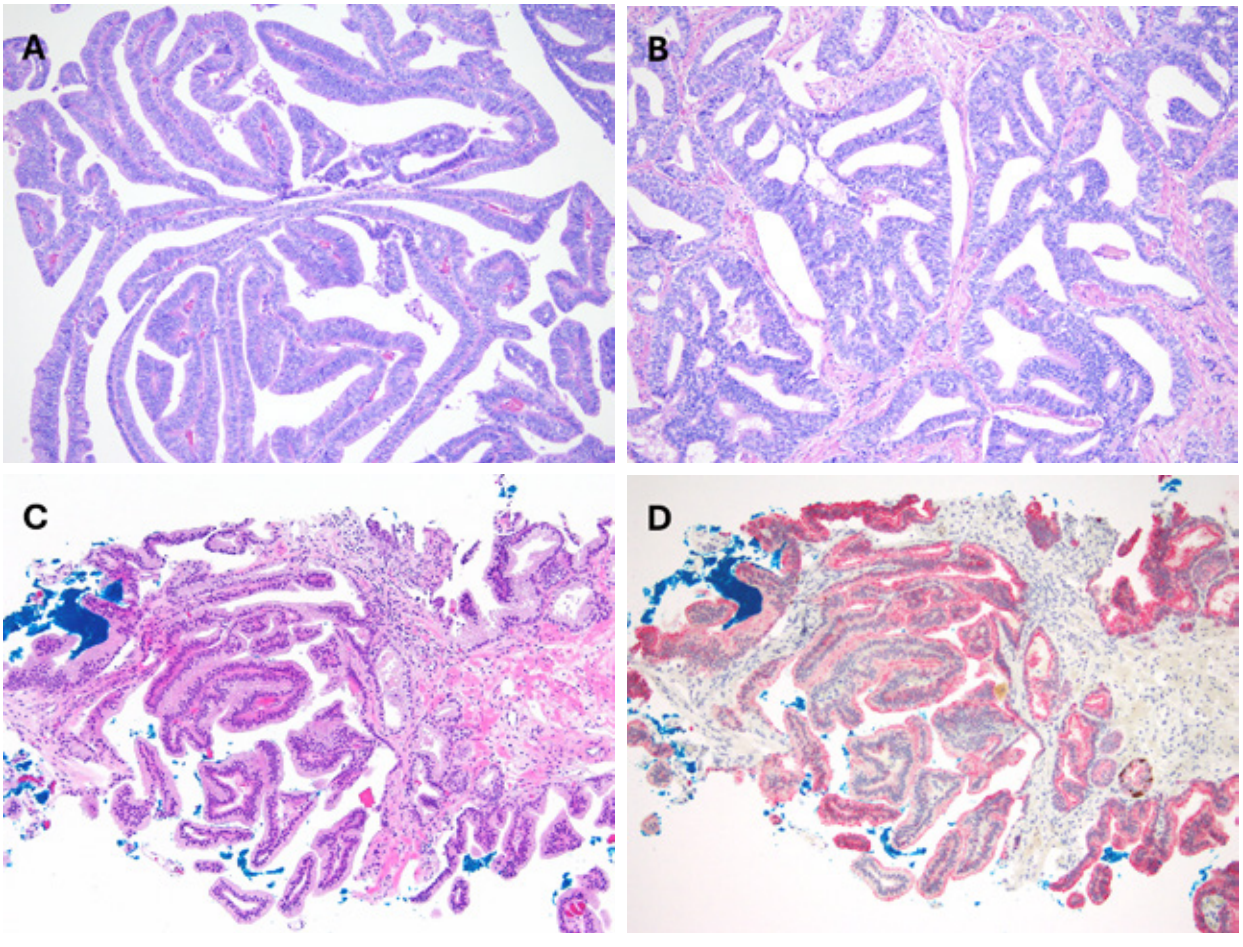
FIGURE 23 (A) PIN-like carcinoma confirmed by PIN4 immunostaining (inset). (B) Biopsy with PIN-like carcinoma.



Ductal Adenocarcinoma

Ductal adenocarcinoma (PDA) is a rare type of prostatic adenocarcinoma characterized by tall columnar pseudostratified cells, often with papillary or cribriform growth (**FIGURE 24**). PDA is reported in < 1% to 1.5% of prostatic adenocarcinomas.[49,50,247,248] However, the incidence of mixed form ranges from 5% to 12.7% if cutoff is lowered to 5%.[49,247,249,250] **PDA is associated with adverse pathologic features in RP and worse outcome.**[49,50,78,80,251] PDA is associated with higher stage, higher rates of PSM and EPE, higher risk for BCR or metastasis, and shorter survival compared to usual acinar adenocarcinoma.[78] Registry-based data shows that PDA has higher metastatic rates and worse CSS and OS than usual adenocarcinoma.[49,50,251] For localized prostate cancer, Packiam *et al.*[247] showed that the 5-year OS of PDA was similar to that of GS 8–10 adenocarcinoma and worse than GS 6–7 adenocarcinoma.[247] In needle biopsy, PDA is associated with adverse pathologic features in RP, including 63% with EPE, 20% with PSM, and with shortened time to progression compared to usual adenocarcinoma.[252] Overall, PDA treated with RP or radiotherapy has worse outcome than usual acinar adenocarcinoma.[249] **Thus, prostate cancer patients with PDA histology should be carefully considered for exclusion from AS.** Uncommonly, PDA presents centrally as urethral polyp emanating from ducts or the verumontanum, and a subset can be locally resected (e.g., TURP).[253,254]

FIGURE 24 Prostatic ductal adenocarcinoma with (A) papillary and (B) cribriform patterns. (C and D) Biopsy with ductal adenocarcinoma confirmed by PIN4 immunostaining.



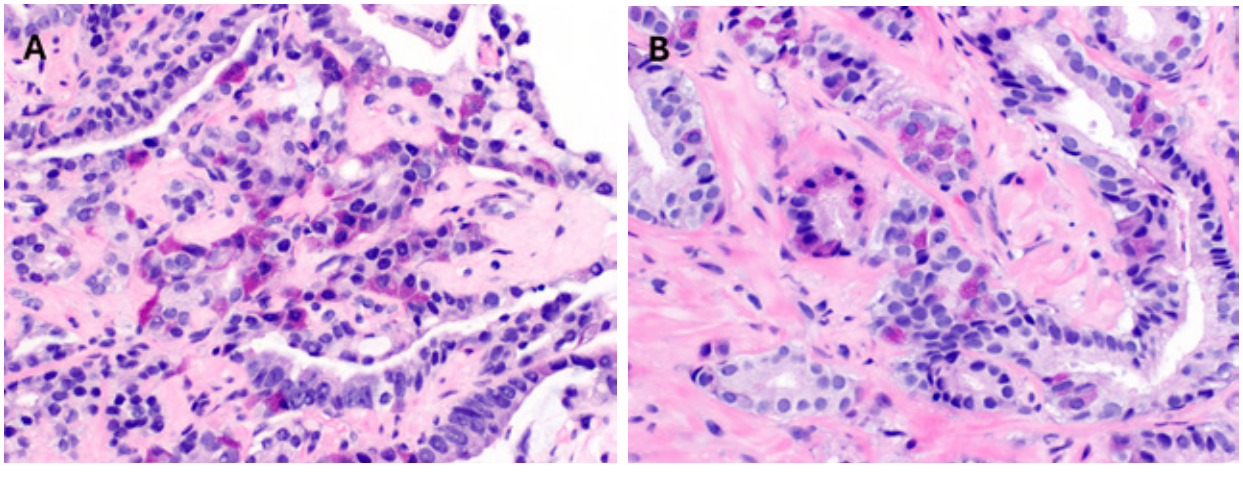
Diagnosis of "pure" PDA requires an arbitrary cutoff of > 50% in RP, and thus, diagnosis of PDA cannot be made in biopsy specimens.[21] **Presence of PDA in biopsy would merit a diagnosis of "adenocarcinoma with ductal features."** Samaratunga *et al.*[250] reported that the proportion of PDA component (5–100%) in RP did not significantly modify the observed association of PDA with EPE. Jang *et al.*[255] in a study of 101 RP with PDA showed that when the PDAs were stratified by % ductal component, freedom from BCR in the high (≥ 30%) ductal component was significantly lower compared to that in the low (< 30%) ductal component.

Other Carcinoma Types

Uncommon non-adenocarcinomas such as neuroendocrine carcinomas and carcinomas with squamous differentiation may arise uncommonly from the prostate, some after treatment. A subset of neuroendocrine carcinomas develops after androgen deprivation therapy (ADT) that can be pure (mostly small cell carcinoma) or mixed with high-grade adenocarcinoma, and is now termed treatment-related neuroendocrine prostate cancer in the most recent WHO classification.[21,45,256–258] Carcinomas with squamous features include adenosquamous carcinoma, squamous cell carcinoma, and adenoid cystic (basal cell) carcinoma.[21,259–264] **High-grade neuroendocrine carcinomas and carcinomas with squamous features often present with locally advanced or metastatic disease and are clinically aggressive.**

Adenocarcinoma with coarse neuroendocrine granules (so-called Paneth cell–like neuroendocrine differentiation) has a favourable behaviour in contrast to aggressive small-cell/high-grade neuroendocrine carcinomas (FIGURE 25).[265–268] Park *et al.*[269] detected aurora kinase A (AURKA) gene amplification in 45% of localized adenocarcinomas with Paneth cell-like neuroendocrine differentiation. *AURKA* amplification has been documented in 67% of hormone-naïve prostate cancers that progress to aggressive CRPC. This tumour may show single cells, cords, or nests akin to GP 5; however, only a minority of these tumours shows association with higher-grade adenocarcinoma and progression after treatment. In the study by Salles *et al.*[265] of 80 cases, 9 patients underwent RP and 6 had organ-confined disease (pT2).

FIGURE 25 (A and B) Adenocarcinoma with Paneth cell–like neuroendocrine differentiation.

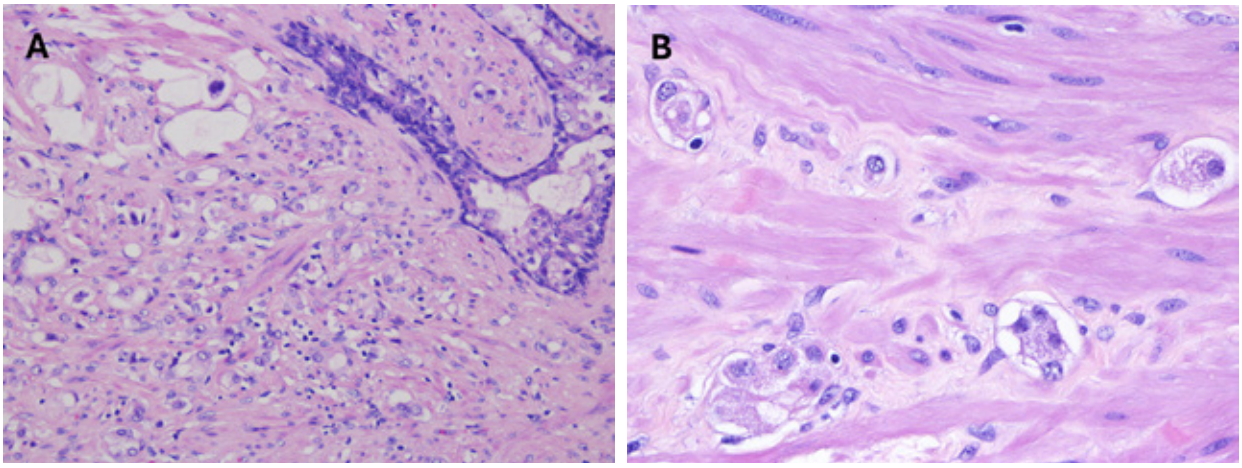


Treatment-Related Effects

Radiotherapy effects

Radiation therapy (RT), such as by external beam delivery or brachytherapy seed implant, is one of the management options for localized prostate cancer. **Radiotherapy can cause alterations in cancer morphology that vary from minimal to marked changes.**[207–209] Follow-up post-treatment biopsy is usually performed at least 2 years after radiotherapy because of the delayed clearance of treated cancer cells that may cause a false-positive interpretation.[270,271] Cancer cells with propound treatment effects will show infiltrative spaced-out or haphazard distorted glands, irregular clusters, or single cells. The tumour cells have vacuolated foamy cytoplasm and nuclei that vary from pyknotic with smudged chromatin to enlarged to bizarre nuclei with prominent nucleoli (**FIGURE 26**). **Carcinoma with radiation treatment effects should not be graded.** Crook *et al.* [271] showed that in biopsies 24 to 30 months after RT, patients with residual tumour cells with severe treatment effects had similar disease-free survival (DFS) as patients who had negative biopsies.

FIGURE 26 (A and B) Adenocarcinoma with radiation treatment effects.



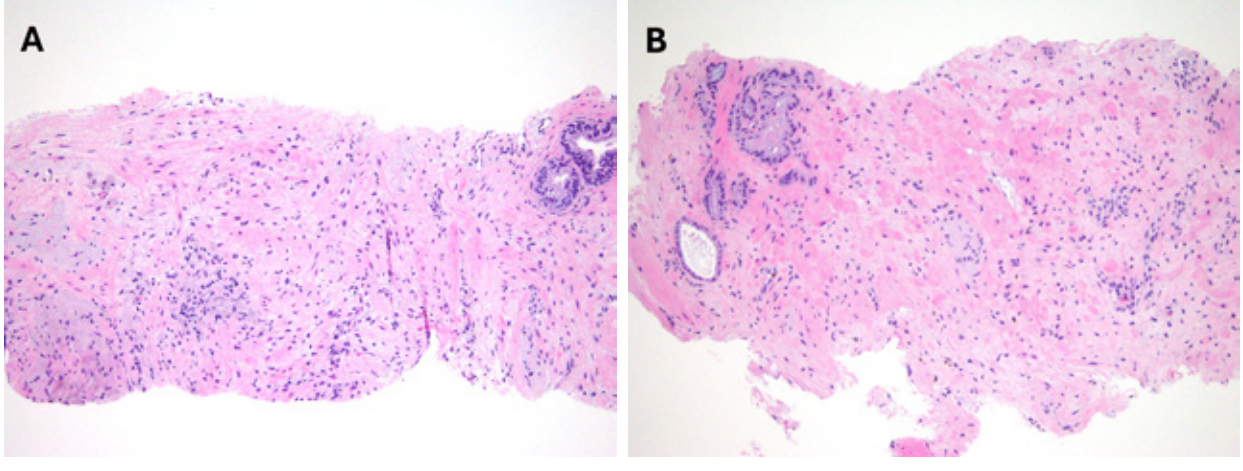
Treatment effects may also be minimal or absent in cancer after RT. Especially in the setting of rising levels of PSA, this may represent a recurrence or new onset (*de novo*) cancer after RT. **GS can be rendered to cancer with absent or minimal treatment effects in the post-RT biopsy setting.**

Ablation treatment effects

Ablative treatment such as high-intensity focused ultrasound (HIFU) and cryotherapy are increasingly used as focal therapies for localized prostate cancer. HIFU delivers ultrasound waves to a target that heats (> 60°C) and causes damage to the prostate tissue.[208] Early changes in HIFU-treated prostate cancer include coagulative

necrosis and inflammation that evolves to reactive fibroblasts, stromal fibrosis, and hemosiderin with time (**FIGURE 27**).[207–209,272–275] Follow-up biopsies taken > 1 year after HIFU will show fibrosis and hemosiderin at the targeted area. The HIFU lesion is typically well demarcated and residual cancer outside the target area will not show significant morphologic alteration. In contrast to HIFU, cryotherapy or cryoablation introduces cold gases for controlled freezing or ice ball formation (-40 °C) at the target area.[207–209] Cryotherapy causes tissue damage similar to other ablative procedures that is characterized by edema, necrosis, and hemorrhage that will evolve to fibrosis, hyalinization, and hemosiderin deposition. Like in HIFU, residual cancer outside of the targeted and damaged area will not show significant morphologic changes. **Grade can be rendered to cancer present after ablative therapies such as HIFU and cryotherapy.**

FIGURE 27 (A) Prostate showing HIFU treatment effects. (B) Residual cancer adjacent to HIFU-treated area.



Abbreviation: HIFU, high-intensity focused ultrasound.

Hormonal treatment effects

ADT monotherapy is usually not recommended for localized prostate cancer unless for palliation of local disease–related symptoms or for poorly differentiated cancer.[1,2] ADT is usually given with RT in localized prostate cancer, and treatment effects overlap with the histologic findings after RT. [207–209] **Similar in RT, prostate cancer with profound hormonal treatment effects should not be graded.**

Tumour Volume/Extent

Tumour volume/extent in biopsy

Measuring tumour volume/extent in biopsy

Tumour quantitation in biopsy has been performed traditionally by reporting the number of positive core(s) and percentage of core involvement by tumour. Inclusion of number of positive cores enhances the predictive accuracy of preoperative nomograms.[10] Furthermore, overall percentage or the greatest percentage in the most involved core is an independent predictor of PSA and clinical outcomes regardless of treatment, with the percentage deemed superior to counting the number of positive cores.[276] **There are several ways of measuring tumour extent in a biopsy set; however, the optimal method remains unclear** (**TABLE 12**). Recently, Berney *et al.*[277] measured cancer extent in 981 men with clinically localized prostate cancers managed conservatively using different approaches—number of positive cores, maximum cancer length in a core, total cancer length, and percentage of positive cores. The study revealed that while all measures showed significant association with prostate cancer death in univariate models, only percentage of positive cores was independently a significant predictor of outcome, with a 10% increase resulting in a hazard ratio of 1.07. Russo *et al.*[278] showed that for patients eligible for AS, the maximum tumour length (longest length of continuous cancer without gap of benign tissue in biopsy) and percentage of cancer involvement in positive cores (CIPC; total cancer length in mm/total cores' length in mm) are independent predictors of unfavourable prostate cancer. Patients who had CIPC ≥ 0.4 mm had significantly lower BCR-free survival. Morselli *et al.*[279] showed that cumulative cancer length (CCL) of > 6 mm and positive core numbers > 3 are associated with adverse pathology in RP for low-risk and favourable intermediate-risk patients.

Measuring discontinuous tumour foci in biopsy

Tumour involvement in a biopsy core can be continuous or discontinuous with intervening benign tissue segments. Discontinuous tumour can be measured either by collapsing the multiple tumour foci and ignoring the benign interfocal segments or by measuring the entire length of tumour foci together with the interfocal benign segments from one end to the other end (end-to-end).[280] Thus, in an extreme example, two small tumour foci involving the ends of a core can be reported as 10% (subtract interfocal benign) or 100% (include interfocal benign) core involvement (**FIGURE 28**). **Several studies showed that measuring discontinuous tumour end-to-end is superior to aggregating the tumour segments and skipping the benign parts.** End-to-end measurement correlates better with tumour extent in RP, organ-confined disease, predominant GS 7 in cores, and risk for margin positivity.[281–285] Furthermore, the study by Arias-Stella *et al.*[282] showed that discontinuous tumours in prostate biopsy corresponded to a single tumour nodule on the corresponding region of the prostate in 78% of cases. Although this study stresses the advantage of end-to-end measurement, it also means that in 22% of cases there is potential overestimation of tumour length.

TABLE 12 Different Methods of Measuring the Extent of Tumour Involvement in Biopsy. Bolded Items Are Measurements That Are Currently Recommended in Practice

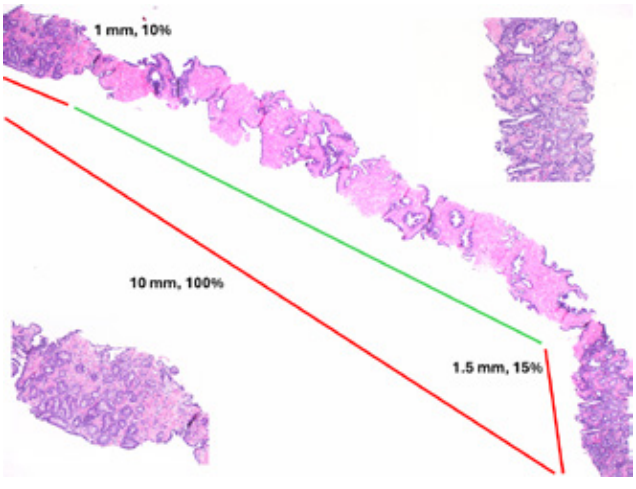
Measurements	ICCR datasets		CAP cancer protocols	
	Recorded	**Status**	**Recorded**	**Status**
Number of positive core(s)	Yes, specimen and case level	Core*	Yes, specimen and case level	Core
Percentage of cancer in a core	Yes, specimen level	Core	Yes, specimen level	Core
Length of cancer in a core	Yes, specimen level	Core	Yes, specimen level	Optional
Greatest percentage of cancer in cores	Yes, case level	Core	Yes, case level	Core
Greatest length of cancer in any core	Yes, case level	Core	Yes, case level	Optional
Total length of cancer (cumulative cancer length [CCL])	No	-	Yes, case level	Optional
Total percentage of prostatic tissue involved by cancer	No	-	Yes, case level	Optional
Percentage of positive cores	No	Can be derived	No	Can be derived
Percentage of cancer involvement in positive cores (CIPC)	No	-	No	-
Discontinuous tumour foci in a core, end-to-end measurement	No	Allowed to use, but not recorded	Yes, specimen and case level	Optional
Discontinuous tumour foci in a core, measurement with skipping benign glands	No	Allowed to use, but not recorded	Yes, specimen and case level	Optional
Discontinuous foci in a core, maximum tumour length of a focus (only the largest focus is measured)	No	-	No	-

*Core is required to be reported.

Tumour volume in biopsy of low-risk patients

Several studies assessed the significance of tumour volume in biopsy of AS cohort.[286–289] Vellekoop *et al.*[286] in a study of 2,205 men with GS 6, cT1/T2 from the National Prostate Cancer Register of Sweden, determined that older age, high PSA, PSA density > 0.15 ng/mL/cm^3, palpable disease, and extent of cancer > 4 mm cancer to be predictors of adverse pathology in RP. Tosoian *et al.*[288] showed that low-risk men in AS had fewer positive cores and lower maximum percent of core involvement compared to low-risk patients who underwent RP. Cooley *et al.*[289] showed that AS patients with high-volume GG 1 had a shorter interval to conversion than those with low-volume GG1 tumours. **Reporting of tumour volume or extent in biopsy should remain integral for monitoring of patients on AS.**

FIGURE 28 Biopsy with discontinuous foci of cancer. Discontinuous cancer can be measured as 100% involvement or as 25% (10% + 15%) involvement of the core.



Tumour volume/extent in radical prostatectomy

The significance of prostate cancer volume in RP has been the subject of debate.[290,291] **Data is conflicting on the significance of tumour volume in RP on predicting outcome.** [290–303] Some studies including more contemporary investigations showed that tumour volume, including the size of index tumour, is an independent predictor of BCR, metastasis, or prostate-specific mortality.[292–297] Ettel *et al.*[295] showed that when dichotomizing 785 organ-confined tumours (pT2) into ≤ 25% and > 25% volume, > 25% was independently predictive of BCRFS. However, other studies failed to show the prognostic significance of tumour volume once other factors were considered.[300–303] Recently, Ito *et al.*[300] investigated total tumour volume (TTV) and/or maximum tumour diameter (MTD) of the index lesion in organ-confined tumours (pT2). Both TTV and MTD of the index lesion were not independently predictive of BCR in a model that incorporated age, preoperative PSA, RP GG, and surgical margin status. Several methods have been described for measuring tumour volume in RP that include nonpractical and simple approaches.[291] **ISUP recommended that at the minimum, some form of quantitative measurement for tumour volume in RP should be undertaken without prescribing a specific method.**[291]

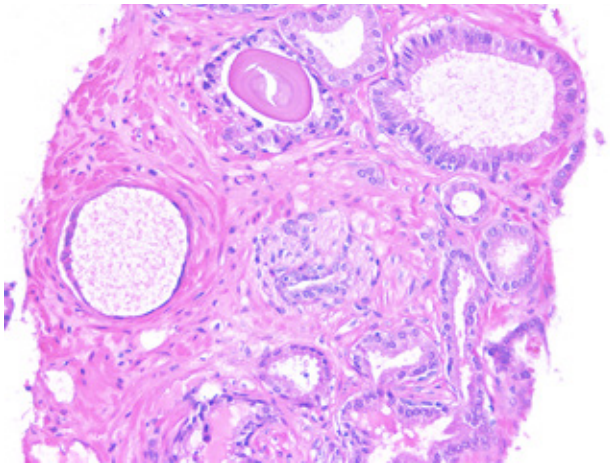
Perineural Invasion

Perineural invasion in biopsy

Prognosis of biopsy with perineural invasion

Perineural invasion (PNI) is defined as cancer tracking or wrapping a nerve (**FIGURE 29**). PNI is reported in 10% to 34% of biopsies of clinically localized prostate cancer.[304–306] **Data has been conflicting on PNI in biopsies as an independent prognosticator, although more recent studies tend to support its importance.**[304–309] A recent systematic review and meta-analysis by Wu *et al.*[310] concluded that biopsy PNI is correlated with adverse pathology in RP and worse BCR prognosis after RP. Another recent systematic review and meta-analysis by Zhang *et al.*[311] concluded that PNI is associated with higher risk for BCR following RP or RT, although the study included PNI in both biopsy and RP. The study by DeLancey *et al.*[305] in 3,226 patients with clinically localized prostate cancer showed that PNI in biopsy was independently associated with adverse features in RP, DFS, and OS. Feng *et al.*[306] showed that presence of PNI in biopsy of clinically localized prostate cancer was independently associated with worse clinical outcome after dose-escalated external-beam radiation therapy. PNI in biopsy was shown to be predictive of bone metastasis after adjusting for other clinicopathological factors.[309,312] The study by Ahmad *et al.*[304] of clinically localized prostate cancer patients from UK cancer registries showed PNI losing its significance as a predictor for BCR once GS, PSA, clinical stage, and extent of disease were considered. Researchers from the University of Rochester Medical Center conducted a series of studies using multiple PNI features in biopsies, including multifocality and bilaterality of PNI, as predictors of poorer outcome after RP.[313–317]

FIGURE 29 Perineural invasion and GS 6 prostate cancer.



Abbreviation: GS, Gleason score.

Perineural invasion in active surveillance

The incidence of PNI at baseline biopsy of patients undergoing AS is low at 2.2% to 7.4%.[318–321] Several studies have investigated the role of PNI in stratifying prostate cancer risk at initiation and during AS. Moreira *et al.*[319] reviewed 302 men on AS for low-risk prostate cancer from the REEDEM study and showed that PNI in baseline biopsy was associated with increased risk for clinical progression. The study by Turner *et al.*[320] in 596 men who met strict criteria for AS and underwent RP showed that PNI in biopsy was associated with adverse pathology in RP. Interestingly, Baraban *et al.*[322] studied AS patients who were reclassified to GS 3+4 and underwent RP and found out that low PSA and absence of PNI had the lowest risk for adverse pathology in RP comparable to GS 6 patients who were not reclassified to GS 3+4 preoperatively. **There is a potential role of biopsy PNI in stratifying risk and monitoring patients under AS, including patients reclassified to intermediate risk (GS 3+4).**

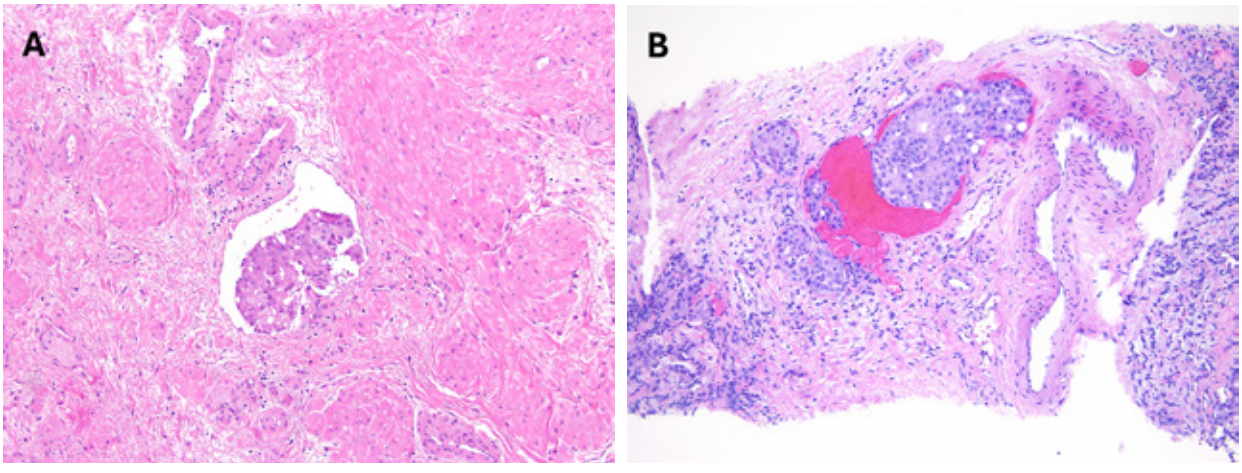
Perineural invasion in radical prostatectomy

The incidence of PNI in RP is higher than in biopsy, reported at 30.5% to 73.5%, attributed to the larger surface area, making PNI almost ubiquitous in RP, especially with larger tumours in the specimens.[323] **Studies on PNI in RP are conflicting, although more studies are against PNI as an independent predictor of BCR.**[324–330] The study by Kraus *et al.*[326] on 1,549 men with organ-confined prostate cancer identified PNI in 60.4% and showed that PNI was not an independent predictor of BCR. The study by Wu *et al.*[325] on 721 men with localized prostate cancer showed PNI was associated with poor BCR prognosis in univariate analysis but this association was lost in multivariate analysis. Interestingly, when PNI was quantified, > 3 PNI or > 1 PNI in 5 high-power fields was identified as an independent BCR prognostic factor, somewhat corroborating the prognostic value of quantifying PNI in biopsy studies.[313–315,331]

Lymphovascular Invasion

LVI is defined as tumour cells confined within an endothelial-lined space devoid of muscular wall (**FIGURE 30**). LVI is reported in 8% of RP cases regardless of stage.[332] **Several studies have shown LVI in RP to be an independent predictor of worse outcome.**[333] In a systematic review and meta-analysis by Jiang *et al.*,[334] LVI was associated with higher BCR in multivariate analysis and closely correlated with EPE, GS ≥ 7, LNI, higher pathologic stage (≥T3), PSM, and SVI. **However, in localized prostate cancer (pT2), LVI in RP has been inconsistent as an independent predictor.** When only pT2 tumours were assessed, some studies did not show LVI as an independent predictor of BCR or OS.[332,335,336] LVI is a rare finding in needle biopsies, with no data available on its significance.

FIGURE 30 Lymphovascular invasion in (A) RP and (B) biopsy.



Abbreviation: RP, radical prostatectomy.

Pertinent Benign Findings in Biopsy With Cancer

Serum PSA level is important in the detection, risk stratification, and management of prostate cancer. PSA can be elevated by inflammation, especially in acute prostatitis,[337] and in some patients may remain elevated for a longer period of time.[338] Nonspecific granulomatous prostatitis, which is of unknown etiology, can also cause marked elevation in PSA.[339] A study on a Finnish population with elevated PSA (≥ 4 ng/mL) and benign prostate biopsy found histologic inflammation in 66% of biopsies.[340] Unlike in acute prostatitis, the effect of chronic inflammation on serum PSA level is not well established.[337] Since serum PSA level is used in risk stratification and management, presence of histologic inflammation concomitant with cancer in biopsy should be documented.

False-positive high PI-RADS lesions in multiparametric magnetic resonance imaging (mpMRI)/TRUS prostate biopsies were reported to be as high as 23%.[341] Sheridan *et al.*[342] showed that for PI-RADS 5 lesions, the histology of subsequent biopsies revealed 71% clinically significant prostate cancer, 10% GS 6 cancer, and 18% benign findings. Common histologic findings in false-positive PI-RADS lesions include hyperplastic stromal and/or epithelial changes and inflammation.[341–344] **ISUP recommends that benign histologic findings in targeted biopsies of high-suspicion lesions (PI-RADS 4–5) that are negative for cancer should be reported.**[17]

Margin Status in Radical Prostatectomy

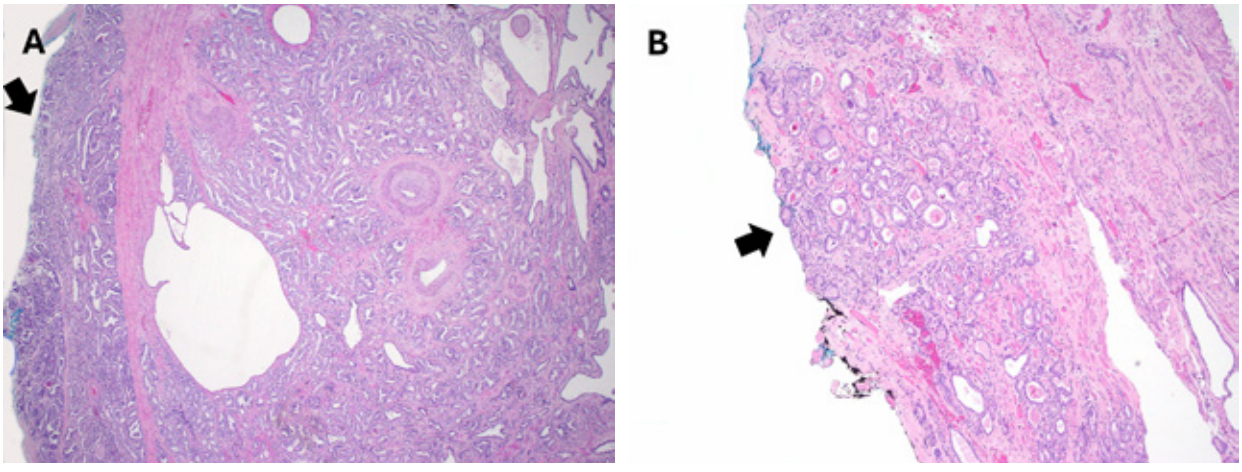
Length of positive margin

A PSM is defined as tumour cells reaching the inked surface margin or unequivocally when a tumour gland or pattern is transected at the inked surface margin. A PSM can be intraprostatic ("capsular incision") or extraprostatic when a tumour is transected at the area of EPE. Intraprostatic PSM can occur in organ-confined (pT2) tumours. **PSM at RP is associated with poorer BRFS, CSS, OS, CSM, and overall mortality (OM).**[345–347] Zhang *et al.*[345] showed that whether patients had pT2 (organ confined) or pT3 pathologic stage, PSM was associated with higher CSM, with CSM higher in pT3 than pT2 disease. **The length of PSM is independently prognostic of prostate cancer outcome after RP.** The impact of the length of PSM has recently been addressed by John *et al.*[348] in a systematic review and meta-analysis showing that PSM length is independently prognostic for BCR after RP. Servoll *et al.*[349] addressed the impact of PSM length in clinically localized cancer and showed that PSM length of > 3 mm was an independent predictor of clinical failure after RP. The study by Kozal *et al.*[350] in 742 localized prostate cancers, showed that > 3 mm PSM, GS, and LVI were independently predictive of BCR-free survival.

Grade at positive margin

Several studies have shown that higher GS at PSM is associated with increased risk for BCR, progression, or death from prostate cancer (**FIGURE 31**).[351–357] In a systematic review and meta-analysis by John *et al.*[352], GS > 6 at PSM was predictive of BCR compared to GS 6, with an increasing hazard ratio for GS: GS 3+4 (HR, 2.35), GS 4+3 (HR, 3.95), GS 8 (HR, 7.17), and GS 9–10 (HR, 12.37). In a study by Viers *et al.*[354] among GS 7 prostate cancers, GP 4 at PSM was independently associated with increased risks for systemic progression and death from prostate cancer among men with PSM (including GP 3 at PSM). Savdie *et al.*[355] compared GS 6 at PSM with a negative surgical margin and found a comparable 5-year BCR-free rate. Hollemans *et al.*[356] compared the impact of length, GS, and cribriform pattern at PSM and found that cumulative length, GS at PSM, and lymph node metastasis were independent predictors of BCRFS. Although important for prognostication, the clinical actionability of these PSM subclassifications is currently minimal.

FIGURE 31 Positive surgical margins (arrow) with (A) GP 4 and (B) GP 3 present at margins.



Abbreviation: GP; Gleason pattern.

pT Stage Categories of Localized Prostate Cancer

Both the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM staging system for prostate cancer no longer subcategorize the pT2 category.[169,358,359] pT2 was previously subcategorized by bilaterality and extent of involvement into pT2a, pT2b, and pT2c. There is peculiarity in the previous pT2 subcategories in that pT2b is extremely rare and small bilateral tumours can be overstaged as pT2c. Two large institutional reviews of pT2 prostate cancer that included > 15,500 patients yielded only < 1% of the RP stage as pT2b.[360,361] Furthermore, there are no reports of a definite correlation between previous pT2 subcategories and the outcome of localized prostate cancer. Several recent validation studies confirmed the lack of predictive value of pT2 subcategorization in terms of BCR, metastasis, cancer-specific death, or overall mortality after RP.[360–362] **Studies on subcategorizing pT2 based on tumour volume are showing conflicting results.**[295,300] However, the 3-tiered T2 categorization is retained in the clinical T (cT) categories, as these cT groupings are important in risk stratification and management of localized prostate cancer.

Reporting Guidelines of Pathological Factors for Prostate Cancer

Standardized prostate cancer reporting checklists are available for use by pathologists. These cancer checklists use standardized terminologies and ensure completeness of the pathology reports. The reporting checklists, which are in synoptic format, have virtually replaced the narrative format of cancer reporting, which can be subjectively written. These reporting tools are dynamic documents, regularly updated by experts based on latest evidence, new tumour classifications, staging revisions, and emerging clinical needs. The cancer checklists, such as those developed by ICCR, CAP, and the Royal Colleges in the United Kingdom and Australasia, are evidence based, developed by experts, and aligned with latest tumour classifications, staging standards, and reporting recommendations from specialty societies.[363–365] The ICCR and CAP prostate cancer checklists include templates for biopsy, RP, and TURP. The prostate cancer biopsy templates are divided into "case-level" and "specimen-level" reporting; the former summarizes the pathological factors into a single report and the latter reports the pathological factors for every positive specimen separately in a biopsy set. The "case-level" report has the advantage of integrating the necessary data into a single synoptic structure and reducing the amount of repetitive granular data reported for each positive site. The elements are considered as "core" or "non-core," with the former considered as essential elements for clinical use. CAP has released an electronic version of the protocol called electronic cancer checklist (eCC) now used by an estimated 35% to 40% of practicing anatomic pathologists in the United States and Canada.[364] **Harmonization of urological guidelines and pathology reporting checklists for prostate cancer is of utmost importance.** This will help ensure that pathological factors included in urological guidelines are being diagnosed with accuracy and reported with consistency by pathologists.[366]

Clinicians' Use of Prostate Cancer Pathological Factors

Two surveys had recently investigated clinicians' practice patterns on the use of pathological factors on prostate cancer for their clinical decisions.[117,367] One was conducted by GUPS with 834 respondents from members of multiple urology and urologic oncology–focused societies and hospital departments,[367] and the other from the UK with 114 respondents from members of the British Association of Urological Surgeons and the British Uro-oncology Group (**TABLES 13** and **14**).[117]. **Results from these surveys show some agreement in line with current pathologists' recommendations, as well as discrepancies and variabilities in the clinical applications of pathologic factors in prostate cancer.** With the evolving practice recommendations, these surveys highlight the areas for communication between pathologists and clinicians and for future research.

TABLE 13 Results of GUPS Clinicians Survey on Practice Patterns Related to Prostate Cancer Grading[367]

Questions	Responses (*N=834*)
1. Do you EVER utilize the quantity of pattern 4 on NB in clinical decision making?	Yes: 80%
	No: 20%
2. In NB with highest grade group 3 prostate cancer, would it be valuable to know the quantity of pattern 4 (e.g., 60% vs. 90% pattern 4)?	Yes: 62%
	No: 38%
3. One NB has grade group 3 involving 10% of a core; 3 other cores show grade group 2. Is it valuable to know if the 3 cores had 10% vs. 40% pattern 4?	Yes: 51%
	No: 49%
4. One NB has grade group 4 involving 10% of a core; 3 other cores show grade group 3. Is it valuable to know if the 3 cores had 60% vs. 90% pattern 4?	Yes: 30%
	No: 70%
5. Would it be valuable to know the % pattern 4 for GS 7 (grade group 2–3) on RP?	Yes: 53%
	No: 47%
6. In RP specimens with GS 7 (grade groups 2–3) and a reported "tertiary" Gleason pattern 5. Do you assume that the "tertiary" pattern is minor (< 5%) or could be any amount (as long as third most common)?	Minor: 52%
	Any: 48%
7. In RP specimens with GS 7 (grade groups 2–3), does a minor (< 5%) component of Gleason pattern 5 affect further therapy?	Yes: 43%
	No: 57%
8. For cases with GS 7 (grade groups 2–3), would knowing if the pattern 4 component was cribriform vs. not cribriform affect patient counselling or management?	Yes: 44%
	No: 56%
9. If you would consider AS in men with GS 3+4=7 (grade group 2) who have over 10-year life expectancy, does whether the pattern 4 component is cribriform vs. not cribriform impact the decision?	Yes: 63%
	No: 37%
10. Would you recommend AS for a man with cancer who is otherwise a candidate in their NB and also shows intraductal carcinoma?	Yes: 29%
	No: 71%
11. If a biopsy shows GS 6 and intraductal carcinoma, do you routinely perform repeat biopsy to look for higher-grade cancer?	Yes: 35%
	No: 65%
12. If a biopsy report indicates that there is intraductal carcinoma in addition to invasive cancer with GS 7–10 (grade groups 2–5), would it affect therapy selection?	Yes: 31%
	No: 69%

Abbreviations: AS, active surveillance; GS, Gleason score; NB, needle biopsy; RP, radical prostatectomy.

TABLE 14 Results of the 2018 UK Survey Responses from Surgeons and Oncologists[117]

Question	Responses (*N=114*)
1. Which tumour extent parameter do you use?	
Number (+) cores	94%
Number (+) cores each side	42%
% number of cores	94%
mm linear extent	60%
% linear extent	84%
2. Which mm linear extent do you use?	
Don't use	40%
mm in each core	22%
Maximum mm in a core	47%
Aggregate mm	15%
3. Which % linear extent do you use?	
Don't use	26%
% each core	26%
Maximum % in a core	31%
Aggregate %	41%
Other	2%
4. MRI/biopsy tumour extent disparity; which would you rely on?	
MRI	26%
Pathology	50%
Depends	5%
Worst	5%
Other	14%
5. 2/10 standard and 3/3 targeted cores positive: how do you interpret tumour extent?	
5 cores positive	71%
3 sites positive	14%
2 standard and 3 targeted	10%
Other	6%
6. Multiple Gleason score (GS) in report: which score would you use?	
Highest GS	78%
Global GS	12%
GS in most involved core	10%
7. How often do you use perineural invasion for patient management?	
Never	28%
< 5% cases	27%
5–50% cases	24%
> 50 cases	20%

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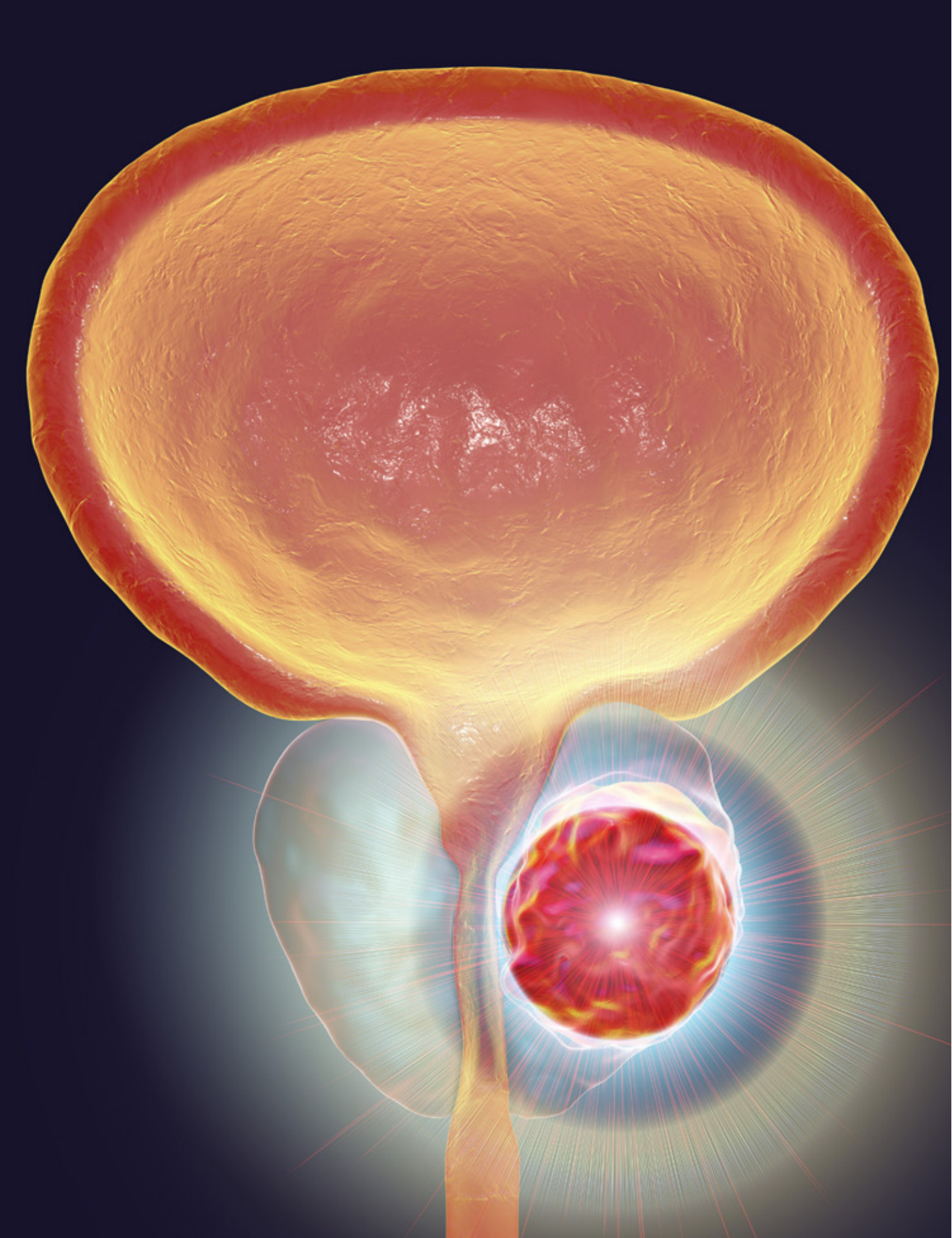

COMMITTEE 3

Screening and Early Detection of Prostate Cancer

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Table of Contents

Introduction

Screening for prostate cancer has been a controversial issue since serum prostate-specific antigen (PSA) was proposed as a screening test in 1987.[1] This chapter explains some basic concepts and summarizes the evidence for the relevant diagnostic methods, the results from completed screening trials, the design and preliminary results of ongoing screening trials, considerations about how men should be informed about the option of early detection and screening, prostate cancer screening policies around the world, and some future perspectives.

With few exceptions, national healthcare authorities do not recommend population-based screening for prostate cancer. The most recent assessment was done by the German Institute for Quality and Efficiency in Health Care, which concluded that the benefits from screening with PSA testing, together with a systemic prostate biopsy for diagnosis, do not outweigh the harms on a population level.[2] Despite absence of official recommendations for screening, unorganized PSA testing is common in many countries. This, together with improved diagnostic methods, in 2022 led the European Union to recommend the member states to evaluate the feasibility and effectiveness of prostate cancer screening programs.[3]

There is level-1 evidence that organized screening programs for prostate cancer can reduce prostate cancer mortality.[4–6] In contrast, the evidence that unorganized PSA testing and early detection campaigns reduce prostate cancer mortality is weak, although ecological studies in Europe and the United States have found lower prostate cancer mortality in regions with widespread PSA testing.[7,8] Other studies have shown that unorganized PSA testing,[9] as well as an invitation for single PSA test, results in substantial overdiagnosis but no significant reduction of men's risk of dying from prostate cancer.[10] Because of the poor evidence for the effectiveness of unorganized screening for prostate cancer, this chapter mainly describes the methods and results of organized screening.

Definitions and Concepts

Definitions of screening and early detection

In this chapter, the term "screening" refers to organized programs targeting a specific population. The World Health Organisation (WHO) defines screening as "the use of simple tests across a healthy population to identify those individuals who have a disease, but do not yet have symptoms." A key aspect of WHO's definition is that screening is an intervention that is offered to a population, i.e., to a specific group of people rather than to individuals. A diagnostic test offered an individual because of, for instance, worries for having cancer is not screening according to WHO's definition.

The decision to implement a screening program is typically made by a healthcare authority on a national level. The WHO considers cancer screening justified if (i) the target disease is common and serious, (ii) a test is available

that can detect in an early stage with sufficient sensitivity and specificity, (iii) if screening has been shown to reduce morbidity and/or mortality with acceptable cost-effectiveness and balance of benefits and harms, and (iv) screening is feasible and regarded as a priority.[11]

According to the WHO, to reduce cancer mortality and to be cost-effective, cancer screening must be delivered as an organized program with a defined diagnostic pathway that leads to effective treatment of those individuals diagnosed with cancer. The WHO stresses that implementation of a cancer screening program is a complex task that requires strong leadership and coordination. Before initiating the process, policy makers must ensure that all steps of the pathway can be provided with high quality.

The term "early detection" in this chapter is used to describe measures aimed at diagnosing prostate cancer before it becomes incurable. Early detection may be initiated by an individual or by a healthcare provider, and be promoted by various people, groups, and organizations. Because prostate cancer is usually incurable when the disease causes symptoms, early detection of prostate cancer equals diagnosing cancer in asymptomatic men and men with nonspecific lower urinary tract symptoms.

Although transwomen may develop prostate cancer, we use the word "men" for brevity throughout this chapter.

Aims of early detection and screening programs

The aims of early detection and screening programs for cancer are to reduce morbidity and cancer-specific mortality in individuals and in the population, respectively. It is important to realize that the aim is not to diagnose as many curable cancers as possible. One reason for this is that merely diagnosing curable cancer does not in itself lead to reduced morbidity and mortality—for these ends, effective treatment with acceptable side effects is necessary. Another reason is that diagnosing cancer in asymptomatic individuals is inherently linked to overdiagnosis. Diagnosing more curable cancers does therefore not necessarily mean that the men diagnosed with those cancers live longer or that fewer advanced cancers are diagnosed; the extra curable cancers diagnosed after PSA testing may represent overdiagnosis (see below).

In individual-based early detection, the man's personal preferences may affect the diagnostic intensity. For example, a man with family members or friends who suffered and died from prostate cancer may be willing to accept overdiagnosis but not even a small risk of missing a clinically relevant cancer. Some important differences between early detection initiatives and screening programs are summarized in **TABLE 1**.

Because of the poor evidence for the effectiveness of unorganized screening for prostate cancer, this chapter mainly describes the methods and results of organized screening.

Population perspective versus individual perspective

Healthcare authorities' primary concern is the health of the population. They need to know the effects on a population level when deciding whether to implement a new screening program. This perspective is reflected by analyzing the results of screening trials according to "intention-to-screen," i.e., the effects of screening in a group invited to screening compared with a control group that was not invited. Healthcare authorities must also need to know that the screening program is cost-effective on a population level and that the necessary diagnostic and therapeutic resources are available for everyone who is offered participation.

The individuals' perspective is different. Individuals want to know their chances of benefit and harm if they decide to obtain testing for early diagnosis or to participate in a screening program. This perspective is not reflected by an intention-to-screen analysis, because this analysis includes nonparticipants in the screening group as well as individuals in the control group that obtained screening in the absence of an invitation. Calculating the chances of benefits and harms for an individual based on results from randomized trials is, however, difficult. First, nonparticipants in the group invited to a screening trial may differ in important aspects from the participants, such as having more comorbidity. Second, the individuals in the control group that obtain the screening test on their own initiative may differ from those who don't. For example, men with a high familial risk for prostate cancer are probably more likely than other men to participate if invited to the screening group and to obtain PSA testing on their own initiative if they are allocated to the control group of a screening trial.

Regardless of these methodological difficulties, one can conclude the potential individual benefit from an effective screening program for an average man is greater than the estimates based on intention-to-screen analyses. On the other hand, restricting the analysis to the participating men in the screening arm (per-protocol analysis) tend to overestimate the effect of screening.[12] The Dutch part of the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 32% relative mortality reduction after 13 years in men who were invited to screening compared with the control group (intention-to-screen analysis), whereas the mortality reduction was estimated to 51% among men in the screening group who chose to participate after correction for both nonattendance and PSA testing in the control group.[13]

TABLE 1 Characteristics of Population-Based Screening and Individual-Based Early Detection of Prostate Cancer

Descriptive element	Population screening	Early diagnosis in individuals
Definition	Organized program inviting specific age groups to undergo screening test(s)	Diagnostic testing in individuals who are asymptomatic or have nonspecific symptoms
Initiation	Healthcare authorities by repeated program invitations	Personal request or provider recommendation
Perspective	Public health priority	Individuals' priority
Purpose	To reduce prostate cancer–specific morbidity and mortality in a population	To diagnose before symptoms for individual benefit: reduce risks for advanced cancer and death from prostate cancer
Considerations	Balance of benefits/harms in the population	Balance of benefits/harms for the individual
Statistical assessment of study results	Intention-to-screen analysis	Per-protocol analysis
Guidelines	Issued by national or regional healthcare authorities	Often issued or adapted by professional societies
Communication	Standardized materials for the population	Individualized discussion and shared decision-making
Testing strategy	Protocolized repeated testing	Single time-point assessments and safety net monitoring
Test performance	Optimized for the population	Varies based on the clinical setting
Risk stratification	Based on average risks	Based on individual risk factors and preferences
Emphasis on specificity vs. sensitivity	Emphasis on high specificity, as missed cancers can be detected at repeat screening	Often emphasis on higher sensitivity because of individual preference
Overdiagnosis tolerance	Low, because harms affect an entire population	Higher, because of individual preference related to cancer worry, family history, and/or symptoms
Preferred biopsy strategy	Targeted biopsy after imaging (if available) to minimize overdiagnosis	Targeted and systematic biopsy to maximize detection sensitivity
MRI cutoffs for biopsy	Higher threshold to minimize overdiagnosis	Lower threshold to minimize missed significant cancer
Resources	Requires organized infrastructure	Uses existing clinical resources
Access	Promotes equal access through program outreach	Depends on clinical access, which may vary
Quality assurance	Accreditation program with systematic monitoring of outcomes	Variable based on clinical setting; multidisciplinary team meetings preferred

Overdiagnosis

Overdiagnosis refers to the diagnosis of a condition that would not cause symptoms or harm to an individual during their lifetime.[14] When diagnosing cancer in an asymptomatic, otherwise healthy individual, it is not possible to know whether the cancer is overdiagnosed or not. The magnitude of overdiagnosis in a screening program can only be estimated from the results of randomized trials and stage-specific incidence statistics. Although the diagnosis of low-grade prostate cancer usually represents overdiagnosis, some men with low-grade cancer at diagnosis will over time develop higher-grade disease that eventually progresses and metastasizes unless effectively treated. And although most high-grade prostate cancers eventually progress and cause symptoms, this may take several years, which means some men with histological high-grade cancer will die from other causes before experiencing any cancer symptoms. This means that the commonly used terms "insignificant" and "clinically significant" prostate cancer are not synonymous with cancers that are and are not overdiagnosed, respectively.

Organ-confined prostate cancer is common in middle-aged and elderly men, with prevalence of latent cancer at autopsy ranging from 10% to 30% in men aged 50–69 years men.[15] Overdiagnosis is therefore an important issue in prostate cancer screening and early detection. Up to half of the cancers diagnosed on systematic prostate biopsy after screening with PSA testing are overdiagnosed.[16]

One way to describe the magnitude of overdiagnosis is through the number needed to diagnose (NND) to prevent one death. NND is calculated as the excess incidence divided by the absolute mortality reduction in screened versus unscreened people (e.g., per 1,000 people). In the ERSPC, the NND was 48 after a median follow-up of 9 years and 18 after 16 years.[4,17] The Rotterdam section of the ERSPC reported an NND of 14 after 21 years.[6] In the Swedish Gothenburg-1 screening trial, the NND was 9 after 22 years.[5] For comparison, for women who are screened for breast cancer with mammography from age 50 to 70 years, the NND has been estimated to 3.[18]

Randomized trials evaluating magnetic resonance imaging (MRI) as a secondary screening test and targeted rather than systematic biopsy are ongoing.[19,20] Results from the first screening rounds suggest that these diagnostic methods do indeed reduce overdiagnosis compared with a systematic biopsy for all men with a raised PSA value.[20,21]

Start and Stop Ages, Screening Intervals

Optimal start and stop ages for prostate cancer screening and early detection

Prostate cancer that requires immediate treatment is rare in men younger than 50 years. The German PROBASE screening trial has reported that very few Gleason score ≥ 7 cancers are detected in 45-year-old men.[22] This suggests that starting at age 45 is too early, at least in the absence of a family history of early-onset prostate cancer. Modelling based on the ERSPC and Gothenburg-1 trials suggests that the optimal start age is 50–55 years.[23]

There is no evidence for any benefit from screening of men over 70 years of age, but the optimal stop age probably depends on the life expectancy of the screened population. Selective screening of men aged 70–75 years detects more high-risk cancer than screening in younger men[24] so extending screening up to 75 years of age may be beneficial for healthier men with longer life expectancy.

Use of PSA for risk stratifying testing intervals

The PSA levels lower than the commonly used cutoff of 3 ng/mL are strongly associated the long-term risk for metastatic and lethal prostate cancer in middle-aged men.[25] Indeed, a PSA value below around 1 ng/mL is associated with a 20-year risk for prostate cancer death that is much under the population average.[26] The median PSA at age 60 years is 1 ng/mL and PSA below 1 ng/mL has a 25-year risk for prostate cancer metastasis/death of 0.5%/0.2% (unscreened).[26] The PSA level is therefore used to risk stratify the test intervals in men who opt for early detection in most ongoing screening trials and pilot projects.[27] Men with a PSA below 0.5–1.0 ng/mL are typically re-invited after 5–8 years. Men aged over 60 years with a PSA below 1 ng/mL have a sufficiently low risk of dying from prostate cancer to stop further PSA testing in the absence of clinical symptoms.[26]

The Diagnostic Pathway

Serum PSA is a nonspecific test for prostatic disease and its specificity is poor for detecting potentially lethal prostate cancer. In the ERSPC and Prostate, Lung, Colorectal and Ovarian (PLCO) screening trials, men with a serum PSA value above 3–4 ng/mL were recommended a systematic biopsy. This diagnostic algorithm resulted in many benign biopsies and high rates of overdiagnosis. Since then, diagnostic methods that more selectively detect potentially lethal prostate cancer have been developed. The use of MRI of the prostate as the first investigation for men with a raised PSA value but a palpably normal prostate significantly reduces the harms of the diagnostic process by lowering the need for biopsies and the detection of low-grade cancers.[28,29] In men with a suspicious lesion on MRI, targeting the lesion rather than taking systematic biopsies helps to further reduce the detection of low-grade cancer while improving the detection of high-grade cancers.[29] MRI is therefore currently considered an essential part of the diagnostic algorithm in early detection programs and screening trials. Despite the introduction of the Prostate Imaging–Reporting and Data System (PI-RADS) to standardize reporting, there are many challenges of an MRI-based screening pathway including quality control, learning curves for radiological interpretation and taking MRI-targeted biopsies, and inter- and intra-observer variability for MRI interpretation. Additionally, 10% to 25% of men have an indeterminate (PI-RADS 3) lesion on MRI,[20,30,31] which can be challenging especially in younger men.[32] Despite its advantages, the utility of MRI as the first diagnostic investigation for men with a PSA over 3–4 ng/mL in population-based screening is limited by low availability of MRI scanners and radiologists in many countries. There is clearly a potential benefit of using an ancillary test to select men with PSA over 3 ng/mL for MRI and a subsequent prostate biopsy. The evidence for MRI in a screening context and for some of the more commonly used ancillary tests is described below.

PSA cutoff

Serum PSA remains the primary screening test in all ongoing programs and large screening trials. The commonly used biopsy thresholds 3.0 or 4.0 ng/mL may, however, not be optimal. Gleason grade group ≥ 2 (Gleason score ≥ 7) cancer may be detected in many men with lower PSA values than that,[33,34] but whether delaying the detection of those cancers until the PSA value rises over 3.0 or 4.0 ng/mL is not known. Cancer detection in men with PSA 1.8–2.9 ng/mL is being evaluated in the Gothenburg-2 screening trial.

PSA density

The calculation of PSA density requires measurement of the prostate volume with ultrasound or MRI. PSA density is a better marker than serum PSA alone for Gleason grade group ≥ 2 cancer. The probability of detecting Gleason grade group ≥ 2 cancer on systematic biopsy in men with a serum PSA of 3.0–10 ng/mL and PSA density 0.10–0.20 ng/mL/cm^3 is less than 10%.[35] Current clinical guidelines recommend the use of PSA density for selecting men with a nonsuspicious (PI-RADS 1-2) or equivocal (PI-RADS-3) prostate MRI for biopsy, with a cutoff value of 0.10–0.20 ng/mL/cm^3. PSA density is included in the diagnostic algorithm in the European Association of Urology's screening project PRAISE-U (**FIGURE 1**), the Finnish randomized ProScreen trial, the Czech national screening program, and the Swedish regional organized prostate cancer testing (OPT) program.

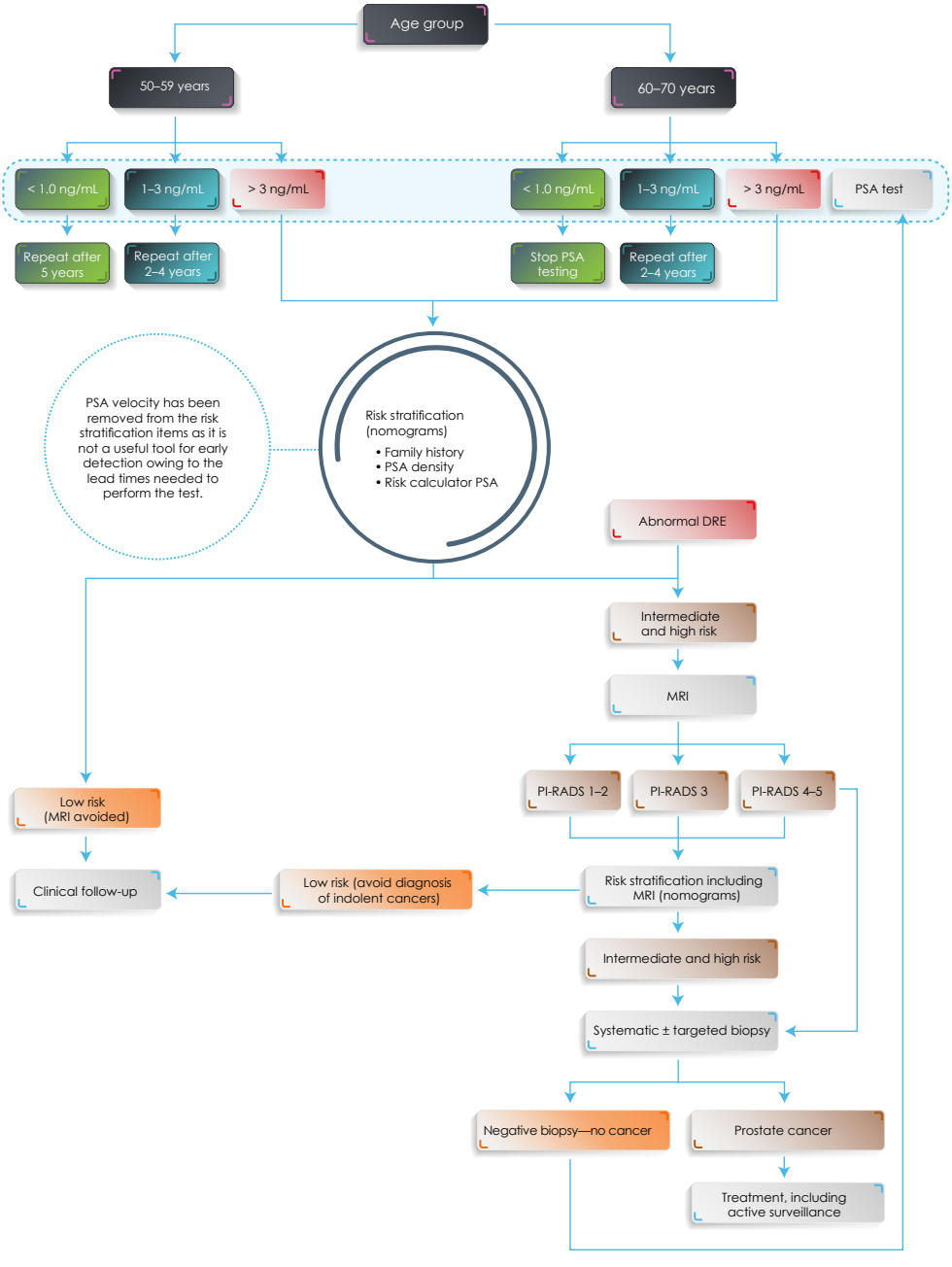
Ultrasound

Ultrasound has poor sensitivity and specificity for detecting clinically significant prostate cancer. Its use in modern diagnostic algorithms is limited to the measurement of the prostate volume for calculating the PSA density and for biopsy guidance. Ultrasound of the prostate is usually done transrectally, but for the purpose of volume measurement transabdominal ultrasound is also feasible.[37] A transrectal ultrasound for prostate volume measurement and PSA density calculation is currently being scientifically evaluated and planned for use as a secondary test, together with a digital rectal examination, in the Czech Republic's screening program.

Digital rectal examination

A digital rectal examination (DRE) cannot exclude clinically significant prostate cancer in men with a raised PSA and rarely detects significant cancer in men with a PSA below 3 ng/mL.[38] A DRE is no longer considered as a valuable standalone screening test but is part of diagnostic pathways that include a transrectal ultrasound for volume measurement and PSA density calculations.

FIGURE 1 The European PRAISE-U test algorithm.



Abbreviations: DRE, digital rectal examination; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.
Source: *Recreated from Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. A European model for an organised risk-stratified early detection programme for prostate cancer.* Eur Urol Oncol. *2021;4(5):731–739. doi:10.1016/j.euo.2021.06.006*[36]

Risk calculators

Prostate cancer risk calculators include a set of clinical variables and can be used to select men with a raised PSA biopsy who need further workup (either biopsy or MRI). Calculators that incorporate ultrasound or MRI-measured prostate volume and other MRI findings (PI-RADS category) result in better identification of men with Gleason score ≥ 7 cancer.[39] The use of a risk calculator for selecting men with PSA over 3 ng/mL is recommended by many urological associations and is, after calibration and external validation to ensure accuracy and population generalizability, included in the European PRAISE-U screening algorithm (**FIGURE 1**).

Examples of risk calculators include the European Randomized Study of Screening for Prostate Cancer (ERSPC) prostate cancer calculators, the Prostate Cancer Prevention Trial (PCPT) Prostate Cancer Risk Calculator (PCPTRC), and the Prostate Biopsy Collaborative Group (PBCG) risk calculator.

Other biomarkers

Several serum biomarkers have been shown to efficiently select men with a raised PSA value for a systematic biopsy or a prebiopsy MRI. The three best studied tests are the 4KScore, PHI, and Stockholm-3 tests. In some studies, the serum analysis has been combined with clinical information.

The *4Kscore* test includes the analysis of serum total PSA, free PSA, intact PSA, and hK2 and information about age. Using the 4Kscore test reduces the need for a systematic biopsy by 30% to 50% without substantially compromising the detection of Gleason grade group ≥ 2 or ≥ 3 cancer.[40] The 4Kscore is currently investigated in the Finnish screening trial ProScreen.

The *Prostate Health Index (PHI)* test is a combination of serum total PSA, percent-free PSA, and proPSA. Its performance is similar to that of the 4KScore test,[41] but PHI has not been evaluated in combination with clinical information. The PHI test is being evaluated for selecting men for MRI in a screening setting in China and the Czech Republic (NCT05603351).

The *Stockholm-3* test comprises of serum total PSA, free PSA, hK2, macrophage inhibitory cytokine-1, microseminoprotein-β, and a polygenic risk score calculated from over 100 single-nucleotide polymorphisms (SNPs). It has been evaluated both as a standalone blood test and in combination with data on age, family history of prostate cancer, and previous biopsy. In a randomized trial of men invited for PSA testing, the Stockholm-3 test reduced the need for MRI by 36%.[42] It is currently being evaluated in the Sthlm3-MRI trial and some of the Swedish regional organized testing programs.

MRI and lesion-targeting biopsy

In clinical early detection settings, the use of MRI and lesion-targeting biopsies substantially reduces the detection of Gleason grade group 1 cancer with some increase in the detection of Gleason grade group ≥ 2 cancers, compared with a systematic prostate biopsy.[29] A systematic review and meta-analysis of 5,831 patients from 26

clinical practice studies compared MRI and lesion-targeting biopsies with systematic biopsies and showed relative detection rates of 0.65 (95% confidence interval [CI], 0.55–0.77) for Gleason grade group 1 and of 1.3 (95% CI, 1.2–1.4) for Gleason grade group ≥ 2 cancer.[29] The benefits of MRI-directed diagnosis are directly related to the consistently high negative predictive value, which allows for reliable 'ruling-out' of significant cancer without a biopsy.[43]

Recently, data from the screening settings have been reported. The population-based Stockholm3-MRI study randomly allocated 1,532 men aged 50–74 years with PSA ≥ 3 ng/mL to either a systematic biopsy only or an MRI and targeted plus systematic biopsies.[44] Gleason grade group ≥ 2 cancer detection was similar in both groups (18–20%). Gleason grade group 1 cancer was detected in 4% of the MRI group and 12% of the systematic biopsy group. The randomized Gothenburg-2 trial has reported similar diagnostic results (see details below).[20,31] In all these reports from screening settings, the proportion of men with PSA ≥ 3 ng/mL who can avoid biopsy because of a negative MRI has been greater (55–65%) than in the clinical early detection setting (20–50%).[20,31,43,44]

MRI has also been evaluated as the primary screening test in the IP1-PROSTAGRAM and ReIMAGINE studies. The IP1-PROSTAGRAM study screened 403 men aged 50–69 years with PSA, transrectal ultrasound, and an MRI.[33] All men with at least one positive screening test had a systematic biopsy; men with an MRI or ultrasound lesion also had a targeted biopsy. For an overall Gleason grade group ≥ 2 cancer detection of 4% (17 men), the diagnostic pathway with an MRI threshold of ≥ 4 on a 5-tier score scale resulted in 11% positive tests, 2.7% detection of Gleason grade group ≥ 2 cancer, and 1.2% Gleason grade group 1 cancer. A PSA threshold of ≥ 3 ng/mL resulted in 24% positive tests and detection of Gleason grade group ≥ 2 cancer in 1.7%, and Gleason grade group 1 cancer in 1.6% of the men.

The ReIMAGINE study was conducted in 303 men in whom 25 (9.6%) were diagnosed cancer. MRI scans were not evaluated on a tier basis but instead with a binary positive/negative scale; 16% of scans were reported positive. Sixteen men (5%) with a negative MRI but PSA density ≥ 0.12 ng/mL/cm^3 were also referred for biopsy. Of 48 men with a positive MRI scan, 52% had Gleason grade group ≥ 2 cancer on biopsy (compared with 26% in PROSTAGRAM). Similar results were recently reported from the randomized MVP study.[34] An important finding in this study was the higher biopsy compliance in men with a positive MRI (96%) than in men with a positive PSA (58%).

Taken together, a growing body of evidence from early detection and population screening settings, including a systematic review with meta-analysis, indicates that MRI reduces the detection of low-grade cancers and biopsy rates while still identifying at least as many clinically significant cancers.[45] Using MRI as the primary screening test is unlikely to be cost-effective, given the extremely low prevalence of potentially lethal cancer in men with a PSA of less than 1.0–1.5 ng/mL who represent half of the screening population.[26,27] The optimal PSA cutoff for a subsequent prostate MRI is not known. It may well be below the currently used cutoffs of 3–4 ng/mL. The randomized Gothenburg-2 screening trial investigates PSA 1.8 ng/mL as cutoff for MRI.[46]

While promising, important limitations of prostate MRI also remain. To address these limitations, careful optimization of MRI is required to maximize its value in screening.[17] Key areas of focus include standardized imaging, interpretation criteria and biopsy protocols, quality monitoring, required reader experience, structured reporting, computer-aided diagnosis systems including artificial intelligence, and integration into multistep diagnostic pathways. Additionally, MRI scanning is expensive, and lack of MRI resources may limit its use in population-based screening to high-income countries. Moreover, an MRI-based screening algorithm may be less beneficial in populations with a greater proportion of palpable and advanced prostate cancer than in the hitherto reported studies from high-income countries.

The optimal use of prostate MRI in a population-based screening setting differs from its use in the standard clinical detection settings. A shorter, single-plane protocol without contrast enhancement is clearly advantageous from a resource perspective. Several meta-analyses conclude that prostate MRI without contrast enhancement has similar diagnostic accuracy as MRI with intravenous contrast medium,[47] but noncontrast MRI is more difficult for nonexperts to interpret.[48] Screening usually involves younger men who have smaller prostates with a different signal intensity compared with older men's prostates and more suspicious MRI findings (due to asymmetric cystic atrophy).[32] In combination with a lower prevalence of clinically significant cancer, this leads to a greater proportion of benign biopsies in younger men.[31,32] These differences, together with the large variability in MRI interpretation, necessitate quality assurance such as structured training, central review, audits, and continuous feedback of biopsy results to reporting radiologists. Optimal use of MRI requires its integration into a multistep diagnostic pathway, supported by a quality-assured and cost-effective infrastructure that ensures community-wide access to imaging.

High-Risk Populations

Defining men at high risk for prostate cancer

Family history is an established risk factor for prostate cancer. The risk of early onset, potentially lethal prostate cancer is particularly high in men with early onset prostate cancer in multiple relatives.[49,50] Also, men with Sub-Saharan African descent have an increased risk for advanced prostate cancer.[51]

The genetic background for inherited susceptibility to prostate cancer is complex (see Chapter 5). Germline mutations in the BRCA2 and HOXB13 genes, as well as in genes associated with the Lynch syndrome (MLH2 & MSH6), Li-Fraumeni syndrome (TP53), and some other rare cancer susceptibility syndromes are associated with aggressive prostate cancers at a younger age than in the general population.[52] Men with such mutations are recommended PSA testing starting at an early age.

Genetic risk scores, combining the results from the analysis of multiple risk modulating SNPs, can also be used to identify men a high risk for prostate cancer as discussed in the section of the *Stockholm-3* test.

Early detection and screening in high-risk men

Several prospective studies evaluate screening for prostate cancer in high-risk populations, defined by family history, ancestry, polygenic risk scores, or germline mutations. The international IMPACT trial investigates prostate cancer screening in men with a BRCA1/2 or mismatch repair gene mutation.[53,54] A prospective single-arm trial in the United States evaluates prostate cancer screening with upfront MRI in BRCA1/2 or ATM mutation;[55] preliminary results suggest that the optimal PSA cutoff for an MRI scan in men with genetic high risk is lower than the traditional 3 ng/mL. A similar prospective trial is ongoing in Israel.[56] Other studies of screening in high-risk populations are ongoing in the United States (NCT05129605, NCT04472338, and others) and Canada (NCT01990521).

The UK BARCODE-1 evaluates a polygenic risk score for defining low- and high-risk populations for selective prostate cancer screening.[57] A modelling study does, however, suggest only a modest gain in efficiency of using polygenic risk scores in prostate cancer screening and that most of the prostate cancers are detected in the 'low genetic risk' group.[58]

Because of the earlier onset of familial and hereditary prostate cancer, many clinical guidelines recommend that PSA testing be initiated some years earlier (at 40–45 years of age) for men with a brother or father with prostate cancer than for men in general. Men with for instance a BRCA2 mutation are commonly recommended PSA testing from age 40 years onwards.[59] American guidelines recommend start of PSA testing at age 40–45 years for men with African American ancestry.[60]

In the PLCO screening trial, such men had a significantly higher risk of dying from prostate cancer if they were allocated to the nonscreening arm compared with the screening arm (hazard ratio [HR], 1.9).[61] In contrast, two analyses from the ERSPC trial did not show different outcomes for men with a family history of prostate cancer.[62,63]

Shorter PSA test intervals and a lower PSA cutoff for further investigations are motivated in men with a particularly high risk for prostate cancer, as the positive predictive value of diagnostic tests is higher in populations with a high prevalence of the disease. Moreover, men with a BRCA2 mutation may develop advanced prostate cancer without much rise of their PSA value.[64]

Screening Trial Results

Except for a few early, small studies, the randomized prostate cancer screening trials that have reported on prostate cancer mortality used serum PSA as the primary screening test and a systematic prostate biopsy as the secondary test for men with a PSA value over a defined cutoff value (2.5–4 ng/mL).[65] These latter trials are summarized below.

The European Randomized study of Screening for Prostate Cancer (ERSPC)

The European Randomized study of Screening for Prostate Cancer (ERSPC) started in the mid-1990s. The trial included centers from 7 countries. Recruitment of participants, randomization procedure, test intervals, number of screening rounds, and age groups differed across centers. The screening interval was 4 years in most centers, 2 years in Sweden, and 4–7 years in Belgium.[17] Men aged 55–69 years at randomization constituted the core age group in the merged analyses of the primary endpoint, prostate cancer mortality. The secondary endpoints included metastatic disease and quality of life.

The PSA cutoff for a systematic prostate biopsy was 3.0 ng/mL in all centers, except in Finland where men with PSA 3.0–3.9 ng/mL had a DRE (1996–1998) or a free-to-total PSA analysis (from 1999, cutoff 16%) to select men for biopsy.

A total of 162,242 men aged 55–69 years were randomized. After a median of 9 years of follow-up, the prostate cancer mortality was 20% lower in men invited to screening than in the control group (rate ratio [RR], 0.80; 95% CI, 0.65–0.98), and the absolute prostate cancer mortality reduction 0.07%.[17] The prostate cancer incidence was 3.4% higher in the screening group (RR, 1.69; 95% CI, 1.63–1.76), which means that 1,410 men were invited ("number needed to invite") and 48 more men were diagnosed with prostate cancer ("number needed to diagnose") in the screening group compared with the control group for each prevented death from prostate cancer.

The latest report on prostate cancer mortality from the ERSPC was after a median of 16 years of follow-up.[4] The number needed to invite had then decreased to 570 and number needed to diagnose to 18. The relative prostate cancer mortality risk reduction was unchanged (20%), but the absolute risk reduction had increased to 0.18%.

Twelve-year follow-up data from 4 centers showed a 50% reduction of metastatic disease at the time of diagnosis and a 30% reduction overall, i.e., including also metastasis detected during follow-up.[66] An analysis accounting for noncompliance and PSA testing in the control group, based on the Dutch part of ERSPC, shows that the net mortality reduction among screening participants was 51% (intention-to-screen analysis, 32%).[13]

Two analyses of generic and disease-specific quality of life did not show any long-term differences between the trial arms.[67,68]

Gothenburg-1 screening trial

The Gothenburg-1 trial started in 1995 as an independent trial but since 1996 constitutes the Swedish branch of the ERSPC. A population-based sample of 20,000 men aged 50–64 years were randomized 1:1 to either biennial PSA screening with a 3 ng/mL threshold for a systematic 6-core biopsy or to a control group. As many as 93% of the screened men with a PSA ≥ 3.0 ng/mL had at least one prostate biopsy.[69] Even though PSA testing was common in the control group (72% had at least 1 PSA test),[70] the Gothenburg-1 trial reported the greatest prostate cancer mortality reduction of all screening trials. After 14 years, the relative reduction was 44% (95% CI, 28–64%);[69] the absolute prostate cancer mortality was reduced from 0.9% to 0.5% (difference, 0.4%; 95% CI, 0.17–0.64%).[69]

After 22 years, the relative reduction was 29% (95% CI, 9.0–0.45%) and the absolute reduction 0.6% (95% CI, 0.15–1.0%).[5] Younger age at screening start (50–55 years vs. 60 years) and primary school education only were both associated with a greater relative mortality reduction.[23,71,72] The number needed to diagnose to prevent one prostate cancer death was 12 after 14 years and 9 after 22 years.[5,69]

A mere 0.6% of the men with a moderately raised PSA (3–9.9 ng/mL) and a negative first biopsy died from prostate cancer within 20 years.[73] Most men (79%) in the screening group who died from prostate cancer either started screening after age 60 years, did not attend, or were diagnosed with prostate cancer after screening had stopped.[5] The protective effect of screening on prostate cancer mortality waned off 10–12 years after screening cessation.[74]

The prostate cancer incidence in the control group had after 24 years still not reached the incidence in the screening group, which means that many screening-detected cancers would never have been clinically diagnosed.[23]

The Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial

The PLCO cancer screening trial recruited 76,693 men from the United States aged 55–74 years from 1993 to 2001. Men in the screening group underwent annual PSA testing for 6 years and annual digital rectal examination for 4 years. After 13 years, this trial did not show any benefit in the screening group compared with the control group: the relative prostate cancer incidence was 1.12 (95% CI, 1.07–1.17) and the relative risk for prostate cancer death 1.09 (95% CI, 0.87–1.36).[75] These results cannot be used for evaluating the effect of screening versus no screening, as almost half of the enrolled men had been tested for PSA levels before entering the study, 90% of the control men were PSA tested, and less than half of the men with raised PSA levels underwent a prostate biopsy.[76–78]

The CAP trial

The UK-based Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) invited 75,707 men aged 50–69 years for a single PSA test via their primary care practice from 2001 to 2009, of whom 36% participated.[10] A control group of almost 350,000 men received standard care, of whom 25% were PSA tested at least once.[79] After 10 years, a greater proportion of men in the intervention group (6.0%) than in the control group (3.6%) had been diagnosed with prostate cancer, but there was no difference in prostate cancer mortality (RR, 0.96; 95% CI, 0.85–1.08). After 15 years, a similar proportion of men had been diagnosed with prostate cancer in both groups (6.9% and 7.1%), but a small reduction of prostate cancer–specific mortality had emerged: 0.69% versus 0.78%, RR, 0.92; 95% CI, 0.85–0.99.[80]

Observational studies

Observational studies of the effects of screening are difficult to interpret because of selection bias (PSA-tested men tend to be in better health and socioeconomic position than nontested men), lead-time bias (simply detecting a cancer earlier results in longer survival time from diagnosis even if time of death is not affected), and length

time bias (slowly growing tumours have longer preclinical phase and are therefore more likely to be detected than rapidly growing tumours). Because of these limitations, observational studies are not systematically summarized in this chapter.

Ongoing Screening Trials

Knowledge gaps

Several well-designed studies followed by systematic reviews have shown that MRI-driven targeted biopsies detect fewer clinically insignificant cancers (Gleason grade group 1) than systematic biopsies, without sacrificing sensitivity for clinically significant cases (Gleason grade group ≥ 2). Detection of Gleason grade group ≥ 2 cancer may even be slightly higher with MRI and targeted biopsies.[28] A crucial issue is whether this will translate into improved outcomes in the screening context, essentially reducing overdiagnosis, which has been the main obstacle. Several trials have been launched to investigate this. When this chapter was written, they had still reported detection at the first screen only. Results for long-term outcomes, crucially prostate cancer incidence and mortality, the direct outcome for demonstrating effectiveness and major harms, are expected within a few years. Another important knowledge gap is how often MRI should be repeated in men with persistently raised PSA values, as this affects the MRI resource demand in a screening program.

Overview of ongoing trials

Four large, randomized prostate cancer screening trials are ongoing. They are described below and summarized in **TABLE 2**. A fifth large screening trial is to be launched in the UK in 2025.

The Gothenburg-2 (G2) trial in Sweden is aimed at assessing whether a screening algorithm with PSA followed by MRI and only targeted biopsies would reduce overdiagnosis compared with a diagnostic pathway based on PSA followed by systematic biopsies.[46] The trial protocol addresses several research questions. It is an efficiency trial with dedicated specialists performing the assessments, e.g., a single pathologist with independent review of the Gleason grading and independent reading of MRIs by two experienced specialists. These features differ from clinical routine procedures, which means that the results may not be directly applicable to routine healthcare.

The Gothenburg-2 trial randomized 58,225 men aged 50–60 years in 2015–2020, with two-thirds allocated to screening and one-third to the control arm. The 17,980 participating men (participation proportion, 46%) in the screening arm were further randomized to a PSA cutoff of either 1.8 or 3.0 ng/mL.

The first reported results of the G2 trial focused on comparison between MRI-based and PSA-based biopsy strategy.[20] The two experimental arms with different PSA thresholds were combined, with biopsy results only from men with PSA ≥ 3 ng/mL analyzed also for the arm with PSA cutoff 1.8 ng/mL. A clinically significant

(Gleason grade group ≥ 2) cancer was detected in 0.9% of the men with MRI-driven targeted biopsy and 1.1% in the control group assigned to PSA-driven systematic biopsy (RR, 0.81; 95% CI, 0.60–1.10). For clinically insignificant cancers, the yield was 0.6% with MRI-driven and 1.2% with PSA-driven biopsy (RR, 0.46; 95% CI, 0.33–0.64). No comparisons between the experimental and control arms had been published when this chapter was written in spring 2024.

The ProScreen trial in Finland aims to assess prostate cancer mortality in a screening arm invited to screening with PSA and a 4-kallikrein panel with MRI and targeted biopsies compared with a control arm without intervention.[19] Mortality analyses are planned at 10 and 15 years. The trial initially recruited approximately 65,000 men aged 50–63 years in 2018–2022 and will enrol an additional 50,000 men. The design is population based (all eligible men in the target population randomized) and pragmatic, with diagnostic procedures and treatment in public health in accordance with standard practices. The pilot study confirmed the predicted performance,[81] with substantial reduction of screen-positive findings by the kallikrein panel as a reflex test, and a high positive predictive value after the two screening blood tests. Participation is higher than in the other ongoing screening trials (51%).

Results from the first screening round were published in 2024.[21] Of the 7,744 participating men in the screening arm, 9.7% had PSA ≥ 3 ng/mL and of those 70% had a kallikrein panel risk score ≥ 7.5% and were referred for an MRI scan. Of the 509 men who had MRI, 41% had a lesion and a subsequent targeted biopsy. Furthermore, 10% had a systematic prostate biopsy because of a PSA density ≥ 3 ng/mL/cm^3. The overall cancer detection in the screening arm (including nonparticipants) was 0.26% Gleason grade group 1 and 1.13% grade group ≥ 2 cancer. After a median follow-up of 3.2 years from randomization in the control group, 0.14% Gleason grade group 1 and 0.62% grade group ≥ 2 cancer were detected. This means that 1 additional Gleason grade group ≥ 2 cancer was detected per 196 invited men and 1 additional Gleason grade group 1 cancer was detected per 909 invited men, compared with those who were not invited to screening.[21]

The German PROBASE trial compares PSA-based screening commencing at 45 years versus 50 years with metastatic prostate cancer by age 60 years as the primary endpoint.[22] Secondary endpoints include proportions of false-positive screening tests. The trial recruited 46,495 men in 2014–2019, after more than 400,000 mailed invitations (participation approximately 11%). Of the participating men, 23,301 were offered immediate screening PSA test at age 45 years. A repeat PSA test was used for men with a PSA above 3 ng/mL. Men with also a repeat PSA ≥ 3 ng/mL were referred to diagnostic examinations at local urology clinics with a recommendation for systematic biopsy. An MRI was also suggested but not required for biopsy, i.e., the protocol was based on PSA-driven biopsies only. The recommended re-screening interval is 2 years for men with baseline PSA 1.5–2.9 ng/mL and 5 years for men with PSA < 1.5 ng/mL.

The first screening results showed a low proportion (1.5%) of men aged 45 years with PSA ≥ 3 ng/mL.[22] Roughly half of those were confirmed on PSA re-testing, so 0.8% of the initially PSA-tested men were referred to biopsy. Biopsy compliance was 65% and 48 cancers were diagnosed. This translated to a positive predictive value of 0.4 and a cancer detection rate of 0.2%. One-third of the cancers (15/48) were clinically insignificant (Gleason grade

group 1) and the rest clinically significant (Gleason grade group ≥ 2). This means that a mere 0.1% of the PSA-tested men had a clinically significant cancer diagnosed.

For the men assigned to deferred screening at age 50 years, a DRE was offered at baseline, with a low uptake of 37%. There were few suspicious findings on DRE (0.9%) and the prostate cancer detection in men with a suspicious DRE was minimal (0.03%, 2 cases, one of which was Gleason grade group 1).[82]

The Swedish Stockholm3-MRI trial was designed as a diagnostic study (see *MRI and lesion-targeting biopsy* and *Other biomarkers* sections above).[42] It was an efficiency trial with centralized procedures performed by a selected team of a few experienced specialists (urologists, uroradiologists, and uropathologists). The trial enrolled 12,750 men aged 50–74 years. The MRI scans were done without contrast medium. Both targeted and systematic biopsies were employed in MRI-positive men in the experimental arm. Men in the experimental arm with PSA ≥ 1.5 ng/mL and no detected cancer were re-invited 2–3 years later; 1,500 men participated in this second screening round.[83] Men with a PSA ≥ 3.0 ng/mL at re-invitation (44% of the participants) were referred for a noncontrast MRI scan, and those with an equivocal or suspicious MRI lesion for a targeted plus systematic prostate biopsy. The proportion of nonsuspicious repeat MRI scans was very high: only 7.7% had an equivocal (5.4%) or suspicious (2.4%) repeat scan. The detection rate of Gleason grade group ≥ 2 cancer was much lower (3.8%) in men with a repeat MRI than in those who had their first MRI scanning in the second screening round (13%). Even if the detection rates were substantially lower at the second round compared with the first, the positive predictive value of MRI remained at a similar level, with Gleason grade group 2–5 cancer detected in more than half of the biopsies. The results from the Stockholm3-MRI re-invitation trial clearly show that most men with a persistent PSA ≥ 3.0 ng/mL in a second screening round after 2–3 years do not need a repeat MRI scan. More research is needed to define the few who do, and when to repeat the scan for those who don't. Results including the Stockholm3 test and from later screening rounds, including men with PSA ≥ 1.5 ng/mL at first testing, are expected soon.

Of these screening trials, the G2 trial entails MRI after PSA, while the Stockholm3-MRI and ProScreen trials use multicomponent reflex tests before MRI. These tests reduce the number of MRI scans but are costly, so their impact of cost-effectiveness is not straightforward. Different age ranges complicate direct comparisons of the results between the trials.

To summarize, the results published from the randomized screening trials with an MRI-driven diagnostic pathway show that using MRI and lesion-targeted biopsies can reduce the overdiagnosis of clinically insignificant low-risk cancer. This suggests that screening involving MRI results in less overdiagnosis than screening with PSA and systematic biopsies.

However, it would be premature to conclude that screening using MRI-driven diagnostic pathway is proven effective or provides a better balance of benefits and harms than PSA-based screening. The studies available so far do not show improved detection of Gleason grade group ≥ 2 cancers, despite favourable results from diagnostic accuracy studies. Therefore, it is difficult to predict the mortality impact relative to the previously reported screening trial ERSPC.

Furthermore, we do not know the sensitivity of the screening regimens, as no report on interval cancer incidence has been published. Moreover, the benefits of screening are derived from repeated screening rounds. When this chapter was written in spring 2024, only results from the initial rounds from the ongoing trials were available. Histologic features of screen-detected cancers are only proxy measures of effectiveness, and not sufficient to demonstrate population-level benefits. For cost-effectiveness, only modelling studies have been published.

TABLE 2 Summary of the Ongoing Large, Randomized Prostate Cancer Screening trials

Trial	Primary outcome measure	Target ages (yrs)	Population size	Participation	Detection of GGG ≥ 2 cancer*	Detection of GGG 1 cancer*
STHLM3-MRI	Detection of GGG ≥ 2 cancer	50–74	12,750 enrolled, 1,532 randomized	26%	1.0% vs. 1.2%† (21% vs. 18%)	0.5% vs. 1.4%
Gothenburg-2	Detection of clinically insignificant (GGG 1) cancer	50–60	58,225	46%	0.9% vs. 1.1%	0.6% vs. 1.2%
PROBASE	Metastatic prostate cancer at age 60 yrs	45 vs. 50	46,495	Volunteer-based (~11% enrolled)	0.06%	0.14%
ProScreen	Prostate cancer mortality	50–63	65,000 enrolled 115,000 target size	53%	Not reported	Not reported

Abbreviation: GGG, Gleason grade group.
*In the experimental arm versus the control arm; †Number of men per arm extrapolated from the enrolled population (12,750 prior to selection of high-risk men to randomization) and 2:3 allocation.

Prostate Cancer Early Detection and Screening Policies

With few exceptions, national healthcare authorities recommend against screening for prostate cancer. In many countries, men are allowed to have a PSA test at their own request after appropriate information and counselling about the potential benefits and harms of early detection. The policies around the world are summarized below.

North America

The current recommendation from the United States Preventive Services Task Force (USPSTF), issued in 2018, for PSA-based screening for prostate cancer in men aged 55–69 years is Grade C.[84] This indicates that the USPSTF "recommends selectively offering or providing this service to individual patients based on professional judgment

and patient preferences," and that "there is at least moderate certainty that the net benefit is small." For men 70 years and older, the recommendation is Grade D, which means that the USPSTF recommends against the procedure and believes with moderate or high certainty that the service "has no net benefit or that the harms outweigh the benefits."

The USPSTF summary of findings in support of the C recommendation stated that there was adequate evidence from randomized clinical trials that PSA-based screening programs in 55–69 year-old men could prevent about 1.3 deaths from prostate cancer over 13 years per 1,000 men screened. Additionally, potential harms of screening were cited, including frequent false-positive tests and psychological harms, along with harms of prostate cancer treatment—erectile dysfunction, urinary incontinence, and bowel symptoms. For men 70 years and over, the summary concluded that harms were at least moderate and greater than for younger men.

The National Comprehensive Cancer Network (NCCN) and the joint guideline by the American Urological Association (AUA) and Society of Urological Oncology (SUO) both recommend PSA-based screening after shared decision-making and appropriate counselling on the pros and cons.[60]

The Canadian Task Force on Preventive Care recommends not screening for prostate cancer with PSA, with the recommendation characterized as strong for men under 55 and over 70, and weak for men aged 55–69 years. This recommendation, from 2014, was based on the "overall balance between the possible benefits and harms of PSA screening … , weighing the possible benefits against potential harms of early diagnosis and treatment of prostate cancer." The task force stated that there was no evidence that PSA-based screening reduced mortality for prostate cancer in men under 55 or over 70, and that in men aged 55-69 years, there was "inconsistent evidence of a small potential benefit of screening and evidence of harms."

Central America, South America, and the Caribbean

Mexico is the only country in Central and South America where the healthcare authorities recommend screening for prostate cancer, but there is no organized screening program.[85] The prostate cancer incidence and mortality in the Caribbean are the highest in the world,[86] but none of the Caribbean nations have a formal screening program for prostate cancer although in some there are awareness campaigns.[87]

Europe

In 2022, the European Union Council updated their almost 20 year-old cancer screening recommendations. The current recommendations encourage the member states to evaluate the feasibility and effectiveness of prostate cancer screening programs.[3] One motive for now including prostate cancer in the recommendations was that risk-stratified screening and the use of MRI scanning plus targeted biopsy for men with raised PSA values reduce overdiagnosis. A second motive was that the widespread opportunistic, unorganized PSA testing is costly and inefficient.

The PRAISE-U project, led by the European Association of Urology and funded by the EU4Health program, takes the center stage in aligning with these updated guidelines.[36,88] This 3-year initiative spans 25 institutions across 12 European countries with pilot sites in Spain, Poland, Ireland, and Lithuania. It focuses on the development of clinical performance indicators and quality-assured population-based screening protocols with a risk-based approach. PRAISE-U includes 6 work packages (WP): WP1 oversees project coordination, WP2 develops an extensive state-of-play report on prostate cancer screening in EU and establishes the knowledge hub platform. WP3 and WP4 focus on designing risk-based screening protocols and coordinating pilot studies across host countries. Finally, WP5 evaluates pilot functionality and WP6 ensures effective communication throughout the project's lifecycle. The overall vision of the project is that EU member states should be able to offer high-quality screening programs that are feasible, cost-effective, and psychologically acceptable and that lead to timely detection of prostate cancer, while reducing overdiagnosis and overtreatment.

Nationally funded prostate cancer screening was initiated in Lithuania in 2006, targeting men aged 50–74 years (start age 45 years for men with a family history of prostate cancer). In 2017 a recommendation for MRI scanning was incorporated. The program has reported a 70% coverage of at least one PSA test in the target population.[89] It led to an increase in prostate cancer incidence from 69 to a peak of 279 new cases per 100,000 men per year in 2007; the incidence then stabilized around 160/100,000 men/year.[90] Mortality increased until 2007 and then slightly decreased. Lithuania is currently implementing improved invitation and monitoring systems, and a risk-stratified test algorithm. Lithuania acts as both knowledge-sharing and implementation pilot site in PRAISE-U.

In Sweden, regional pilot projects with population-based organized prostate cancer testing (OPT) were first launched in 2020. They are managed by the regional public healthcare providers outside primary care and administered by regional OPT offices.[91] The programs target men aged 50–74 years who are invited by letter to PSA testing with risk-stratified intervals. Men with PSA ≥ 3 ng/mL have an MRI scan. PSA density is used to select men with a negative or equivocal MRI scan for biopsy. Alternative test algorithms are being evaluated. Up to June 2024, 170,000 50- to 56-year-old men were invited to participate, with 35% taking part. The diagnostic outcomes of 24,000 participating men aged 50 years have been reported.[31] The OPT framework, algorithm, and diagnostic pathways are offering valuable insights for PRAISE-U and others planning similar early prostate cancer detection programs.

Czechia is planning for the introduction of a pilot for a national screening program for prostate cancer in 2024. Primary care and urology services will inform men aged 50–69 years about the pros and cons of screening and invite them to the program. Selected men aged over 70 years with a long life expectancy will also be informed and invited. The screening will be based on PSA testing with risk-stratified intervals. Men with PSA ≥ 3.0 ng/mL will be evaluated by a urologist with a DRE and transrectal ultrasound. Those with a positive DRE, a high PSA density, or a high PSA velocity will have a prostate MRI and, if positive, a targeted biopsy.

Africa

Prostate cancer mortality rates in Sub-Saharan Africa are among the highest in the world, whereas they are low in Northern Africa.[86] The number of prostate cancer deaths in Africa is expected to double from 2020 to 2040. However, due to low per capita health expenditure and competing public health problems, there is no population-based prostate cancer screening program. Consequently, prostate cancer is generally diagnosed at an advanced stage with metastasis.[92] Some African countries have guidelines for prostate cancer screening,[93] but the general population's understanding of prostate cancer screening and early detection modalities is poor.[94–96] DRE and PSA testing are to some extent used for the early detection of prostate cancer by urologists, general practitioners, oncologists, and other healthcare professionals in the Sub-Saharan countries.[93] Testing for prostate cancer is usually paid by the individual man or through public health insurance schemes.

Asia

Prostate cancer incidence and mortality differ between Asian and Western countries. In East and South Asia, they are among the lowest in the world.[86] This is believed to be related to both genetic and dietary factors. Along with the rapidly ageing population and increasing PSA testing, the Asian incidence of prostate cancer is rising fast.[97,98] In 2020, prostate cancer was one of the top three most prevalent cancers in men in 20 of 47 Asian countries.[99] In all Asian countries, apart from Japan, the proportion of men diagnosed with advanced disease is higher than in the United States.[100] This shows the importance of screening for prostate cancer in Asia, although there is scarce evidence on the effect on incidence and mortality in Asian countries. The Japanese Prospective Cohort Study of Screening for Prostate Cancer is the only ongoing, prospective, controlled prostate cancer screening study in Asia, but no results are yet available. Nonetheless, increasing proportions of patients are diagnosed with localized disease in China, India, and some other Asian countries.[99–101]

Japan introduced municipality-based prostate cancer screening programs in the 1990s. Currently, over half of the cities and towns offers population-based screening with PSA.[102]

In China, some hospitals offer screening with PSA and a prebiopsy MRI for men with a raised PSA value,[98,103] and the proportion of men who obtain PSA testing is rising.[98] In 2022, the National Cancer Center in China issued recommendation for how prostate cancer screening should be conducted.[104] Early results from an ongoing prostate cancer screening program in China were presented in 2019.[105] Of 2,159 enrolled men with a median age of 70 years, 13% had a confirmed PSA ≥ 4.0 ng/mL. Only 21% of the men with PSA ≥ 4.0 ng/mL underwent prostate biopsy; prostate cancer was detected in 60% of the biopsied men. The prostate cancer detection rate in the first screening round was 1.6%.

In most other Asian countries men can obtain PSA testing on an individual basis. Kazakhstan started a government-funded screening program in 2013 but it was closed in 2017 because of poor efficiency.

Australia, New Zealand, and Oceania

Australia and New Zealand report among the world's highest prostate cancer incidence rates but intermediate mortality rates.[86] In contrast, the Oceanian nations report intermediate incidence rates and high mortality rates,[86] reflecting low early detection activity. The high incidence in Australia and New Zealand is attributed mainly to widespread PSA testing in the community, which is free and easily accessible.

The National Health Medical Research Council of Australia and Prostate Cancer Foundation Australia released the "Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer" in 2016. New Zealand has similar guidelines, which primarily set the criteria for further evaluation in the public health system. General practitioners are advised to discuss PSA testing with at-risk men and employ shared decision-making in screening to address disparities in testing access. Educational initiatives by the Urologic Society of Australia and New Zealand and the Prostate Cancer Foundation of Australia promote risk-stratified screening awareness. However, despite extensive PSA testing and guidelines, regional disparities in prostate cancer outcomes persist, influenced by varying access to PSA testing. This significantly affects men in lower socioeconomic areas.[106]

To mitigate the overdiagnosis of low-risk prostate cancers and related harms, several strategies are in place. Both countries predominantly use prebiopsy multiparametric MRI scans and encourage active surveillance for such cases. The Binational Prostate Cancer Outcomes Registry (PCOR) tracks quality outcomes in diagnosis, treatment, and life quality post-treatment, guiding policy making with national data. Additionally, the potential of prostate-specific membrane antigen positron emission tomography (PSMA PET) scans to further reduce overdiagnosis of low-grade prostate cancers is under evaluation.

How to Inform Men Who Ask for Early Detection or Are Invited to Screening

Most healthcare authorities around the world support informed decision-making for men who actively ask for testing for early detection of prostate cancer. Many provide specific information for this purpose in a brochure or online. These decision aids typically include a background on prostate cancer and the diagnostic methods, and list the most important potential advantages and disadvantages of PSA testing.[107]

A recent systematic review concluded that decision aids are underused and that it is not clear to what extent they contribute to shared decision-making.[108] Another systematic review suggested that although prostate cancer screening decision aids improve men's knowledge about the potential benefits and harms of PSA testing, they do not sufficiently promote shared decision-making because of shortcomings in design and implementation, not least as most of them lack consideration of the men's perspective.[107] Explaining the concept of overdiagnosis is particularly challenging.[109] Developing better decision aids for unorganized PSA testing and organized prostate

cancer screening programs is therefore of high priority. The optimal amount of information and its form may be quite different for men who actively ask for testing and for men who receive an invitation to a screening program, as the knowledge and needs in these two groups of men may differ. The information also has to be adapted to specific medical and cultural characteristics of the target population.

Future Perspectives

Many important knowledge gaps about population-based screening for prostate cancer remain (**BOX 1**). The ongoing screening trials and the population-based pilot projects will gradually fill these gaps over the next several years. There is still no level-1 evidence that screening for prostate cancer with modern diagnostic methods provides a favourable long-term balance between benefits and harms. There is, however, strong evidence that modern diagnostic methods provide more favourable diagnostic outcomes than a diagnostic pathway with a systematic biopsy for all men with a PSA value over 3–4 ng/mL. There is also some evidence that unorganized PSA testing is less effective, more socioeconomically unequal, and leads to a less favourable balance between benefits and harms than organized screening.[9] Some have therefore argued that informed individual decision-making, the currently most common policy for early detection of prostate cancer, is the worst available option (the others being organized screening and restricting PSA testing to men with a clinical suspicion of prostate cancer).[110] The disadvantages of the widespread, unorganized PSA testing were one motive for the EU Commission to include prostate cancer screening in their 2022 cancer screening recommendations. Consequently, an increasing number of pilot screening projects are now started across Europe.[88] Various initiatives to organize the prostate cancer testing have been taken in many other parts of the world.

The knowledge gaps about population-based screening for prostate cancer include several organizational aspects (**BOX 1**). A population-based cancer screening program requires adequate decision aids, effective coordination, a defined diagnostic pathway to investigate individuals with a positive primary screening test, prospective outcome registration for quality control, and governance. Countries with a high prevalence of unorganized PSA testing that are switching to organized testing programs must consider how to avoid parallel PSA testing within and outside the program. As the primary screening test (PSA) is available also outside the program, men may obtain testing and urological follow-up in the screening intervals and after the program's stop age. Such parallel PSA testing and follow-up are probably not cost-effective, and it may be necessary to make special measures to prevent or reduce it.

BOX 1 Important knowledge gaps about prostate cancer screening

- How are men best informed about the potential advantages and disadvantages?
- Which are the optimal PSA cutoff values in different age groups?
- Which are the optimal start and stop ages?
- What is the outcome of repeated screening rounds with modern diagnostics?
- Which are the optimal screening intervals for men with a raised PSA and negative further investigations?
- What is the value of an ancillary test to select men for MRI or biopsy in repeated screening?
- What is the cost-effectiveness and health economics of different screening algorithms?
- Which are the long-term mortality and overdiagnosis outcomes after modern screening?
- How transferable are results from a screening trial to other populations and ethnic groups?

Even with improved general knowledge about screening for prostate cancer, many specific factors need be considered in each country such as the incidence and mortality of prostate cancer, the healthcare structure, available resources for diagnostic evaluations and treatment, and the geography. In countries with low prostate cancer mortality and other, more compelling healthcare needs, early detection of and screening for prostate cancer is of low priority. In some countries, the population structure and the healthcare system do not allow for an organized screening program, meaning that directed information campaigns with an offer of early detection may be the best available option.

Although many obstacles remain, there is an obvious trend toward earlier diagnosis, more effective subsequent treatment, and declining prostate cancer mortality in most parts of the world. Overdiagnosis is still an important issue to overcome. The way forward to do this is through organization, outcome registration, and stepwise evidence-based refining of the test algorithm.

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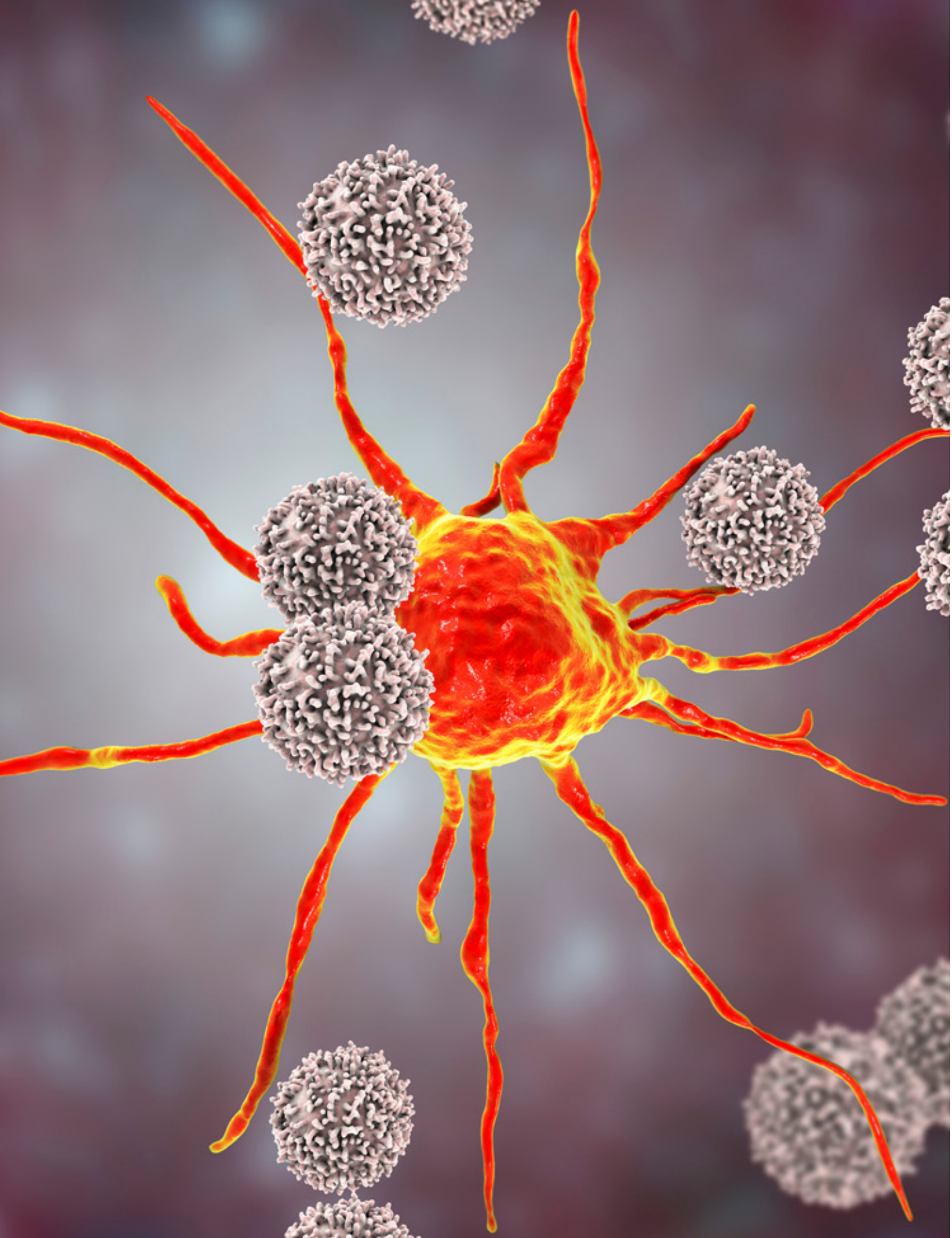
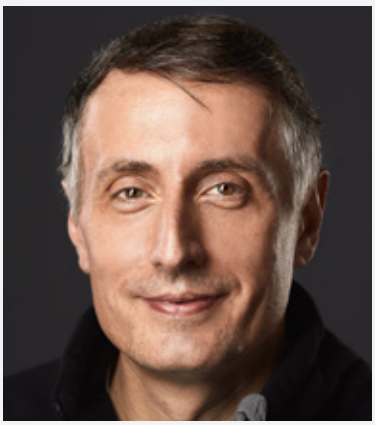


COMMITTEE 4

Prevention of Lethal Prostate Cancer via Modifiable Lifestyle Changes, Metrics, & Repurposed Medications



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Introduction & Committee Clinical Summary

Preventing lethal prostate cancer harbours latitude in terms of a clinical definition, as it does with this committee.[1] It could apply to any or all the following clinical scenarios utilizing modifiable lifestyle metrics and repurposed medications: general primary prevention; men with enhanced germline genetic, familial, or other enhanced risk; preventing progression or potential lethality of this disease postdiagnosis (active surveillance included); and secondary prevention after definitive treatment. The repetitive theme in preventing lethal prostate cancer is the behavioural patterns and metrics consistently responsible for reducing the risk for cardiovascular morbidity or mortality and premature death (all-cause mortality) appear to also mirror meta-analyses, systematic, and novel recent data to espouse preventing a portion of the lethal common cancers, including prostate cancer.[1–7] This approach allows for the largest potential population and patient success since cardiovascular disease (CVD) is the primary cause of death in men, the primary cause of death in men diagnosed with localized prostate cancer, the primary cause of mortality in men treated for localized prostate cancer, one of the primary etiologies of enhanced adverse effects in men treated for prostate cancer, and a notable source of morbidity and mortality in men with advanced disease.[8–12]

The inflammatory nature of progressive cancer or even cardiovascular disease itself on the tumour milieu, as well as the potential adverse effects of systemic cancer treatment, especially in patients with cardiovascular comorbidities also highlight the imperative need for improved cardiovascular health at all stages of prostate cancer.[13,14] Echoing this theme, recent preliminary studies of men with an established higher risk for hereditary prostate cancer and the potential for lethality have observed notable reductions in risk with proven cardiovascular risk-reducing behaviours (diet, exercise, healthy weight/waist, eliminating tobacco, etc.).[5] Again, aggressively reducing the risk for cardiovascular morbidity or mortality in men at risk for lethal prostate cancer appears to espouse the larger public health goal of improving quality and quantity of life. It is also for this reason this chapter and committee emphasized and espouses heart healthy lifestyle interventions and an arduous pursuit of proven cardiovascular healthy medicines that could be repurposed for those that qualify, again based primarily on their prescriptive approved indications, to potentially also reduce the risk for lethal prostate cancer (aspirin, metformin, statins, GLP-1 agonists, etc.).[1,15,16] If some of these lifestyle metrics or medications are not successful in this goal (association rather than causation) then they still harbour a positive record in assisting the patients who qualify for these lifestyle metric improvements or medications to at least prevent cardiovascular events and potentially improve all-cause mortality. This philosophy should be addressed when discussing lethal prostate cancer prevention with patients to place risk and benefit in the appropriate clinical perspective.

The primary limitation of the current and past data on the prevention of lethal prostate cancer should also receive attention, which is the dearth of randomized long-term data with morbidity and mortality endpoints. This is expected since there are ethical issues in assigning some participants to a nonintervention group knowing the proven potential consequences of such a heart unhealthy comparison protocol. Also, utilizing a preventive agenda requires enormous numbers of participants to achieve adequate statistical power and with an intimidating cost. More interventional studies are needed for those at high risk for lethal prostate cancer in primary and secondary preventive settings, as are large, long-term, prospective studies with multiple evaluation intervals

during the observational period, which statistically adjust for a variety of variables (multivariate analysis). It is challenging to determine statistically and realistically what if any behaviours or metrics unambiguously reduce total prostate cancer incidence in the post-PSA era, which is just one of the numerous reasons to accentuate the prevention of lethality. Regardless, perhaps the prostate and cardiovascular healthy themes found in this chapter could also assist in improving the current milieu of low adherence rates to these and other lifestyle changes and parameters.[17,18]

Exercise, Cardiovascular Health, and Cancer

There is strong epidemiological evidence of an association between volume and intensity of physical activity and the risk of developing several major chronic diseases including heart disease (20–30%[19]), stroke (10–20%[19]), and type 2 diabetes (26–65%[20,21]). Physical activity is also associated with a reduced risk of developing many cancers including colon cancer (19%[22]), breast cancer (12–21%[22]), and lung cancer (21–25%[22]). In this section we explore the evidence for physical activity influencing prostate cancer risk and the potential underlying mechanisms.

Exercise and prostate cancer incidence versus advanced & lethal disease

The association between physical activity and overall prostate cancer risk appears to be small and inconsistent.[23] Differences in self-reporting methods of physical activity and the high heterogeneity of prostate cancer ranging from low-grade to aggressive disease may contribute to conflicting findings from epidemiological studies. In a meta-analysis examining highest versus lowest physical activity level that included 105,079 men with prostate cancer from 27 cohort studies and 23 case-control studies, the relative risk (RR) for overall prostate cancer incidence was 0.99 (95% confidence interval [CI], 0.94–1.04).

Conversely, several studies suggest an association between physical activity and a reduction for advanced forms and fatal/lethal prostate cancer in older men. For example, Giovannucci *et al.*[24] found no association between level of physical activity and prostate cancer incidence. However, on subsequent analysis the authors reported a significant reduction in risk of 54% for metastatic prostate cancer but only for the category of vigorous physical activity. In a subsequent study, reporting data from the 14-year follow-up to this cohort, a very similar RR emerged with no effect of exercise regardless of how vigorous it was for the overall study population.[25] However, for men over 65 years and undertaking vigorous exercise, there was a significant and meaningful reduction (70%) in risk for advanced and fatal prostate cancer if they achieved at least 3 hours of vigorous activity each week.

It appears that a relatively high volume of vigorous exercise is required to reduce the risk for prostate cancer and this primarily applies to advanced prostate cancer.[26] In a large cohort of over 72,000 men in the US who did not have cancer at study enrollment, 5,503 developed prostate cancer in the subsequent 9 years and although physical activity was not associated with overall risk for prostate cancer, higher levels of physical activity were associated with a 31% reduction of aggressive prostate cancer.[26] In another prospective study conducted in Norway of 29,110 men, frequency and duration of exercise were inversely related to incidence of advanced prostate cancer.[27]

Compared to men who were sedentary, men in the highest category of physical exercise had a RR of 0.64 for advanced prostate cancer and 0.67 for prostate cancer death. The authors concluded that reduced risk for advanced prostate cancer and prostate cancer death is associated with higher levels of recreational physical exercise. Another large prospective cohort study of 45,887 men examined association of lifetime physical activity and prostate cancer incidence and mortality.[28] In this study, fatal prostate cancer increased about 2-fold (rate ratio, 1.85; 95% CI, 0.89–3.86) in men who rarely ever walked or cycled compared with those in the highest average lifetime walking/cycling of 120 minutes per day; however, the 2-fold increase was not statistically significant.

Using data from the Health Professionals Follow-Up Study, Giovannucci *et al.* further examined 10 potential factors (cigarette smoking history, physical activity, body mass index [BMI], family history of prostate cancer, race, height, total energy consumption, and intake of calcium, tomato sauce, and a-linolenic acid) for prostate cancer risk.[29] Interestingly, higher level of vigorous physical activity was the only factor associated with protection/lower risk for fatal prostate cancer. In contrast, recent smoking history, taller height, higher BMI, family history, and high intakes of total energy, calcium, and a-linolenic acid were associated with an increased risk for fatal prostate cancer. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study examining levels of physical activity and risk of prostate cancer, 127,923 men from 8 European countries were followed for a median of 8.5 years with 2,458 cases of prostate cancer reported.[30] The authors reported that although there was no relationship between leisure time, physical activity, and incidence of prostate cancer, higher levels of occupational physical activity were associated with reduced risk for advanced prostate cancer.

Although several cohort studies have indicated an association between vigorous physical activity and lower incidence of advanced and fatal prostate cancer, others have reported no associations. For example, Moore *et al.* reported that physical activity was not associated with advanced or fatal prostate cancer including older men in the large (~300,000) cohort from the NIH-AARP Diet and Health Study.[31] As suggested by the authors, these differences could have been related to multiple statistical tests in previous studies and the possibility of distinctions in screening procedures including prostate-specific antigen (PSA) testing and prostate biopsies between physically active and inactive men contributing to differences in findings across studies. Of interest to note regarding prostate biopsy data, Antonelli *et al.* reported that higher physical activity levels were associated with lower incidence of prostate cancer and importantly a lower risk for high-grade disease.[32]

More recently, a prospective cohort analysis showed a moderate association between long-term physical activity of vigorous intensity and reduced risk of developing advanced and fatal prostate cancer.[33] In this cohort study of 49,160 men in the Health Professionals Follow-up Study, 6,411 developed prostate cancer and 888 developed fatal disease at 26 years follow-up. Men undertaking the highest level of vigorous physical activity had a 30% reduction in developing advanced prostate cancer and 25% reduction of fatal prostate cancer compared to those with the lowest level of vigorous physical activity.[33] Interestingly, 945 men undertook assays for TMPRSS2:ERG gene fusion, a common prostate cancer molecular subtype, with 48% having ERG-positive disease. A novel finding was that higher levels of vigorous physical activity were associated with reduced risk for ERG-positive prostate cancer and not ERG-negative disease. The authors suggested that vigorous physical activity could prevent the progression of tumours with TMPRSS2:ERG fusion.

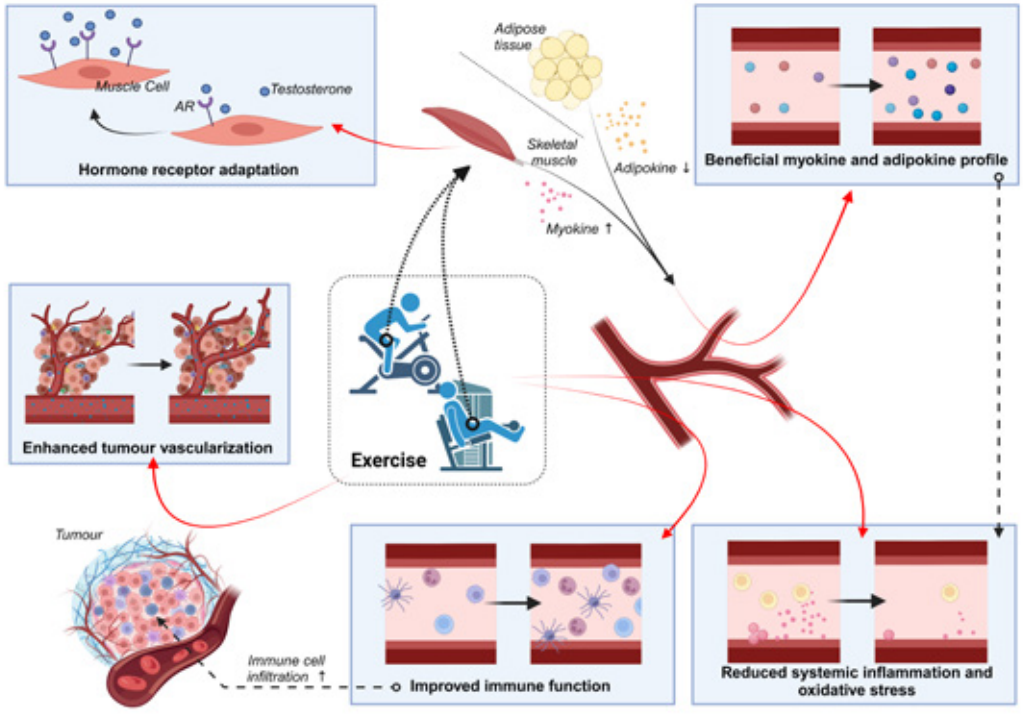
Exercise and lethal prostate cancer clinical conclusions

While conflicting, these exciting and novel results require further validation and confirmation in prospective studies and clinical trials including the potential biological mechanisms underlying physical activity influencing risk for prostate cancer. On current evidence, there appears to be an association between physical activity volume and intensity with the risk of developing prostate cancer with greater influence for more aggressive and lethal prostate cancers.

Exercise, lethal prostate cancer, and potential biological mechanisms

We have previously proposed several biological mechanisms by which physical activity might prevent development and progression of prostate cancer (see **FIGURE 1**).[34] While these are speculative in suppressing progression of precancerous cells in the prostate of humans, there is extensive evidence from preclinical studies that can inform our understanding for disease prevention.

FIGURE 1 Potential pathways or mechanisms proffered by which exercise volume or intensity could prevent prostate cancer progression or lethality. No single mechanism dominates from research, rather multiple mechanisms, or pleiotropism, appear to contribute to the potential benefit.



Abbreviation: AR, androgen receptor.

Source: *Image courtesy of Robert U. Newton, PhD, Professor of Exercise Medicine and Deputy Director of Edith Cowen University Exercise Medicine Research Institute, Western Australia, Australia.*

Being physically fit and having healthy muscle-to-fat mass composition produces a systemic myokine (cytokines produced by skeletal muscle) and adipokine (cytokines produced by adipocytes) profile, which is beneficial for suppression of cancer cells through direct signalling for cell cycle arrest, decreased proliferation, and increased apoptosis.[35] This effect occurs at rest and is enhanced during bouts of physical activity.[36] Moderate-to-vigorous physical activity increases mobilization of natural killer cells and T-cells, and myokines signal these cells for increased infiltration and cytotoxicity[20] to destroy precancerous and cancerous cells in the prostate.[15,37] This enhancement of immunity may be a key mechanism of prevention of prostate cancer.

An adequate volume and intensity of physical activity results in a more optimal homeostasis of circulating factors such as insulin, growth factors, and sex-steroid hormones, and conversely, sedentary behaviour results in a more cancer-promoting systemic milieu.[34] Low levels of physical activity, in particular if combined with high body fat, result in chronic systemic inflammation and oxidative stress, which further contributes to an environment more conducive to development of cancerous prostate cells.[38]

Testosterone and the more potent form dihydrotestosterone (DHT) are primarily responsible for stimulating the growth of prostate cells. Excessive levels of DHT can lead to increased cell proliferation, and potentially the onset and progression of prostate cancer.[39] While physical activity can acutely elevate testosterone, in particular resistance training, vigorous exercise also increases the concentration of androgen receptors in skeletal muscle,[40] binding testosterone and potentially reducing the amount of testosterone chronically signalling cells in the prostate.[34] Conversely, being physically inactive may result in more testosterone signalling to prostate cancer cells, increased DHT, and potential for development of cancerous cells.

Finally, it has been demonstrated that chronic exercise training over the course of a prostate tumour developing results in a more normal microvasculature within the tumour tissue compared to the disrupted and dysfunctional arteriole-capillary-veniole network that usually forms.[41] This long-term exercise effect supports greater blood perfusion and reduced hypoxia within the tumour, with each acute exercise bout further facilitating the delivery of oxygen, cancer-suppressing cytokines, and immune cells in closer proximity to the prostate cancer cells.[41] The overall effect is a more slowly growing cancer that is less likely to metastasize, which is an important explanation of reduced risk for prostate cancer, especially more aggressive and lethal forms.

Exercise summary

On balance, higher volume and intensity of physical activity over a man's lifetime likely confers some protection from development of prostate cancer, in particular more aggressive and lethal forms. The mechanisms are somewhat hypothetical currently, but knowledge is accumulating. Regardless, meeting physical activity guidelines is strongly recommended by all health agencies including prostate cancer–specific associations because of the strong associations with almost all health and survival outcomes. A recent example from the ERASE trial mirrors this summarized philosophy.[42,43] This was a 12-week, randomized, phase 2 trial of active surveillance patients that demonstrated the potential for exercise intensity to display anticancer effects in a short period of time (PSA, PSA velocity, and prostate cancer cell growth) and promoted cardiorespiratory fitness and mental health outcomes. The heart and prostate healthy effects of exercise promote overall health.

The Roles of Diet in Prevention of Development and Progression of Prostate Cancer

Roles of diet in prevention of prostate cancer

Growing, but still limited, evidence does point to dietary factors or patterns as influencing prostate cancer disease progression and mortality.[44] The evidence however remains preliminary, with more prostate cancer–specific studies needed to examine postdiagnostic intake of foods and nutrients related to recurrence and cancer-specific mortality. Still, the theme of a dietary pattern that can protect cardiovascular health or improve all-cause mortality mirrors what could provide some protection against lethal cancer, including prostate cancer.[45,46] For example, healthy dietary patterns including a greater consumption of vegetables, fruits, fish, legumes, and whole grains while minimizing processed, red meats, higher-fat dairy, refined grains, sodium replete products/snacks, and sugar-sweetened beverages. Thus, it is primarily a plant-based eating pattern.

Individual foods or food groups are interesting and were only covered briefly by the committee to retain the focus on the overall pattern of consumption. For example, the antioxidant lycopene has garnered adequate preclinical and observational cancer inhibitory data to currently be included (synthetic form) in a recent study of men receiving conventional treatment for metastatic prostate cancer.[47] Although these investigations are of interest, currently some of the most robust recent prospective studies conducted continue to suggest the intake of this compound from healthy food sources is associated with a lower risk for lethal prostate cancer.[48] Thus, this data espouses an increase in fruits and vegetable intake or a healthier dietary pattern, which again is associated with an increased probability of reducing cardiovascular and all-cause mortality.[49] This is also the theme of other components of a healthy diet. For example, there is evidence from *in-vitro* and *in-vivo* studies suggesting anticarcinogenic effects of metabolites of cruciferous vegetables including glucosinolates, isothiocyanates, and indoles, which can support their beneficial role; however, more studies are necessary to establish causality.[50.] Meta-analysis of observational studies examining soy intake and incident prostate cancer have suggested an inverse association with incidence, but the impact on lethal disease has not been adequately addressed.[51] A unique, past, randomized, masked clinical trial examining a soy protein supplement versus placebo for men at high-risk for recurrence demonstrated no impact.[52] Healthy food sources of cruciferous vegetables or traditional soy foods continue to demonstrate cardiovascular and all-cause mortality advantages.[53,54] Legumes are beginning to receive greater attention in terms of cardiovascular benefits, but whether they impact lethal prostate cancer needs more investigation.[55] Past prospective studies suggest fish intake is associated with a healthier lifestyle and appears to minimally impact incidence but could reduce the risk for aggressive or lethal prostate cancer.[56] Interestingly, the suggestion of this trend continues from a recent systematic review and meta-analysis of 25 prospective cohort studies.[57] Coffee and tea (green and perhaps others) consumption may be associated with healthier dietary patterns in some geographic areas. Overall, there is a suggestion of a lower risk for advanced or fatal prostate cancer or all-cause mortality with increased intake.[58,59] Again, the association of a beverage with an overall heart healthier lifestyle should receive more attention with patients rather than the individual dietary component providing the *sine qua non* for prostate cancer lethality prevention.

Alcohol reduction/elimination and tobacco elimination

Alcohol has carcinogenic potential and recent increasing global morbidity, mortality, and addictive issues are concerning.[60] It is plausible no safe level of alcohol exists. Both the PCPT and REDUCE prostate cancer prevention trials observed a notable risk for high-grade cancer among men consuming higher quantities of alcohol on a regular basis, and the potential for the attenuation of these medications also occurred with enhanced exposure (heavy drinking).[61,62] Recently, a meta-analysis of 19 independent investigations found the potential for alcohol to be associated with an increased risk for fatal prostate cancer, but inconsistences in the data were also noted.[63] The current robust meta-analyses on the risk for alcohol intake, even in some cases light-to-moderate intake, and the risk for gastrointestinal cancers of numerous types (esophageal, laryngeal, and colorectal) should be sufficiently concerning.[64] Moderate-to-heavier drinking associations with breast, stomach, liver, pancreas, and prostate cancers suggest diverse carcinogenic potential, which should be discussed with patients. Smoking or tobacco exposure also has carcinogenic potential, and it is of interest that the accumulating recent cumulative data suggests an increased risk for lethal prostate cancer with this behaviour despite the lower incidence risk.[65] Rather than search for limitless specific mechanistic reasons, it is plausible that part of the reason for the lower incidence and higher mortality with alcohol or smoking is the reduced compliance with cancer screening (prostate or other).[66]

Obesity and cumulative metabolic health parameters (metabolic syndrome)

Arguably, the impact on obesity and other health-related parameters could occupy a separate committee and chapter. The plethora of the past and primarily recent cumulative data suggests no impact, or a reduced incidence of prostate cancer, but an increased risk for advanced and lethal prostate cancer with an unhealthy weight status, whether it is measured by BMI or another associated central obesity parameter.[6,7,67–70] Whether this is a screening compliance issue, enhanced hormonal resistance, inflammatory, or another etiology, it is difficult to ignore the impact of obesity on a variety of other urologic issues, and the concomitant increased risk for cardiovascular and all-cause morbidity and mortality.[71–73] Another area of interest is the preliminary data suggestive of a reduced impact of 5-alpha-reductase inhibitors with obesity, which could partially explain their lack of known effectiveness in some patients.[74,75] How many other medications are attenuated by an unhealthy weight or metabolic status? The increased risk for lethal prostate cancer with numerous or cumulative unhealthy metabolic parameters (prediabetes, diabetes, hypertension, dyslipidemia, etc.), or metabolic syndrome also appears plausible, and is part of the reason for the ongoing pursuit of cardiovascular risk–reducing methods to reduce the risk for aggressive or lethal prostate cancer.[1,4,76]

Heritability of Prostate Cancer, Lifestyle Behaviours, Metric Lessons & Cardiovascular Health

Germline or familial risk for prostate and other common cancers is becoming more notable.[77,78] Increased testing is available for pathogenic variants or polygenic risk scores (PRSs), but what should receive equitable recognition is the novel data for cumulative heart healthy lifestyle behaviours to offset hereditary prostate risk for some patients.[5,79] These are the same lifestyle changes recommended by the committee and found in this chapter. Patients at higher genetic risk may not be aware of recent data suggesting such a formidable potential reduction in their predicted risk with greater adherence to heart healthy lifestyle behaviours and parameters. This current data is empowering and can be provided on a case-by-case basis.

Dietary supplements and prostate cancer

Currently, there is no strong evidence for any single or combination dietary supplement to reduce progression or death from prostate cancer.[1] Thus, this data will not be belaboured. The phase 3 SELECT study showed no benefit of selenium alone or in combination with vitamin E for prostate cancer chemoprevention.[80] Further follow-up with SELECT found a significant increased risk for prostate cancer with high-dose (400 IU) vitamin E supplementation.[81] A notable observational study suggested an increased risk for prostate cancer mortality with higher-dose selenium supplementation.[82] Overall, again no robust cumulative data currently exists to reduce the risk for fatal prostate cancer from a dietary supplement. Healthy dietary sources of these nutrients have not been the concern and could be protective.[83] Perhaps the focus on dietary supplementation for prostate cancer prevention needs to be redirected toward preventing and mitigating the side effects of some conventional treatments. This appears to be a more promising area of research.[1]

Repurposed Medications (Metformin, Statins, Combinations, and Aspirin)

The roles of metformin and statins in prevention of development and progression of prostate cancer

Anticancer mechanisms of metformin

Metformin (1,1-dimethylbiguanide hydrochloride) is one of the most prescribed medications worldwide, with approximately 120 million prescriptions filled annually.[84] It belongs to the biguanide class of oral hypoglycemic agents and is commonly prescribed for a treatment of diabetes mellitus. Metformin reduces hepatic glucose

production, increases insulin sensitivity, and increases glucose use by peripheral tissues, thus decreasing serum glucose levels in patients with type 2 diabetes mellitus.[85] Metformin exerts its antineoplastic properties via multiple pathways including AMP-activated protein kinase–dependent and kinase–independent pathways, alteration of insulin and insulin-like growth factor signalling, and suppression of androgen signalling.[85]

AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase that regulates cellular energy metabolism. AMPK suppression has been associated with tumour growth pathways, including the mammalian target of rapamycin (mTOR). Metformin activates AMPK and thus decreases mTOR signalling, which decreases protein and fatty acid synthesis and inhibits cell proliferation.[86] The suppression of *de novo* lipogenesis is directly responsible for AMPK-mediated inhibition of prostate cancer growth.[87] Multiple AMPK-independent mechanisms, including reduction of cAMP levels, which inhibit protein kinase A activity and block glucagon-dependent glucose production, have also been associated with the treatment of diabetes mellitus and antineoplastic properties of metformin.[88] Insulin, insulin growth factor (IGF) 1, and IGF 2 have shown to promote cancer growth by binding to insulin receptors and activating the PI3K/AKT/mTOR pathway leading to abnormal cell proliferation, and inhibition of apoptosis and carcinogenesis.[85] By reducing hyperglycemia, metformin may also reduce cancer growth, as the tumour cells require high levels of aerobic glycolysis to generate sufficient energy (the Warburg effect). Metformin inhibits gluconeogenesis and decreases circulating glucose and insulin levels, thus antagonizing the effects of hyperinsulinemia and hyperglycemia.[89] Metformin reduces the activity of cyclin D1, which has been shown to be a central regulator in androgen-dependent transcription and cell cycle progression of prostate cancer cells.[90] Additionally, metformin may disrupt androgen signalling by directly acting against androgen receptor pathways. These antiandrogenic effects may act against the development and progression of prostate cancer.[91]

Joshua *et al.* investigated the role of metformin on cellular indices relevant to prostate cancer in a phase 2 single-arm trial on men with biopsy-proven prostate cancer planned for radical prostatectomy.[92] Neoadjuvant metformin was consumed over 4–12 weeks preceding surgery. Metformin was shown to be well tolerated and significantly reduced the Ki-67 mitotic index by 29.5% (p=0.0064) per patient. Additional effect was also seen on the mTOR pathway signalling mediator responsible for oncogenic proteins, phosphorylated 4E-binding protein 1 (P-4EBP1), which had reduced staining on whole mount specimens. The authors also noted a trend toward PSA reduction preoperatively; however, it did not reach statistical significance (p=0.08).

Roles of metformin in prevention of prostate cancer

The data supporting the role of metformin in prevention of prostate cancer has demonstrated conflicting results. Margel *et al.* demonstrated in a cohort of 3,873 patients with incident diabetes and prostate cancer, the cumulative duration of metformin treatment after cancer diagnosis was associated with a significant decreased risk for disease-specific and all-cause mortality in a dose-dependent fashion.[93] For each additional 6 months of metformin use, there was 24% (adjusted hazard ratio (HR), 0.76; 95 CI%, 0.64–0.89) decrease in prostate cancer–specific mortality and 8% (adjusted HR, 0.92; 95% CI, 0.88–0.97) decrease in all-cause mortality. A meta-analysis conducted by Stopsack *et al.* did determine that metformin was associated with improved overall survival (HR, 0.52–0.88; p<0.001) and lower risk for biochemical recurrence (HR, 0.79; p=0.047).[94]

Similarly, another meta-analysis suggested that metformin is associated with a 17% lower risk for biochemical recurrence.[95] However, it also must be noted that two other meta-analyses did not demonstrate any positive effect for metformin on risk for biochemical recurrence.[96,97] Till now, no randomized study has evaluated the role of metformin in secondary prevention of very low risk prostate cancer on active surveillance. The Metformin Active Surveillance Trial (MAST) is a phase 3, randomized, double-blind, placebo-controlled trial that evaluated whether metformin could delay time to progression in men on expectant management for low-risk prostate cancer.[98] Men with biopsy-proven, low-risk (Gleason score ≤ 6), localized prostate cancer choosing expectant management as primary treatment, serum PSA ≤10, and clinical stage T1c-T2a were followed for 36 months to determine whether metformin delays time to progression, defined as primary therapy for prostate cancer (radical prostatectomy, radiation, or hormone therapy) or pathological progression (at least 4 cores involved, at least 50% of any 1 core involved, or Gleason pattern ≥ 4). Additional secondary outcomes included changes in disease-related patient anxiety as evaluated with the MAX-PC score and changes from baseline in decisional satisfaction and decisional conflict as measured by the decisional regret scale. Preliminary results released from MAST at the time of this chapter's publication found no significant difference in progression-free survival (PFS) in participants on metformin (n=204) versus placebo (n=203), and some concern over adverse effects. The impact of this trial would suggest metformin may not be appropriate in the active surveillance (AS) setting, but questions also abound. For example, since MRI-guided biopsy and monitoring has recently become a standard for AS patients, does a trial which took a decade to complete reflect today's AS protocols and accuracy? Is a higher dosage of metformin (850 mg bid utilized in MAST) appropriate in some patients, who in some cases would not qualify for the medication either based on a lack of hyperglycemia/hyperinsulinemia, or having not been previously diagnosed with type 2 diabetes? Additionally, the growing impact of glucagon-like peptide 1 (GLP-1) agonists may eliminate the need for older more modest glucose-controlling medications in many patients.[71] The broadening indication and the more profound effects of the newer GLP-1 medications should receive more attention based on the disappointing results of MAST. Regardless of the final published results of MAST, the researchers and participants should be appreciated for providing novel insight and thought-provoking data, which will further enhance the knowledge of how best to utilize (or not) this and other repurposed medications for future patients.

Statins

Anticancer mechanisms of statins

Statins are a class of medications that effectively lower serum cholesterol levels by inhibiting 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme for cholesterol synthesis in the liver. Statins are becoming one of the most prescribed medications, with more than 200 million people taking them worldwide.[99] The chemopreventive role of statins for prostate cancer may be the result of cholesterol-mediated and noncholesterol-mediated pathways.[100]

Cholesterol-mediated pathways

A positive correlation between cholesterol accumulation in prostatic tissues and presence of prostate cancer was first reported in 1981.[101] Several mechanisms have since been shown to contribute to dysregulation of cholesterol homeostasis in prostate tumours. A major cholesterol-mediated mechanism through which statins inhibit tumour growth involves specialized cholesterol-rich regions of the cell membrane known as lipid rafts.[102] These domains facilitate membrane-initiated signalling events in the cell through compartmentalization of signalling pathways that can enhance tumour growth. Cell signalling pathways implicated in prostate cancer development and progression that might be affected by lipid rafts include the androgen receptor,[103] epidermal growth factor receptor (EGFR),[104] and the luteinizing hormone receptor.[105] Statins through their effect on intracellular cholesterol homeostasis are thought to disrupt the organization of lipid rafts and thus interfere with those downstream intracellular signalling pathways.[106] In a xenograft model of LNCaP cells, inhibition of cholesterol synthesis decreased the cholesterol content in lipid rafts, attenuated AKT signalling, and induced tumour cell apoptosis.[107] Cholesterol levels might also affect prostate cancer development via androgen signalling pathways, as cholesterol is the precursor of androgens. Lowered cholesterol levels utilizing statins might reduce prostate cancer growth by reducing serum or intratumoural levels of androgens. However, the effect of statins on serum androgen levels remains unclear.[108] Some studies have suggested that statins reduce serum testosterone levels,[109] albeit these were small reductions with supra-therapeutic statin dosages. However, a study of 1,812 men in the Boston Area Community Health Survey cohort, of which 237 men were statin users, found no association between statin use and serum androgen levels.[110]

Noncholesterol-mediated pathways

Statins inhibit the conversion of HMG-CoA to mevalonate, thereby reducing cellular mevalonate concentrations. Mevalonate is a precursor for a class of compounds called isoprenoids such as farnesyl pyrophosphate and geranyl pyrophosphate. These isoprenoids facilitate the recruitment of signalling proteins such as G-proteins of the Ras and Rho superfamilies by bridging their attachment to the plasma membranes where their signalling activities can promote prostate cancer survival and proliferation.[111] Thus, statins by reducing mevalonate and downstream isoprenoids might inhibit cancer cell proliferation. Statins have also been found to induce cancer cell apoptosis independently of their effect on cholesterol levels.[112] For example, in prostate cancer statins can inhibit cyclin-dependent kinase 2 and stimulate cell cycle arrest.[113] Statins also have direct anti-inflammatory and antiangiogenic properties that might also inhibit cancer growth and progression.[112] One study of men undergoing radical prostatectomy found statin users were 69% less likely to have inflammation within prostate tumours than nonusers (p=0.047) on specimen whole-mount examination.[114]

Role of statins in prevention of prostate cancer

Results for statins and prevention of prostate cancer are also mixed-similar to metformin. Most clinical data evaluating the effect of statins on the development and progression of prostate cancer is based on observational studies utilizing large databases or meta-analysis of statin randomized controlled trials (RCTs).[91] Since these studies were often focused on cardiovascular outcomes, they were underpowered to evaluate the true effect of statins on prostate cancer, unsurprisingly most did not detect a significant effect.[115] In a large population-based study, Yu *et al.* identified 11,772 men with newly diagnosed nonmetastatic prostate cancer and reported that the

postdiagnostic use of statins was associated with a decreased risk for prostate cancer mortality (HR, 0.76; 95% CI, 0.66–0.88) and all-cause mortality.[116] Recent *in-vitro* experiments have demonstrated a differential inhibition of HMG-CoA conversion by hydrophilic statins (pravastatin and rosuvastatin) as compared to hydrophobic statins (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin), leading to insufficient apoptosis in prostate cancer lines.[117] Although both groups have similar cholesterol-reduction properties, they hold different pleiotropic effects, caused by differences in their lipophilicity. The two groups of statins were investigated in a large population-based cohort study by Goldberg *et al.*, showing both groups to be associated with a lower hazard of prostate cancer–specific mortality at 32.4% (95% CI, 12.9–47.5%) for the hydrophilic group and 17% (95% CI, 2–31%) for the hydrophobic group at a median follow-up of 9.42 years.[118] Additionally, hydrophilic statins were shown to have decreased rates of prostate cancer diagnosis. The different results between the groups prompted the authors to call for more randomized trials in this area. Statins have been shown to be associated with lower PSA levels, which could lead to reduced cancer detection from fewer biopsies.[119] Freedland *et al.* sought to assess the association of statins and prostate cancer diagnosis in the REDUCE study population, who had mandatory biopsies irrespective of PSA levels.[120,121] Statins were not associated with overall prostate cancer diagnosis (p=0.54) or with low-grade (p=0.75) or high-grade cancer (p=0.46).

Roles of metformin and statin therapy combination in prevention of prostate cancer

At present time there is minimal literature on combination between metformin and statins in secondary prevention of prostate cancer patients on active surveillance. Most studies are on patients with advanced disease, with some indication of synergism in improving cancer-related outcomes. Currently, a randomized, double-blind, phase 2 trial, the LIGAND (Lipitor and Biguanide to Androgen Delay Trial), is examining the effects of combination metformin and Lipitor® on men with PSA between 2 and 5 and experiencing rising PSA levels despite definitive therapy (surgery and/or radiation). Over a 3-year period, this trial primarily aims to determine whether this combination therapy affects time to disease progression (defined as PSA rise to 10 ng/mL or greater, development of clinical overt metastases or patient/physician desire for androgen deprivation therapy).[122] The results are eagerly awaited.

Aspirin, cancer, lethal prostate cancer & the ADD-ASPIRIN phase 3 trial

Aspirin is known to have a role in adenoma and colon cancer risk reduction.[123,124] There is also randomized data of high-dose aspirin to reduce the risk for Lynch syndrome colorectal cancers and other potential cancers after a 10-year follow-up period.[125] Interestingly, cumulative recent and past preliminary robust observational data suggests the potential for aspirin to reduce the risk for lethal prostate cancer, which has also been preliminarily observed in African-American men.[126–129] Higher dosages and for longer durations may be more effective, but the question of adverse effects with age and a lack of direct randomized trials have been the issue.[130,131] However, these past and current concerns are being addressed in the ongoing phase 3 ADD-ASPIRIN trial, which includes men previously treated for localized prostate cancer at a higher risk for recurrence.[132] Two dosages of aspirin are being utilized (100 mg and 300 mg based on age of entry) versus placebo for 5 years, and over 1,900 men were randomized. This trial has already demonstrated the ability to inhibit platelet aggregation or thromboxane synthesis with aspirin, which could be a potential pathway to reducing recurrence risk or progression of some common cancers.[133]

5-Alpha-Reductase Inhibitors (5-ARIs) in Prevention of Development and Progression of Prostate Cancer (Finasteride, Dutasteride)

Anticancer mechanisms of 5-ARIs

The use of 5-ARIs in chemoprevention of prostate cancer is based on the androgenic nature of prostate cancer and the absence of prostate cancer among men with congenital deficiency of 5-alpha-reductase.[134,135] The enzyme 5-alpha-reductase resides in prostatic tissue and converts circulating testosterone into localized dihydrotestosterone (DHT), a more potent agonist of androgen receptors in prostatic cells. 5-alpha-reductase has two isoforms: type II 5-alpha-reductase is the isoform common in benign prostatic tissue; type I predominates in localized prostate cancer.[136] Finasteride is a selective inhibitor of type II enzyme, while dutasteride inhibits both isoforms.[134] The decreased levels of DHT induced by 5-ARIs may inhibit prostate cancer development and progression, thus explaining the chemopreventive roles of these drugs.

The roles of 5-ARIs in prevention of development and progression of prostate cancer

There were two generally positive large randomized controlled trials demonstrating the effects of 5-ARIs in primary prevention of prostate cancer.[137,138] The Prostate Cancer Prevention Trial (PCPT) reported a 24.8% relative reduction (95% CI, 18.6–30.6; $p<0.001$) in the risk for prostate cancer in patients receiving finasteride over the 7-year study period.[137] Similarly, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial reported a relative reduction of 22.8% (95% CI, 15.2–29.8; $p<0.001$) in prostate cancer events over the 4-year study period.[138] However, in both studies there was an increased likelihood of developing high-grade tumours when 5-ARIs were given as preventive agents to healthy men, which led the Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA) to recommend against prostate cancer chemoprevention labelling for the 5-ARI finasteride (Proscar®) and dutasteride (Avodart®). Therefore, it would follow that a more attractive strategy would be to use the 5-ARIs in secondary prevention of progression.

Multiple studies including one randomized controlled trial have examined the role of 5-ARIs in secondary prevention for men with low-risk localized prostate cancer under active surveillance.[139,140] In an initial single-institution, retrospective cohort study, Finelli *et al.* compared 70 men started on 5-ARI at variable time points after their diagnostic biopsy with 218 men who were not treated with 5-ARI while on active surveillance for low-risk prostate cancer.[139] Progression was defined as Gleason score > 6, maximal core involvement > 50% or > 3 positive cores on follow-up biopsy. At a median follow-up of 38.5 months, men treated with 5-ARI experienced lower rates of progression (18.6% vs. 36.7%; $p=0.004$) and were less likely to abandon active surveillance (20% vs. 37.6%; $p=0.006$). These findings remained significant on multivariate analysis. The trial faced some criticism for not

relating the use of 5-ARI as a time-dependent covariate, thereby allowing for potential overestimation of benefit. In a subsequent re-analysis using Cox proportional hazards model with time-dependent covariates, lack of 5-ARI treatment continued to be associated with pathological progression (HR, 4.55; 95% CI, 1.61–12.5; p=0.004).[140] In contrast, Ross *et al.* reported a retrospective study of 587 men enrolled into an active surveillance program, 47 of whom received 5-ARI during surveillance. The main study outcome was progression on surveillance biopsy, with 5-ARI use treated as a time-dependent covariate. On univariate analysis, progression occurred in 17% of 5-ARI users compared with 31% of nonusers (p=0.04). This significance was however lost on multivariable analysis.[141] The Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial is the only phase 3 RCT to evaluate the safety and efficacy of 5-ARIs in secondary prevention of men with low-risk prostate cancer followed by active surveillance.[142] In this randomized, double-blind, placebo-controlled trial, men aged 48–82 years who had low-volume Gleason score 5-6 prostate cancer and PSA ≤ 10 ng/mL on active surveillance, were randomized to receive once-daily dutasteride 0.5 mg/day (n=147) or matching placebo (n=155). The total follow-up was 3 years, with 12 core biopsy samples obtained at 18 and 36 months. The primary endpoint was time to disease progression. Secondary endpoints included improving anxiety, quality of life (QoL), and urinary symptoms in men undergoing active surveillance. At 3 years of follow-up, 54/144 (38%) in the dutasteride group had disease progression compared with 70/145 (48%) in the control group (HR, 0.62; 95% CI, 0.43–0.89; p=0.009). Subjects treated with dutasteride were more likely to have no cancer detected on follow-up biopsies (23% in placebo arm vs. 36% in dutasteride arm, p=0.024). Overall anxiety measured by the memorial anxiety scale for prostate cancer (MAX-PC) remained almost constant for controls and decreased for patients who received dutasteride throughout the study, specifically patients who received dutasteride reported a lower fear of recurrence. Overall rates of adverse events were similar. The authors concluded that in men on active surveillance, dutasteride may delay time for cancer progression and decrease prostate cancer–related anxiety, thereby providing a useful adjunct to active surveillance. Whether or not 5-alpha-reductase inhibitors reduce the risk for lethal prostate cancer is questionable, and currently long-term follow-up from trials such as PCPT have not found survival advantages or disadvantages.[143] The benefits versus limitations of these medications should be individualized.[144]

Miscellaneous (environmental, nonmodifiable risks, sleep, etc.)

Multiple miscellaneous options were considered by this committee, but most were not deemed relevant to elaborate on given the data concerning them is still at a nascent stage, or they do not fit a realistic, practical, and modifiable lifestyle or repurposed medication approach. There are several reputable reviews encompassing some of these and other modifiable or nonmodifiable topics that the reader is encouraged to peruse.[145,146] For example, environmental or occupational concerns exist in terms of prostate cancer risk and this will continue to be an area of interest.[147] Enzalutamide for earlier-stage prostate cancer has initial results from a preliminary trial.[148] This and other prostate cancer–directed medications should continue to receive research. Sleep duration and quality concerns are gaining momentum in terms of their associations and causation with different cancers, including prostate carcinoma.[149,150] Sleep is potentially modifiable, associated with a plethora of conditions, and it was recently added as a behavioral factor that is garnering more research in terms of its relation to cardiovascular and overall healthy lifestyle patterns.[2,3]

Conclusion of the Committee

The potential for modifiable lifestyle changes or repurposed medications to prevent lethal prostate cancer abounds. Yet, the question becomes which interventions or changes harbour the highest probability of success and the optimum benefit-to-risk ratio not only in preventing lethal prostate cancer but also other major causes of morbidity and mortality. A quick summary of the most promising options fulfilling these criteria for the committee is found in **TABLE 1**.

TABLE 1 Potential Risk-Reducing Lifestyle Changes, Metrics & Medications to Reduce the Risk for Lethal Prostate Cancer, Cardiovascular Disease, and All-Cause Mortality

Higher exercise volume and intensity (aerobic and resistance activities).
Primarily plant-based dietary pattern including generally whole unprocessed healthier foods and beverages also associated with a healthier lifestyle, but also other dietary patterns associated with an improvement in cardiovascular metrics.
Alcohol reduction and tobacco elimination.
Cardiovascular healthy metabolic metrics (weight/waist circumference, blood sugar/insulin sensitivity, cholesterol, blood pressure, inflammatory markers, etc.).
Repurposed medications (aspirin, metformin, statins, GLP-1 agonists,[71,151–155] etc.) for those who would qualify based primarily on cardiovascular disease (CVD) risk assessment. Prostate cancer research data available soon should help further guide this category and discussion (results of ADD-ASPIRIN trial, MAST, etc.).
Other modifiable changes such as sleep quality and quantity may have a future role in prostate cancer risk prevention akin to what has been observed recently in cardiovascular medicine. Regardless, healthy sleep is currently associated with the other healthy lifestyle recommendations in this table.

The goal of this committee was to highlight tangible options to enhance current clinician and patient communication. Otherwise, our contribution as a committee would be compromised since yet another manuscript on prevention is always important, but not always necessary. Again, clinicians need more pithy recommendations that have the highest probability of benefiting their patients not only against prostate cancer but also simultaneously for cardiovascular disease and all-cause mortality improvements. Interestingly, it is remarkable that the lifestyle changes and repurposed medications of most promise today are the same options that reduce cardiovascular disease events and promote longevity. They are also the same recommendations that can improve mental health and overall quality of life. This is what should be highlighted and lauded with verve knowing that what appears to be healthy for the prostate mirrors what is healthy for the mind and overall body. This is wonderfully serendipitous and gives patients a higher probability of a better outcome wherever they find themselves on their prostate cancer journey.

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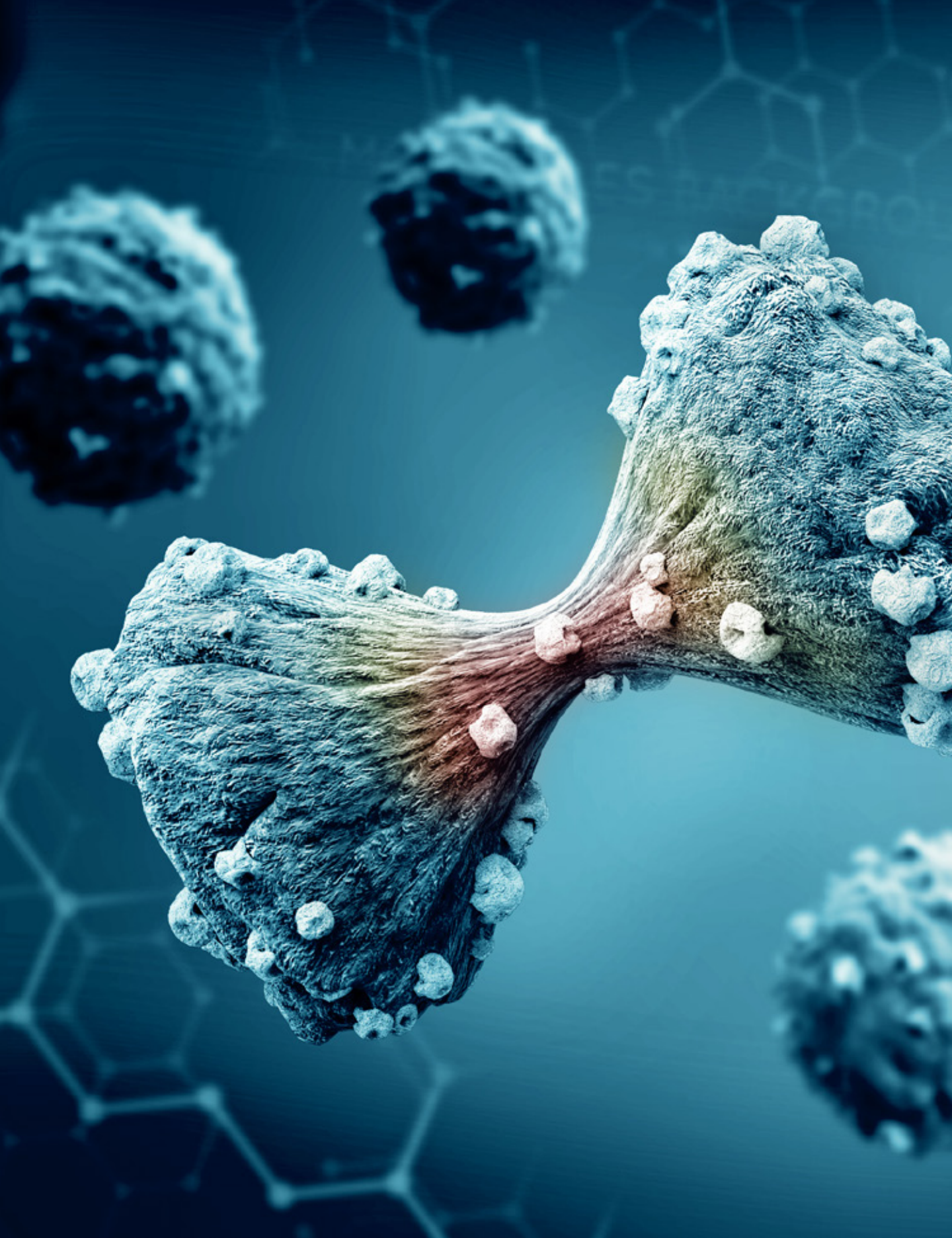

COMMITTEE 5

Germline Genetic Susceptibility to Prostate Cancer: Utility and Clinical Implementation

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Main chapter sections:

A – Genetic Assessment: Three Required Components

B – Rare Pathogenic Mutations and Prostate Cancer Susceptibility

C – Key Characteristics of PRS for Prostate Cancer Risk Assessment

D – Better Performance for Prostate Cancer Risk Assessment Than FH and RPMs

E – Inability to Differentiate Risk Between Indolent and Aggressive Prostate Cancer

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N – Future of Genetic Information That Is Employed in Clinical Practice

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Q – Satisfaction with Genetic Testing

Funding: Drs. Giri, Loeb, and Vadaparampil would like to acknowledge Supported by the Department of Defense (HT9425-23-1-1040) to SL/VNG/SV and the Prostate Cancer Foundation to SL/VNG for helping fund their contribution to this chapter.

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Introduction

Prostate cancer is the most common malignancy affecting men worldwide and the second most common cause of cancer-related death.[1] Based upon its prevalence, it is associated with a significant health burden due to its overall cost of diagnostic tests and treatments. Within recent years, it has become increasingly recognized that many prostate tumours follow a more "indolent" course and do not affect overall survival whether these men are monitored or actively treated.[2] However, over 30,000 men in the United States continue to succumb to prostate cancer annually. Therefore, controversies continue to exist around the role of prostate cancer screening and the ability to distinguish those patients most likely to harbour lethal tumours. Serum measurement of prostate-specific antigen (PSA), the most widely used screening blood test, has been scrutinized because it detects many indolent cancers and has a poor performance at discriminating between men with indolent and aggressive tumours.

Strategies that optimize the benefits of screening can be implemented by identifying men who are believed to be at the highest risk of developing prostate cancer, including aggressive disease, and then subsequently screening them at earlier ages when the tumours are organ confined. Authoritative groups differ regarding what defines this "high-risk" population and how they should be screened in terms of initiation and frequency.[3–5] However, since prostate cancer is considered to be the most heritable cancer among solid tumour types,[6] virtually every guideline recommendation suggests that men with a positive family history of prostate cancer have a significantly increased risk for the disease.[7] In addition, guidelines also acknowledge increased risk among men of black race, which also likely reflects a heritable component.

In the United States, approximately 1 in 8 white men without a family history of the disease will be diagnosed with sporadic prostate cancer throughout their lifetime.[1] In comparison, it has been demonstrated on countless occasions that family history increases the risk for the disease. For example, it has been demonstrated that men with a father with prostate cancer have approximately 1.5-fold higher risk of being diagnosed with prostate cancer and men with a brother with the disease have a slightly higher 1.7-fold higher risk of being diagnosed. Men with a limited number of first-degree relatives afflicted are referred to as familial disease. Men who have the greatest risk for prostate cancer often meet the criteria of hereditary disease defined by at least 3 generations affected, 3 first-degree relatives affected, or 2 relatives affected before age 55 years.[8] In addition, inherited risk for prostate cancer has been well established through twin and family studies that have reported up to 58% heritability for prostate cancer.[9–12] Taken together, family history information is commonly incorporated into risk evaluation for estimating an individual's disease susceptibility.[13]

For men with a strong family history, germline genetic testing for cancer-related variants may be recommended by a genetic counsellor.[14,15] Genetic testing should also be recommended for men diagnosed with hereditary prostate cancer, those with first-degree relatives who died of prostate cancer before 75 years of age, and/or those with multiple primary cancers. In addition, genetic counselling should be offered to men with a family history of other malignancies such as breast, ovarian, colon, pancreatic, and endometrial cancers, and melanoma that may

be associated with inherited risk for prostate cancer through common germline mutations. Therefore, men with a family history meeting the criteria for hereditary breast and ovarian cancers, hereditary prostate cancer, or Lynch syndrome should also undergo genetic testing.

However, family history data alone is often insufficient for identifying high-risk individuals, as most clinicians gather only first-degree family information, patients often do not know their family histories, family history information changes throughout a lifetime, and clinicians seldom recommend genetic testing for prostate cancer patients.[16] Thus, there is a need to include genetic findings that can objectively identify men at risk for cancer who would benefit from targeted screening and specific treatments, even if their family history is "negative."

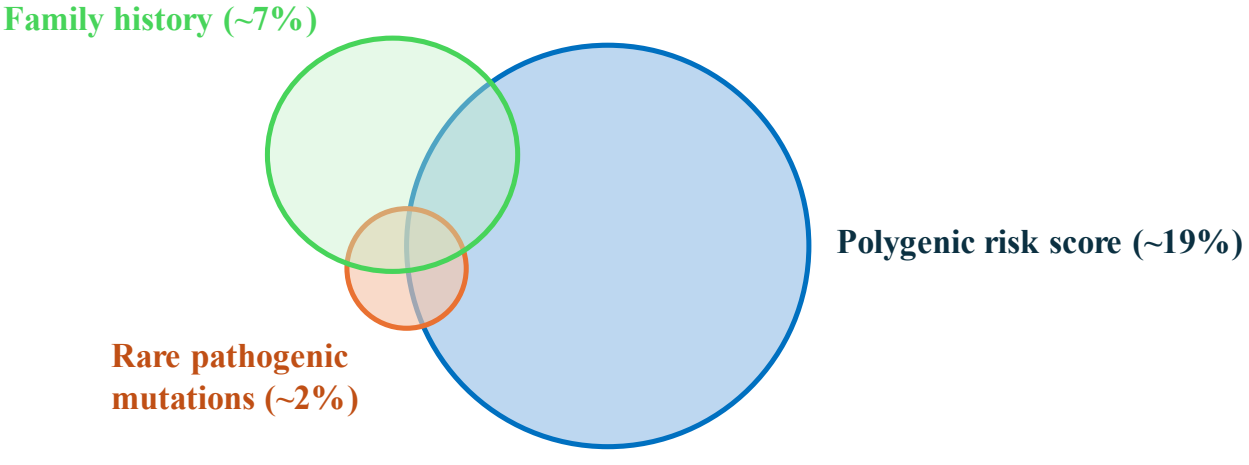
Prostate cancer is considered to be a complex genetic disease and includes both monogenic (evaluation for single gene mutations) and polygenic (evaluation of single nucleotide polymorphisms [SNPs]) components. Thus, it has been recommended that a complete genetic assessment should be performed and should include documentation of family history as well as testing for both of these germline components. The remainder of this chapter will provide an update on the utility of genetic assessment throughout a patient's prostate cancer journey. Specifically, it will discuss the influence of genetic assessment on the timing and intensity of screening, decisions for radical treatment for newly diagnosed patients, choice of medical therapies for patients with metastatic disease, and their implications on cascade screening among family members.

Genetic Assessment: Three Required Components

As mentioned above, family history information has been used as the gold standard for identifying high-risk individuals. This risk, however, is likely overestimated due to recall and screening biases. Family history information as an indirect measurement of disease risk was historically a reasonable approach when direct measurement of DNA variations was impractical. However, advances in DNA sequencing technologies and identification of validated prostate cancer susceptibility genes and germline variants have now provided direct and feasible mechanisms to measure inherited risk. These measurements include assessment of mutations in specific genes that are generally considered to be rare in the population (termed rare pathogenic mutations [RPMs]). The frequency of these genes in the general population has been estimated to be around 2–3%. In addition to RPMs, more than 300 prostate cancer risk–associated SNPs have also been identified through genome-wide association studies in the past decade.[17] The evidence for the association of these SNPs with prostate cancer risk is strong and reproducible; they all meet the stringent statistical criterion ($p<5 \times 10^{-8}$) and have been replicated in independent study populations. In contrast to RPMs, risk-associated SNPs are common but each has a small individual effect on disease risk. However, because these SNPs are independent and act additively, they have a stronger cumulative effect.

In order to obtain a complete genetic risk assessment on any individual, data suggests that three components are required: 1) family history, 2) rare pathogenic mutations, and 3) polygenic risk score (PRS) based upon SNPs. **FIGURE 1** is a schematic Venn diagram to show the proportion of high-risk men in the general population that can be identified by these three measures. The size of each circle indicates the proportion of high-risk men identified by each genetic measure. Approximately 7%, 2%, and 19% of men in the US population have a positive family history of prostate cancer, RPMs, and high polygenic risk score (top decile), respectively, and can be identified as having higher disease susceptibility.[3,6] The modest overlaps of these circles indicate that they are independent. Compared to family history, RPMs and PRS can identify more men with considerably higher risk. This Venn diagram clearly illustrates that the current standard of care of inherited risk assessment (family history alone) would miss more than 50% of high-risk men, including many at considerably higher risk. The sections below detail the relevant genes and variations that are part of the genetic assessment and how they can be used throughout the patient prostate cancer journey.

FIGURE 1 Schematic Venn diagram showing the proportion of high-risk men in the general population that can be identified by family history, rare pathogenic mutations, and polygenic risk score.



Rare Pathogenic Mutations and Prostate Cancer Susceptibility

Germline testing for prostate cancer came to the forefront at a unique time in history when multigene testing capabilities were available and precision medicine discoveries opened the door for advanced therapeutic options for men with metastatic prostate cancer.[18–21] Results of pathogenic variants from hereditary cancer gene testing can have significant impact on prostate cancer screening, managing risk for additional malignancies, treatment

of metastatic disease, and hereditary cancer assessment for men and their families.[22–24] Key genes associated with increased risk for prostate cancer include *BRCA2, BRCA1, HOXB13,* and DNA mismatch repair genes particularly *MSH2* and *MSH6*.

The National Comprehensive Cancer Network (NCCN) guidelines currently recommend genetic testing for high-risk individuals including those with a strong family history of prostate cancer and other cancers, those of Ashkenazi Jewish ancestry, and those with a known family history of high-risk RPMs.[25] The guidelines suggest multipanel gene testing for at least 10 different genes including *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6,* and *PMS2*. However, it is important to note that not all of these genes have similar utilities for patients throughout the prostate cancer journey. Only 4 of these genes (*HOXB13, BRCA2*, *ATM*, and *CHEK2)* have been validated in a large prospective population-based cohort to be associated with a significantly increased risk for prostate cancer.[26] In this same dataset, a different panel of RPMs (*NBN*, *BRCA2*, *ATM*, *CHEK2,* and *PALB2)* were associated with a significantly heightened propensity for aggressive disease.[27]

Most RPMs included in the NCCN guideline multigene panel are within genes that play significant roles in DNA damage repair mechanisms. These genes include *BRCA1, BRCA2, CHEK2, ATM, NBN,* and *PALB2*, alongside mismatch repair (MMR) mutations linked to Lynch syndrome, such as *MLH1, MSH2, MSH6*, and *PMS2*. BRCA1 and BRCA2 are pivotal in homologous recombination repair (HRR), and mutations in these genes have long been recognized for elevating the risk for breast and ovarian cancers in women. Germline *BRCA2* mutations in men significantly increase the risk for prostate cancer. Individuals with pathogenic *BRCA2* mutations typically are diagnosed at younger ages and present with higher Gleason grade tumours, leading to shorter median survival compared to those with sporadic prostate cancer. Among men under 65 years of age, BRCA2 carriers are at significantly higher risk for prostate cancer and aggressive disease compared to noncarriers (between 3.3–8.6-fold increased risk).[28]

While Lynch syndrome is commonly associated with colorectal, gynecologic, stomach, and upper urinary tract cancers, men with Lynch syndrome also face an elevated risk for prostate cancer. Grindedal *et al.* examined Lynch syndrome–related genes and found a standardized incidence ratio of nearly 6 for developing prostate tumours.[29] Among MMR carriers developing prostate cancer before the age of 70 years, 63% exhibited high-grade tumours, compared to 17% in non-MMR carriers. Another study involving 821 male Lynch syndrome carriers demonstrated an approximately 10-fold increase in the relative risk for prostate cancer among MSH2 carriers.

Other notable genes involved in double-strand DNA break repair include *ATM, CHEK2*, and the homeobox protein *HOXB13*. Hale *et al.* conducted a pooled analysis of 5 studies, revealing that *CHEK2* carriers had a prostate cancer odds ratio (OR) of 1.98 and 3.39 in unselected and familial cases, respectively.[30] The *HOXB13* G84E variant emerged as a significant prostate cancer risk gene through familial linkage studies, with the prostate cancer relative risk increasing by 4.51-fold in mutation carriers.[31,32] The prevalence of HOXB13 mutations varies widely across populations, ranging from 22% in Finland to 6% in North America and 1% in France.[33] A germline deletion variant in HOXB13 (X285K, rs77179853) has been found in black populations that increases prostate

cancer susceptibility and aggressive disease.[34] HOXB13 X285K has been associated with 2.4-fold increased odds for prostate cancer, with higher risk observed for more aggressive and advanced disease (Gleason ≥ 8: OR, 4.7; stage T3/T4: OR, 4.5; metastatic disease: OR, 5.1).

Single Nucleotide Polymorphisms, Polygenic Risk Scores, and Prostate Cancer Susceptibility

Polygenic risk score is a broad term to describe all methods measuring cumulative effect of multiple risk-associated SNPs. Many PRS methods for prostate cancer have been reported since 2008.[35] Earlier methods were simple summation of OR-weighted risk genotypes of prostate cancer risk–associated SNPs that met the genome-wide association studies (GWAS) significance level ($p<5 \times 10^{-8}$).[17,36] While the mean PRS values are consistently higher in cases than controls among all published studies, their face values change with the number of SNPs and do not indicate specific risk. To overcome this limitation, an alternative population-standardized OR-weighted method, called genetic risk score (GRS), was used.[37–40] For each SNP, OR-weighted genotype is first divided by the ancestry-specific effect of the SNP in the population (based on ancestry-specific OR and allele frequency) and then multiplied for all independent risk-associated SNPs. Due to this population-standardized feature and multiplication of all independent SNPs, the GRS value can be interpreted as relative risk to the ancestry-specific population, regardless the number of SNPs used in the calculation—e.g., a GRS of 1.5 for an individual indicates a 1.5-fold increased risk relative to the population. GRS is ancestry specific using ancestry-specific risk–associated SNPs, their corresponding OR, and allele frequency.

In contrast to PRS methods that are based only on GWAS-significant SNPs, recent PRS methods utilize a broader spectrum of risk-associated SNPs in the genome regardless of whether they reached the GWAS significance level.[41–43] These methods, sometime referred as polygenic score (PGS) or genome-wide polygenic risk scores (GW-PRS), utilize summary statistics of GWAS from development cohorts. They compare the performance of various algorithms for modelling linkage disequilibrium (LD) among risk-associated SNPs and validate the best algorithm in additional independent cohorts. Commonly used LD modelling algorithms are pruning and thresholding (P+T),[44] Bayesian genomic prediction methods (LDpred),[45,46] LASSOSUM,[47] and polygenic prediction via continuous shrinkage (PRS-CS).[48] An important feature of PGS is the ancestry-adjusted score value based on principal components (PCs) of subjects derived from ancestry informative markers.[49] This feature makes PGS applicable to all ancestries (pan-ancestry) and addresses a major concern of previous PRS methods that were limited to European ancestry. Despite this pan-ancestry feature, PGS generally performs better in European ancestry because most subjects in the PGS development and validation cohorts were from this ancestry population.

As of April 2024, 86 PRS methods for prostate cancer have been published and deposited in the PGS catalog.[50] Most of these PRS methods generally performed well for prostate cancer risk assessment where higher percentiles of PRS and higher prostate cancer risk were consistently observed. In addition, for GRS, predicted risk is well

calibrated by observed risk. For example, in a published study from a large cohort with > 125,000 individuals, 4 prior developed ancestry-specific GRSs for European (232 SNPs), East Asian (138 SNPs), African (128 SNPs), and Hispanic (67 SNPs) populations were independently validated where estimated prostate cancer risk was corroborated by observed risk.[40]

An interesting observation of various prostate cancer PRS methods is their similar performance as measured by the area under the curve (AUC). In a study comparing the performance of several PRS methods in the REDUCE (REduction by DUtasteride of prostate cancer Events) trial, AUC for predicting prostate cancer in European subjects was 0.62, 0.62, and 0.60, respectively, for GRS (110 SNPs), P+T (397 SNPs), and LDpred (3,023,543 SNPs).[38,51] Furthermore, in the most recently published large study, Darst and colleagues compared the performance of a GW-PRS method with a PRS of 269 established risk-associated SNPs (PRS_{269}) in 136,875 cases and 583,454 controls of European and African ancestries.[43] The best GW-PRS approach had AUCs of 0.656 (95% confidence interval [CI], 0.635–0.677) in African and 0.844 (95% CI, 0.840–0.848) in European ancestry men. In comparison, PRS_{269} had similar AUCs (0.679, 95% CI, 0.659–0.700 and 0.845, 95% CI, 0.841–0.849, respectively).

Currently, either ancestry-specific GRS or pan-ancestry PGS can be used for prostate cancer risk assessment. Ancestry-specific GRS is a good option for subjects of European, Asian, African, and Hispanic ancestry because it is well calibrated in these ancestry populations. On the other hand, pan-ancestry PGS is a better option for subjects of other or mixed ancestries.

Germline mutations associated with prostate cancer susceptibility have an evolving impact on the clinical management of prostate cancer ranging from prediagnosis genetic counselling to screening and early detection to newly diagnosed localized prostate cancer and metastatic disease. Given emerging evidence and guidelines, clinical pathways are now needed to facilitate germline testing in appropriately selected patients to inform treatment plans. This is particularly relevant since a significant number of patients with mutations currently don't meet guideline recommendations for genetic testing.[52,53] Therefore, future consideration of either population-based testing or expansion of guideline criteria is necessary.

Key Characteristics of PRS for Prostate Cancer Risk Assessment

As mentioned above, PRS, family history (FH), and RPMs of monogenic genes are three well-established genetic risks for prostate cancer.[51] PRS, however, has several unique and important characteristics for prostate cancer risk assessment. First, PRS is a direct measurement of genetic risk based on an individual's own DNA and is independent of environmental risk factors. This is in contrast to FH, which is an indirect measurement of genetic risk from relatives and reflects both shared household lifestyles and genetic risk.

Second, PRS, due to its combination of hundreds and thousands of SNPs, is a personalized measurement of an individual's genetic risk. Each person, even within a family, may have a unique PRS value. This is different from FH, where all first-degree relatives have the same genetic risk even though they only share 50% of genetics among them. This is also different from RPMs, where first-degree relatives have 50% chance of sharing the RPM. Therefore, the PRS test is required for assessing each individual genetic risk regardless of PRS values of other family members.

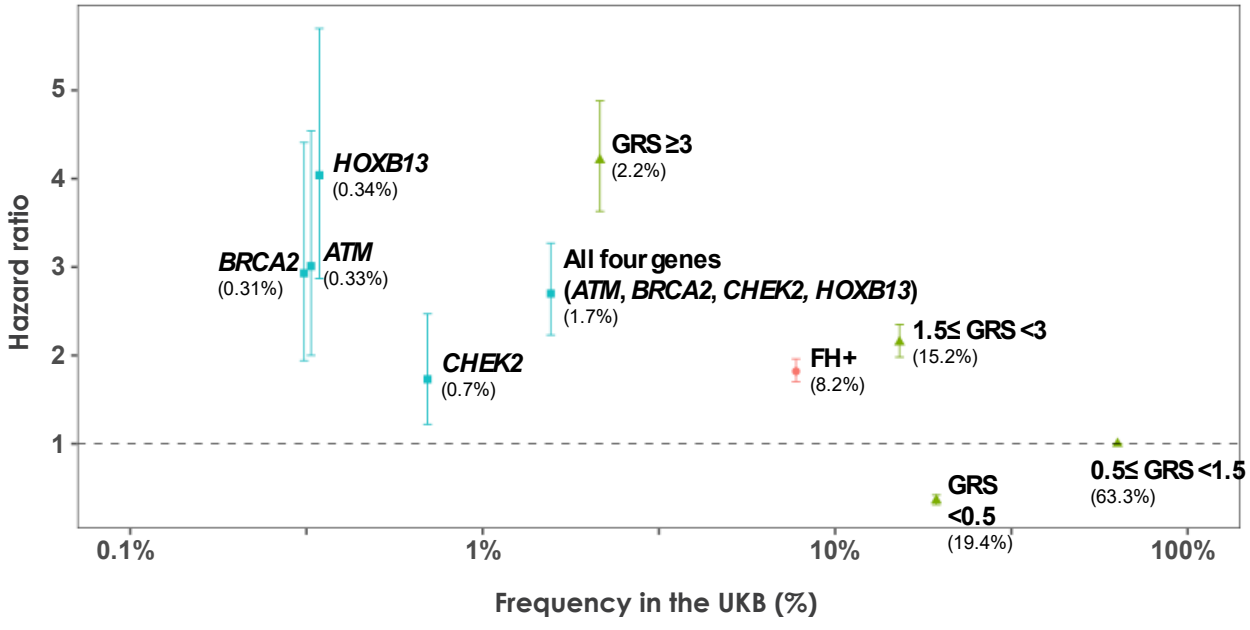
Third, PRS is more informative than FH and RPMs for stratifying prostate cancer risk. As mentioned above, while FH and RPMs can identify ~7% and 2% men at high risk for prostate cancer, respectively, PRS can identify ~19% men at risk similar to the relative risk of FH and RPMs (**FIGURE 1**).[39,51] In addition, unlike FH and RPMs, where negative subjects are less informative and generally considered as average risk, PRS can identify ~20% of men whose risk is half of the general population. The ability of identifying low-risk subjects is unique to PRS.

Better Performance for Prostate Cancer Risk Assessment Than FH and RPMs

With these unique and important characteristics, PRS is an ideal genetic risk assessment tool. Several studies reported that PRS performed better than and complementary to FH and RPMs for prostate cancer risk assessment.[39,54] For example, in a study that systematically and prospectively evaluated the performance of FH, RPMs, and GRS for risk stratification in the UK Biobank (UKB), a large population-based cohort with 211,014 European men without a prostate cancer diagnosis at recruitment and followed for ~10 years, each of the three genetic risk factors was independently associated with prostate cancer diagnosis (**FIGURE 2**).[51] Specifically, positive FH was found in 8.2% of men in the cohort (red). Compared to men without FH, men with FH had significantly increased prostate cancer risk (HR,1.82; p=3.64 x 10^{-64}). In addition, RPMs in the four previously established genes (*HOXB13, BRCA2*, *ATM,* and *CHEK2*) were found in 1.7% of men in the cohort (blue).[26] Compared to men without RPMs, men with RPMs had significantly increased prostate cancer risk (HR, 2.70; p=3.03 x 10^{-24}). In contrast, GRS was more informative for stratifying risk: 19.4%, 63.3%, 15.2%, and 2.2% of UKB men had low (< 0.5), average (0.5 to < 1.5), moderately high (1.5 to < 3), and high GRS (≥ 3), respectively (green). Compared to men with average GRS, HR for prostate cancer was 0.36 (p=1.32 x 10^{-38}), 2.15 (p=9.71 x 10^{-69}), and 4.21 (p=4.86 x 10^{-82}), respectively, for those with low, moderately high, and high GRS.

When all three inherited measures (FH, RPMs, and GRS) were used, they identified 25.0% of men with high prostate cancer risk (positive FH, RPM carriers, or GRS ≥ 1.5) and 17.9% of men with low prostate cancer risk (negative FH, RPM noncarriers, and GRS < 0.5). Compared to the remaining men, their HR for prostate cancer was 2.3 and 0.38, respectively. This represents a considerable improvement in risk stratification over current clinical guidelines, which are based on FH and RPMs.[55]

FIGURE 2 Observed prostate cancer risk (hazard ratio) and 95% CI of three inherited risk measures for prostate cancer in a prostate cancer incidence cohort from the UK Biobank (European descent, *N*=224,613).



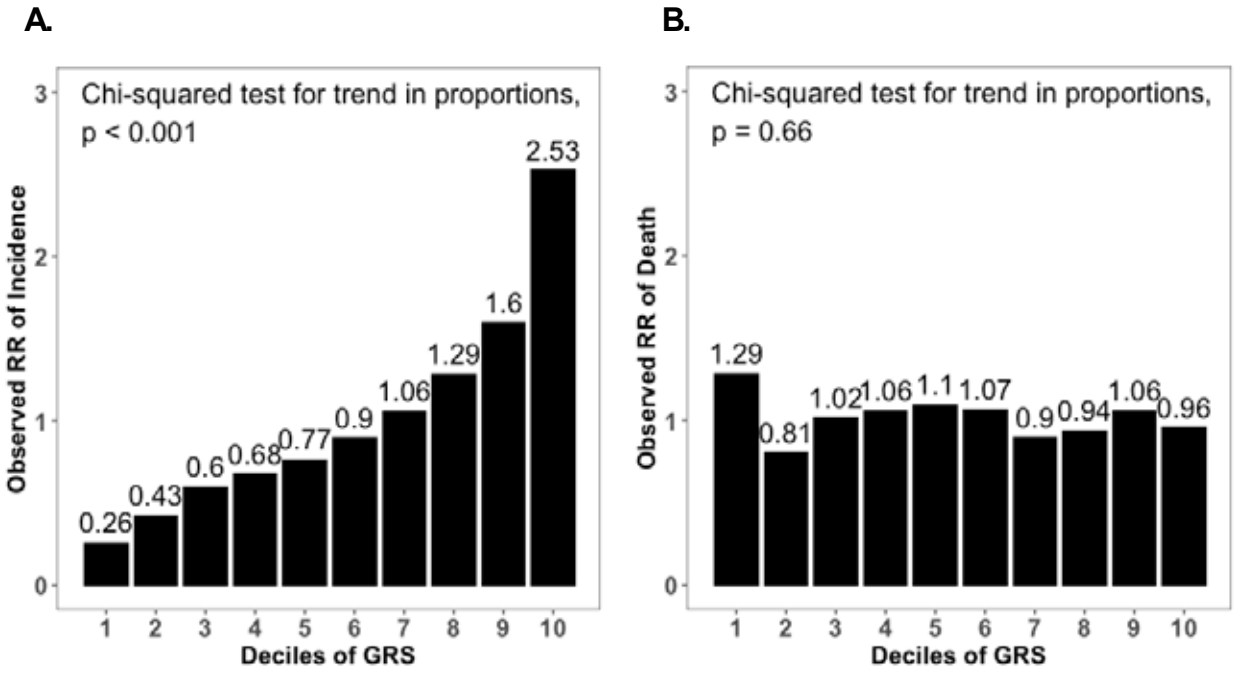
Abbreviation: GRS, genetic risk score.

Source: *Reprinted with permission from Springer Nature. Xu J, Resurreccion WK, Shi Z,* et al. *Inherited risk assessment and its clinical utility for predicting prostate cancer from diagnostic prostate biopsies.* Prostate Cancer Prostatic Dis. *2022;25(3):422–430. doi:10.1038/s41391-021-00458-6.*[51]

Inability to Differentiate Risk Between Indolent and Aggressive Prostate Cancer

It is important to note that PRS is associated with susceptibility to prostate cancer, including both indolent and aggressive prostate cancer (metastatic and/or lethal disease).[36,39,51,56–59] However, to date, none of the published PRS methods can differentiate risk between indolent and aggressive prostate cancer.[51,56,58] For example, among prostate cancer patients of European descent in the UKB, mean GRS was 1.53 and 1.60 among 415 lethal and 6,364 nonlethal prostate cancer cases, respectively (p=0.37).[51] Furthermore, while the risk for prostate cancer incidence during the follow-up increased with increasing GRS deciles (p<0.001) (**FIGURE 3A**), no significantly different risk for prostate cancer–specific mortality was found (p=0.66) (**FIGURE 3B**). Therefore, PRS is useful for predicting overall prostate cancer risk prior to a cancer diagnosis, but it does not have clinical utility for predicting disease prognosis once prostate cancer is diagnosed.

FIGURE 3 Observed rate ratio (RR) for prostate cancer incidence.



Abbreviation: GRS, genetic risk score.

Source: *Reprinted with permission from Springer Nature. Xu J, Resurreccion WK, Shi Z,* et al. *Inherited risk assessment and its clinical utility for predicting prostate cancer from diagnostic prostate biopsies.* Prostate Cancer Prostatic Dis. *2022;25(3):422–430. doi:10.1038/s41391-021-00458-6.*[51]

Challenges and Opportunities for Routine Implementation of PRS

Supplementing PRS to FH and RPMs for better genetic risk assessment has several potential clinical utilities, including an opportunity to develop a more effective personalized prostate cancer screening strategy,[58] better estimate penetrance of prostate cancer for carriers of RPMs,[54] and better estimate the detection rate of prostate cancer from prostate biopsy.[51] Despite these promising clinical utilities and consistent evidence for PRS in risk assessment, adoption of PRS in the clinic remains extremely limited. A major factor for this poor adoption in the clinic is that PRS has not been endorsed by professional guidelines, including the United States Preventive Services Task Force (USPSTF), the National Comprehensive Cancer Network (NCCN), and the American Urological Association (AUA). These organizations call for additional supporting evidence from prospective and randomized blinded trials for the validity and clinical benefits of PRS.

While there is agreement that more studies are helpful, consistent results from many large population-based cohorts such as UKB and Million Veteran Program (MVP) have already provided adequate evidence for the clinical validity of PRS in prostate cancer risk assessment.[39,43,54,57,58] There are two major rationales for this argument. First, if FH and monogenic testing are appropriate for genetic risk assessment and recommended by guidelines, PRS should also be included because its performance is better and its evidence is stronger. When considering a novel risk assessment tool, the principle should be whether it performs better than the current standard of care. Second, PRS, a germline biomarker that always precedes occurrence of disease, is practically prospective and not susceptible to reverse association. Furthermore, because neither patients nor researchers are aware of their PRS status in these study cohorts, PRS studies are practically double-blinded and their results are not susceptible to various observation bias. The potential benefits of adopting PRS in the clinic for genetic risk assessment likely outweigh potential harms, even though additional improvement in PRS is expected, especially in ancestry minority population.

Significant efforts are needed to implement PRS in the clinic for genetic risk assessment. In addition to making clinical-grade CLIA-certified PRS tests available in the clinic, there is a need for integration of PRS tests in electronic medical record, development of PRS-based clinical workflow for primary care physicians and urologists, as well as development of education material for physicians and patients.

Genetic Variation Among Different Racial Groups

Prostate cancer is an important health burden in African descent men (ADM), including among ADM in Sub-Saharan Africa (SSA): The number of prostate cancer deaths in SSA is predicted to more than double in the next 20 years.[60] Among the highest prostate cancer mortality rates in the world have been reported in African-American and African cases.[61] These observations demand that diverse data informing prostate cancer etiology are generated to have an impact on diverse populations worldwide.

Prostate cancer is unique among common cancers in that few modifiable risk factors are known. In contrast, prostate cancer has one of the highest heritabilities of any major cancer.[6,62] Not surprisingly, similar to men of white race, in men of African descent there are multiple lines of evidence that suggest genetics play a particularly important role in their prostate cancer risk and management. Early age at diagnosis is a hallmark of prostate cancer in SSA and may reflect a higher rate of hereditary cancer in SSA than in other high-risk populations. Numerous RPMs have been identified within key genes that may be clinically actionable, either by identifying high-risk individuals who may benefit from enhanced screening or who may benefit from targeted therapies.[63] Although comprehensive population studies of hereditary prostate cancer in SSA do not yet exist, unique *BRCA1/2* mutations of SSA origin have been reported in ADM, and the type of mutations in *BRCA1/2* differs between SSA and non-SAA populations.[64] Friebel *et al.*[64] reported the existence of *BRCA1/2* PV that are of African origin and may represent unique inherited susceptibility RPMs in men from SSA. White *et al.*[65] reported elevated

RPM frequencies compared with TCGA in *APC*, *BRCA1,* and *BRCA2* that were associated with increased African ancestry. Variant allele frequencies greater than 10% were identified at prostate cancer susceptibility genes including *BRCA1*, *BRCA2*, *ATM*, *MLH1*, and *PMS2*. These results suggest that RPM frequencies may be elevated in prostate cancer cases from SSA compared to other groups.

Again, similar to white men, in ADM SNPs identified through genome-wide association studies also confer substantial prostate cancer risks in aggregate, although each individual variant contributes only a small amount to overall risk.[36] In a large, multiethnic genome-wide association study of prostate cancer, Wang *et al.*[66] reported 451 variants to be associated with prostate cancer across ethnicities. When the authors computed a PRS using this panel, genetic risk was highest in ADM, with Caucasian and Hispanic men having nearly identical and lower risk than ADM. Asian men had the lowest polygenic predicted risk of all races/ethnicities. These results are consistent with the observed incidence of prostate cancer and reflect the importance of genetic susceptibility in prostate cancer etiology. Until recently there has been limited evidence of germline variants that predispose to aggressive prostate cancer. However, ADM in the top decile of a multi-ancestry PRS including 278 risk variants had a significantly higher risk for aggressive prostate cancer (OR, 1.23).[67]

Given the major contribution that genetics plays in estimating prostate cancer susceptibility in ADM and the increasing rates of prostate cancer in SSA, diversity in data used to inform prostate cancer etiology and progress is crucial. It is well documented that most cancer genetic testing data does not represent global racial and ethnic diversity, and that studies of the genetic architecture of disease in SSA are needed.[68] For example, the worldwide CIMBA consortium of *BRCA1/2* mutation carriers includes fewer than 5% of non-white individuals (and less than 1% African-descent individuals) from among more than 55,000 total carriers.[64] This deficit of diverse multiethnic data in cancer genetics research limits the ability to discover and translate genetic information to clinical practice.

It has been widely recognized that studies of genetics and genomics are not optimized if the data used to generate clinical interventions does not include data from ethnically diverse populations. Teo *et al.*[69] have demonstrated how multiethnic studies in African populations can yield novel insights about the underlying genetic architecture of human disease because of the unique nature of the African genome. Genomic studies based in African populations are more generalizable to other world populations compared to the same studies done in non-African populations due to the features of African genomic architecture.[70,71] Population-specific variants, substantial differences in variant frequencies across populations, effect-size heterogeneity, locus heterogeneity (i.e., differences in causal variants across populations), and haplotype diversity (i.e., linkage disequilibrium differences across populations) all contribute to limited translational capacity of genomic data if multiethnic populations are not studied.[72,73] Furthermore, design and sample size considerations for genomic research studies are highly dependent on accurate knowledge of allele and genotype frequencies.[74] For example, an intronic variant in *KLK3* (rs62113212) has been associated with aggressive prostate cancer,[75] yet this variant is absent in Africa. Population frequency differences such as this in part explain why there exist genome association studies that differ by geographic ancestry. Importantly, Manrai *et al.*[76] reported that genetic misdiagnoses may occur if genomic tests are developed using only white populations, and this misdiagnosis extends to both majority and minority populations. Thus, limited diversity in research data can impact the accuracy of genetic testing and clinical decision-making for all populations.

Clinical Implementation Along the Prostate Cancer Journey

As mentioned above, the majority of men are diagnosed with localized disease confined to the prostate, while a small population is diagnosed or will go on to develop metastatic disease. Among these latter advanced cohort patients, many will continue to progress to various castrate-resistant states and ultimately succumb to the disease. Genetic assessment plays a strong role throughout this prostate cancer journey, both for patients and their family members. The three components of the genetic assessment (discussed above) are emphasized at various points along the journey (**TABLE 1**). The following sections will discuss their importance at various disease states after diagnosis.

TABLE 1 Three Components of Genetic Assessment at Various Points Along Patient Journey

Genetic assessment information	Unaffected men: screening	Newly diagnosed: localized prostate cancer	Metastatic prostate cancer	Family members
Family history	++			++
Rare pathogenic mutations	+++	+++	++++	+++
Polygenic risk scores	++++	+		++++

Clinical Implementation of Genetic Assessment: Utility for Unaffected Individuals

Prostate cancer screening guidelines in the United States have undergone significant evolution in the past 10 to 15 years. The USPSTF initially recommended against prostate cancer screening in all men in 2012.[77] This recommendation was ultimately updated in 2018, when the USPSTF recommended that men aged 50 to 69 years engage in shared decision-making prior to the initiation of prostate cancer screening.[55] Multiple professional organizations, including the AUA,[78] the American Cancer Society (ACS),[79] the NCCN,[25] and European Association of Urology (EAU)[80] have issued prostate cancer screening guidelines statements recommending screening in appropriately selected men after undergoing shared decision-making. The key commonality between all these guidelines is what constitutes an appropriately selected man. Established factors such as age, race, and family history of prostate cancer have traditionally been the most important factors to consider prior to recommending prostate cancer screening. Adding germline genetic information has the potential to significantly improve clinicians' ability to discriminate who may be at higher risk for prostate cancer, thus additionally informing who may benefit from prostate cancer screening.

As previously discussed, RPMs and PRS can provide information regarding a man's risk of developing prostate cancer before they even begin being screened for prostate cancer. In particular, PRS shows a great deal of potential for identifying men who may benefit from prostate cancer screening. A study of the UKB demonstrated the potential for strong clinical utility in using GRS to estimate prostate cancer risk.[39] The UK Biobank is a prospective cohort study that includes genetic and phenotype data for approximately 500,000 individuals across the UK, aged 40 to 69 years.[81] Genetic data is available for all participants, and clinical data was derived from medical records and registries. Findings from the UKB confirm that rare pathogenic mutations are infrequent and occur in only 1.6% of men. Additionally, only 8.2% of men reported a positive family history of prostate cancer. This suggests that even if there were no overlap between RPM patients and those with a family history of prostate cancer, only 9.8% of men would be deemed at higher risk, and thus worthy of earlier or more intensive prostate cancer screening. In comparison, PRS identified 19.4% of men as low risk for prostate cancer and 17.4% of men as being high risk for prostate cancer.[51] If low-risk men were screened less frequently or not at all, and high-risk men were screened more frequently or beginning younger, the GRS could significantly influence screening decisions in 36.8% of men.

This concept has been further validated using data from the REDUCE trial.[82] There were 1,654 white men in the placebo arm of the REDUCE trial who consented to genetic studies. All of these men underwent prostate biopsy on study, and 410 men were found to have prostate cancer on biopsy (370 scheduled, 40 for-cause). Predictive models for prostate cancer diagnosis using best clinical data (age, FH, PSA, prostate volume, and cores sampled in baseline biopsy) had an AUC of 0.62. When a PRS was added to the model, the AUC significantly increased to 0.66. Furthermore, accounting for germline genetic risk increased the ability to predict diagnosis of high-risk prostate cancer on biopsy.[37]

Multiple additional polygenic risk scores have been evaluated in other populations. Aly *et al.* retrospectively studied the impact of adding a 35 SNP panel to clinical information to predict prostate cancer on biopsy in the Stockholm-1 cohort of 5,241 men biopsied between 2005 and 2007. They found that 480 (22.7%) of biopsies could have been avoided while missing only 3% of patients with cT3-4, N1, M1, or Gleason grade group ≥ 3 prostate cancer.[83] Similarly Black and colleagues reported on the utility of a polygenic risk score to predict prostate cancer diagnosis. This was a case-control validation study of 1,972 prostate cancer cases and 1,919 controls who underwent prostate biopsy. The authors found that susceptibility for prostate cancer increased significantly across PRS quartiles, with the highest-risk quartile having 3.98 times likelihood of having prostate cancer.[84]

While numerous PRS and multi-SNP panels have been validated for estimating prostate cancer disease susceptibility and are discussed throughout this chapter, there remains a significant gap in evaluating the clinical utility of using PRS for unaffected patients. One significant gap is that most polygenic risk score cohorts consist of patient populations that are overwhelmingly white. It is important to validate and calibrate these panels for multiple racial and ethnic groups. For example, Shi *et al.* calibrated a prostate cancer GRS 4 racial/ethnic groups using data from 23andMe. They found that ancestry-specific genetic risk scores were significantly more predictive of prostate cancer diagnosis than an all-ancestry risk score ($p<0.001$).[40] While specific racial calibration may be desirable, using a multiethnic model may be a reasonable and practical first step.

Plym and colleagues created a polygenic risk score using 269 genetic variants from a multiethnic GWAS of 107,247 prostate cancer cases and 127,006 controls. White and black men in the top quartile of risk had similar chances of developing prostate cancer, with odds ratios of 3.89 and 3.81, respectively.[85] There have been calls to increase ethnic diversity in clinical trial enrollment and sharing of genetic data in multiethnic cohorts,[86] but much work remains to increase equity in the use of germline genetic risk across racial and ethnic lines.

Many practical barriers also exist that hinder the use of genetic information for assessing prostate cancer risk in unaffected individuals. Men with rare pathogenic mutations can only be advised to commence or intensify prostate cancer screening if they know they have the mutation, and no standards exist for population-wide genotyping. Furthermore, most prostate cancer screening guidelines issued by authoritative groups do not currently make any recommendations regarding the routine use of genotyping or polygenic risk scores as a component of prostate cancer screening or to inform decisions about the initiation of prostate cancer screening. In addition, commercial availability of PRS is currently limited. Furthermore, while the costs of sequencing and genotyping have significantly decreased, an expense of several hundred US dollars on average may still be a barrier. While the data on polygenic risk scores and their utility in unaffected men are well validated and clinically meaningful, significant work is still required to get them incorporated into routine clinical practice.

Clinical Implementation of Genetic Assessment: Utility for Active Surveillance Patients

Germline genetic assessment of men with prostate cancer became more common following the 2016 work by Pritchard *et al.*[87] demonstrating that 4.6% of men with localized prostate cancer harboured mutations within DNA-damage repair (DDR) genes, and that only 2.7% control patients harboured similar mutations. Using a 53-gene BROCA panel, they found that 11.8% of men with *metastatic* prostate cancer had germline mutations in DNA repair genes. *BRCA2* mutations predominated and were found in 5.3%, and *ATM, CHEK2*, and *BRCA1* mutations were next most common at frequencies of 0.9–1.9% each. The authors then used the Cancer Genome Atlas to identify men with localized prostate cancer and found that only 2/43 (4.6%) with grade group 1 ([GG1]; aka Gleason grade 3+3) and 4/144 (2.7%) with grade group 2 ([GG2]; aka Gleason grade 3+4) patients harboured germline RPMs. If high-risk patients from within these subsets were excluded, the frequencies of germline mutations were 3.1% and 3.2%, respectively. The most significant relative risks conferred by heritable mutations between metastatic cases and clinically localized cases were noted for *BRCA2* and *CHEK2*. It was since demonstrated in a large screening study (IMPACT) that germline *BRCA2* mutation carriers have an increased risk for prostate cancer diagnosis, aggressive prostate cancer diagnosis, and a younger age at diagnosis, than noncarriers.[88] Shi and colleagues performed a meta-analysis of available data and concluded that a panel of mutations including *BRCA2, ATM, NBN, CHEK2,* and *PALB2* increases the risk for metastatic and lethal cancer.[27] Together, this suggests that specific mutations within panels of RPMs confer more aggressive disease.

In 2019, Carter and colleagues assessed germline mutational frequencies in a cohort of men from Johns Hopkins (JH; *N*=882) and North Shore University (NS; *N*=329) Hospitals who were under active surveillance (AS).[89] They used a similar 51-gene panel as the Pritchard group, but they focused their attention on a panel of three genes (*BRCA1*, *BRCA2*, and *ATM*) associated with aggressive disease: 2.1% (26/1211) of men from the joint cohort had mutations in one of these genes. Such germline mutations were significantly associated with upgrading during active surveillance. Grade reclassification was more common in men with mutations in one of these genes than in those without, with mutation carrier rates in this three-gene panel of 3.8% versus 2.1% in men who did versus those who did not reclassify. The primary statistical driver for upgrading outcomes was *BRCA2* mutation (despite its overall incidence of only 0.9% in the joint cohort), conferring a relative risk of 2.74 (95% CI, 1.26–5.96) for grade reclassification on multivariable analysis. The carrier rate of pathogenic mutations in the other 51 genes was very low, and it was not significantly different for any gene in men who upgraded after their cancer diagnosis than in men who did not. The median follow-up in these two cohorts was 3 years (NS) and 4 years (JH).

Three years later (2022), the multicentre Canary PASS cohort reported on germline genetics in 437 of their AS participants with an impressive 7.3 years of follow-up.[90] Overall, 6.6% (29/437) of study participants harboured a pathogenic germline mutation in one of 30 cancer predisposition genes on a multigene panel test, of which 19 (4.3% overall) occurred in a gene involved in DNA repair. Eight men (1.8%) had pathogenic germline mutations in the same three-gene panel reported on by Carter *et al.* (*BRCA1, BRCA2, ATM*), while most of the other mutations were in *CHEK2* and were low penetrance variants in many cases. In their study, which identified a low number of patients with these mutations, Brady *et al.*[90] found that the presence of pathogenic germline mutations in DNA repair genes was not predictive of either grade reclassification or adverse pathology, with comparable carrier rates of pathogenic mutations in men who did and who did not undergo grade reclassification (1.9% vs. 1.8%). Interestingly, the overall prevalence of pathogenic germline mutations did not differ between men with (5.1%) or without (7.3%) a first-degree relative with prostate cancer, confirming that prostate cancer heritability is polygenic in the majority of cases.

A small prospective AS study has also been reported from Israel, where a germline screening program identified rare pathogenic mutations in men who then underwent intense cancer screening.[91] Fifteen male carriers of DNA-repair mutations who were diagnosed with GG1 disease and who selected AS were identified—*BRCA1* and *BRCA2* germline mutations predominated in this 15-patient cohort. Over a mean follow-up of 28 months, there appeared to be no increase in upgrading and outcomes were similar to those men without mutations on AS from North America and Europe with GG1 disease.

There are of course other ways of studying inherited risk, including assessment of prostate cancer family history, extended family history of prostate and other cancers, and use of polygenic risk scores. Research is underway using combinations of the above factors and rare pathogenic mutations to predict prostate cancer risk, and lethal prostate cancer risk, in specific populations. For example, in a cohort from UKB it was shown that there are interactions between pathogenic germline mutations in *HOXB13, BRCA2, ATM,* and *CHEK2* and polygenic risk scores in terms of prostate cancer risk.[54] These interactions have not been well characterized in an AS or favourable-risk prostate cancer population in terms of predicting grade

reclassification or other measures of progression. Given how rare it is to find pathogenic germline mutations in known prostate cancer predisposition genes in low-risk populations, it appears likely that a prostate cancer patient's suitability for surveillance may depend on other factors associated with hereditary risk. These factors (e.g., family history of prostate cancer, polygenic risk score) are assessable in more men than is the presence of rare pathogenic mutations, and therefore require dedicated study to determine their impact on AS outcomes. It will be fascinating to see the interplay of these factors, as well as environmental and lifestyle factors such as diet and activity level, in terms of developing a personalized, evidence-based surveillance regimen in the years to come.

At present, guideline panels do not make strong recommendations on how to perform AS or on the safety of AS in men with RPMs with much evidence due to both a paucity of data and the mixed findings from the cohorts described above. For the time being, it seems prudent to intensify AS regimens in men with known germline rare pathogenic mutations in BRCA2 and perhaps a few other DNA repair genes such as *BRCA1, ATM*, and *CHEK2*, rather than to exclude them from AS completely. Concerns with continued AS should be apparent when such individuals also have other features associated with early-grade reclassification such as high PSA density, high tumour volume, perineural invasion, high somatic expression burden, and/or grade group 2 disease.[92,93] Prudent personalized intensification or de-intensification of AS follow-up regimens based on such hereditary and acquired characteristics is a worthy and achievable goal over the coming decade.

Polygenic risk scores have also been evaluated among men with localized disease. As mentioned above, most studies demonstrate that PRS values are associated with the risk for all types of prostate tumours, including high-grade tumours. To further clarify, PRS values do not routinely discriminate between aggressive and nonaggressive tumour types. However, it has been demonstrated that PRS values are positively associated with the multifocality of prostate tumours.[94] This could have potential in selecting appropriate patients for active surveillance or emerging focal therapies, as individuals with increased PRS may not be as suitable candidates.[95]

Clinical Implementation of Genetic Assessment: Responsiveness to Treatment for Metastatic Cancer

Few studies have specifically evaluated the influence of RPMs or PRS among individuals with either nonmetastatic or metastatic castrate-sensitive prostate cancer. It would be surprising if PRS predicted disease response in this cohort, based upon the fact that PRS does not distinguish aggressive tumours from nonaggressive tumours. However, specific variations within genes have been associated with response time to androgen deprivation therapies (ADTs). DDR genes have been associated with shorter response time to ADT and lower overall survival.[27,96] In addition, other gene variants have been validated to be associated with hormone response time. For example, the adrenal androgen–metabolizing 3β-hydroxysteroid dehydrogenase-1 enzyme, encoded by

the *HSD3B1* gene, is necessary for nontesticular testosterone and dihydrotestosterone production. The common adrenal-permissive *HSD3B1* allele is responsible for encoding the 3β-HSD1 protein with decreased susceptibility to degradation, resulting in higher extragonadal androgen synthesis. Retrospective studies have suggested an association of the *HSD3B1* adrenal-permissive homozygous genotype with ADT resistance in prostate cancer.[97–101] McKay *et al.* reported that a homozygous variant *HSD3B1* genotype was associated with increased prostate cancer–specific mortality in a cohort of 5,287 individuals undergoing prostate cancer treatment at the Veterans Health Administration system.[102]

Within recent years, observations have been made that individuals with metastatic tumours who harbour RPMs within HRR genes (which include DDR genes and MMR genes) have improved clinical responses to certain pharmacotherapies. No conclusive data is available regarding the potential use of germline or somatic alterations in DDR genes for selecting the most appropriate management of advanced prostate cancer patients beyond the use of poly (ADP-ribose) polymerase inhibitor (PARPi) in patients with certain HRR alterations and anti–programmed cell death 1 receptor (PD-1)/programmed cell death 1 ligand 1 (PD-L1) inhibitors in patients with MMR defects. Most of the evidence regarding the impact of germline DDR alterations on the benefit of standard therapies for this disease comes from retrospective series, often focused on germline *BRCA2* mutations, as these are the most abundant pathogenic germline variants in prostate cancer and multiple studies have consistently demonstrated that inherited pathogenic *BRCA2* mutations are an independent prognostic factor for poor prostate cancer outcomes.[89,103–105]

In the metastatic hormone-sensitive prostate cancer (mHSPC) setting, patients with certain germline and somatic DDR alterations, including *BRCA2* and *MSH2*, have been reported to progress to castration resistance after initiation of continuous ADT more rapidly than patients without those alterations.[106–111] At present, there is no data on the potential benefit of intensified treatment with docetaxel plus an androgen receptor signalling inhibitor (ARSi) in these patients compared with the use of either of them for mHSPC. Three currently ongoing trials (NCT04497844, NCT04821622, NCT06120491) will address the benefit of treatment intensification with a PARPi plus an ARSi (abiraterone, enzalutamide, or darolutamide).

In metastatic castration-resistant prostate cancer (mCRPC), three retrospective studies have reported conflicting results when assessing the role of germline DDR alterations on the cause-specific survival of patients treated with ARSi and taxanes. Annala *et al.*[106] observed worse outcomes in germline DDR carriers than in noncarriers, while Mateo *et al.*[112] found no difference and Antonarakis *et al.*[113] described improved survival in carriers. To date, PROREPAIR-B has been the only prospective study to address the outcomes of germline DDR mutation carriers in a cohort of 419 mCRPC patients.[107] In this study, the median prostate cancer–specific survival was halved in *BRCA2* carriers compared with noncarriers (17.4 vs. 33.2 months). Carriers of mutations in other DDR genes also tended to shorter survival but the difference did not reach statistical significance. Similar response rates to taxanes and ARSi were observed in carriers and noncarriers, with a trend to rapid progression to these therapies in *BRCA2* carriers. Aldea *et al.*[114] focused on the benefit of cabazitaxel in mCRPC patients with germline or somatic DDR defects and found no difference in response rates in patients with and without such alterations. However, the benefit for cabazitaxel was diminished in patients previously treated with PARPi.

Radiopharmaceutical therapy involves the targeted delivery of radiation to tumour cells. It could be expected that tumours unable to repair DNA damage would be more sensitive to these treatments; however, the antitumour efficacy of Radium^{223}– and Lu^{177}–prostate-specific membrane antigen ([PMSA]; α- and β- emitter, respectively) in DDR-deficient tumours has not been well characterized.

Radium^{223} has been associated with improved outcomes in mCRPC patients with germline and somatic DDR alterations in a retrospective[115] and a prospective[116] series, although the limited number of patients with DDR-deficient tumours included in both series precludes drawing definitive conclusions. Increased PSMA expression has been reported in DDR-deficient prostate tumours[117] and an association between *BRCA2* alterations and response to Lu^{177}-PSMA has been suggested;[118] however, further studies are needed to confirm these preliminary observations.

More recently, the Capture study has shown that when conventional therapies discussed above are used to treat advanced prostate cancer, patients with either germline or somatic BRCA1/BRCA2 alterations have shorter survival than patients with no-BRCA HRR alterations or without HRR defects.[119] The cohort included 729 patients followed for 26 months from initiation of the first line of therapy for mCRPC. Overall survival of patients with *BRCA1/2*, non-BRCA HRR, and non-HRR alterations was 18.2, 21.9, and 29.6 months, respectively. No differences between BRCA1/2 patients with germline and somatic alterations were observed.

The Capture study clearly reflects the need for alternative treatment strategies for these patients with HRR defects. Fortunately, PARP inhibitors have demonstrated notorious antitumour activity in patients with HRR deficiency, particularly in those with BRCA1/2 alterations. In prostate cancer, phase 2 trials have investigated the efficacy and safety of various PARP inhibitors in patients with HRR-altered mCRPC and disease progression to several treatment lines, with the primary endpoints being objective response rate (ORR) and/or prostate-specific antigen reduction ≥ 50% (PSA50). TOPARP-B,[120] TRITON2,[20,121,122] TALAPRO-1,[123] and GALAHAD,[124] have, respectively, assessed the efficacy of olaparib, rucaparib, talazoparib, and niraparib. In all of them, a marked benefit was seen in the *BRCA 1/2* population, with ORR ranging from 34% to 52% and PSA response from 43% to 76%. The antitumour activity associated with alterations in non-BRCA HRR genes is heterogeneous; while the clinical benefit of PARP inhibitors in patients with *ATM, CDK12*, or *CHEK2* alterations seems to be limited at best,[120,121,123,124] relevant response rates have been reported in patients with *PALB2* alterations.[120,122,123] PROFound[19] was the first randomized biomarker-driven study in mCRPC. After progression to an ARSi, olaparib was demonstrated to prolong the overall survival of patients with BRCA1, *BRCA2*, and *ATM* alterations compared to a second ARSi. An exploratory gene-by-gene analyses suggested significantly less benefit for patients with *ATM* alterations than for those with *BRCA2* defects. These differences in response have been confirmed in the TRITON-3 study,[125] which assessed rucaparib monotherapy for the treatment of mCRPC patients with *BRCA1, BRCA2*, or *ATM* after progression to an ARSi. In this study, olaparib was superior to docetaxel and to a second ARSi for patients with BRCA1/BRCA2 alterations, but no differences in time to radiographic progression (rPFS) between treatment modalities were noticed for ATM patients. Exploratory analyses conducted in these studies did not observe differences in antitumour efficacy or survival benefit in patients with germline *BRCA1/BRCA2* mutations compared to those with somatic alterations.[122,126] Poly (ADP-ribose) polymerase inhibitors have also

been investigated in combination with other therapies for mCRPC, although only the combination with ARSi has derived positive results. In PROpel,[127] TALAPRO-2,[21] and MAGNITUDE,[128,129] the addition of a PARPi to an ARSi resulted in improved radiographic progression-free survival (rPFS) and overall survival compared with ARSi alone. These studies have demonstrated a consistent hierarchy in benefit that is aligned with biology: tumours with BRCA2 alterations benefit more than those with other HHR alterations, and patients with both do better than patients without alterations. It has not been reported whether the germline or somatic origin of the alterations has any impact on the response to these combinations. Recently, the phase 2 study BRCAAway has suggested that the combination of olaparib plus abiraterone may be superior to either agent in monotherapy for patients with BRCA1/BRCA2 alterations.[130]

Another treatment strategy for patients with HRR defects could be the use of platinum-based chemotherapy. Platinum salts that cause DNA cross-links have proven to be a successful strategy for the treatment of breast[131,132] and ovarian[133] cancers with pathogenic mutations in *BRCA1* or *BRCA2*. However, this is not a standard-of-care option in prostate cancer, although retrospective studies suggest that patients with DDR defects, particularly those with *BRCA*2 alterations, may benefit from this approach,[134–136] and the efficacy of platinum-based chemotherapy for DDR-defective prostate cancer is currently being evaluated in clinical trials. Importantly, Mota *et al.*[136] have reported some prolonged responses to platinum-based chemotherapy in *BRCA2*-altered patients whose disease had progressed to treatment with PARPi. This observation warrants further prospective studies to validate the efficacy of this strategy.[137]

Different studies are currently investigating potential strategies to overcome the resistance to PARPi and platinum that eventually occurs. Preclinical studies have shown that PARPi and platinum-resistant cancer models may be resensitized to PARPi when combined with other drugs that target molecular vulnerabilities, including cell cycle checkpoints[138] and replication stress.[139] Early-phase trials have shown signal of activity with PARP inhibition rechallenge in combination with ATR or Wee1 inhibition in various tumour types. Other potent inhibitors that target different key nodes along the DNA damage repair cascade are also in clinical development, including CHK1/2, DNA-PK, ATM, and POLθ,[140] which may represent other potential combination partners for PARPi.

MMR gene alterations are present in 3.1% of advanced prostate tumours and *MSH2* is the most commonly altered MMR gene in prostate cancer.[141] A significant proportion of these alterations is germline.[142] MMR defects have also been associated with aggressive features and more advanced disease at diagnosis.[109,143,144] However, conflicting results have been reported on the clinical outcomes of MMR-defective patients,[143] as a study suggests favourable response to androgen deprivation, while others have found that these patients develop castration resistance earlier than the MMR-proficient ones.[109,115,145] Immune checkpoint inhibitors are approved for patients with MMR defects and/or microsatellite instability high (dMMR/MSI-H) and the NCCN guidelines recommend their use after progression to taxanes and ARSi.[146] However, variable responses to pembrolizumab have been reported in a retrospective analysis,[141] with no clear correlation between responses to pembrolizumab and DDR defects or MMR deficiency in clinical trials.[147]

Ongoing Clinical Trials Involving Germline Genetics and Initial Results

International studies of large case-control samples such as those from the PRACTICAL consortium have reported that the largest component of genetic predisposition to prostate cancer risk is due to common variants (present in > 1% of the population), each conferring a small per allele odds ratio of risk, but as these are numerous and the risks are multiplicative, the overall relative risks for prostate cancer can therefore be substantial.[66] Most of these are noncoding and map to controlling regions (usually enhancers) in the genome. The latest common variant risk profile that was reported in individuals from diverse populations has shown that a total of 451 variants (SNPs) is associated with prostate cancer development. Of note, some of these are unique to men of African ancestry and have a high-per-allele odds ratio, which may account for the fact that men of such origin have a higher risk (on average, 2-fold) of prostate cancer compared with men of European origin. This paper has shown that men of African ancestry reach the same risk for prostate cancer at age 66 years as men of European ancestry when the latter are 85 years old. The relative risk for prostate cancer in individuals of European origin in the top 1% of the risk distribution with the latest 451 SNP profile is 9.99-fold and in those of African origin is 6.39-fold compared with the average of the population. McHugh *et al.* have reviewed the potential for screening in men of diverse ancestries.[148]

There are reports that rare variants increase prostate cancer risk and the majority of these are in DNA repair genes, such as *BRCA1, BRCA2, MMR* genes, *ATM, CHEK2,* and *NBN*. These are mainly coding alterations, and each confers substantial prostate cancer risks. For example, these are 1.8, 5, 3, 4, 2.5, and 16-fold, respectively (reviewed in Hall *et al.* and Eeles; JMG review in press 2024). Furthermore, in some of these cases the prostate cancer is more aggressive (more likely to have a higher Gleason score and poorer survival).

Targeted Prostate Cancer Screening in Individuals with Alterations in Rare Variants

The IMPACT consortium of 65 centres in 20 countries was started to screen men with germline mutations in *BRCA1* and *BRCA2* versus controls (men with a negative *BRCA* test). The study was an annual PSA with a threshold > 3 ng/mL (as this is what the ethics committee would approve) and did not use magnetic resonance imaging (MRI) (as this was in 2006 in the pre-MRI era). The baseline paper reported on 2,481 men (791 *BRCA1* carriers, 531 *BRCA1* controls; 731 *BRCA2* carriers, 428 *BRCA2* controls); 199 men (8%) had a PSA of > 3.0 ng/mL and 59 prostate cancers were diagnosed (18 in *BRCA1* mutation carriers, 10 *BRCA1* controls; 24 *BRCA2* mutation carriers, 7 *BRCA2* controls); 66% of the tumours were classified as intermediate- or high-risk disease. The positive predictive value (PPV) for biopsy using a PSA threshold of 3.0 ng/mL in *BRCA2* mutation carriers was 48%; this is twice that reported in population screening studies.[149] The 3-year screening data were reported in 2019 in 2,932

individuals (919 *BRCA1* mutation carriers, 709 *BRCA1* controls, 902 *BRCA2* mutation carriers, and 497 *BRCA2* controls). A total of 527 men had a PSA of > 3.0 ng/mL, 357 biopsies were performed, and 112 prostate cancers were diagnosed (31 *BRCA1* mutation carriers, 19 *BRCA1* noncarriers, 47 *BRCA2* mutation carriers, and 15 *BRCA2* noncarriers). Cancer incidence rate per 1,000 person years was higher in *BRCA2* carriers than in noncarriers (19.4 vs. 12.0; p=0.03); *BRCA2* carriers were diagnosed younger (61 vs. 64 yrs.; p=0.04) and were more likely to have clinically significant disease than *BRCA2* controls (77% vs. 40%; p=0.01). No differences in age/tumour characteristics were seen in the *BRCA1* carrier and control groups.[88]

As a result of this report, the EAU now has a guideline that recommends annual PSA screening in *BRCA2* mutation carriers from the age 40–69 years. The NCCN also updated its guidelines to advise prostate cancer screening to start at age 45 years for male *BRCA2* mutation carriers and to consider the same for *BRCA1* mutation carriers. However, there are no guidelines in the UK or internationally for *MMR* carriers presently.

Lynch syndrome is a multicancer syndrome caused by constitutional mutations in *MMR* genes and prostate cancer has been reported in these families.[150] Alterations in the *MMR* genes *MSH2*, *MSH6*, and *MLH1* have been reported to increase prostate cancer risk between 2–10-fold, and there is also an association between higher-grade tumours and younger age of onset reported, particularly in *MSH2* mutation carriers.

Bancroft *et al.* recently published the results from the first screen of the *MMR* cohort in IMPACT, which confirmed a higher prostate cancer incidence in *MSH2* mutation carriers versus noncarriers (4.3% vs. 0.5%; p=0.01) and in *MSH6* mutation carriers versus noncarriers (3% vs. 0%; p=0.04). We confirmed that *MSH2* carriers were diagnosed at a younger age (60 vs. 66 years) and that 85% of the *MSH2* carriers and 75% of the *MSH6* carriers had more advanced prostate cancer requiring interventional treatment rather than active surveillance.[144]

Targeted Prostate Cancer Screening Among Individuals with Alterations in Common Variants

The discovery of numerous constitutional variants that can be typed to produce a PRS enables the genetic profiling of populations for risk stratification and targeted screening. Helfand and colleagues[151] have proposed a PSA screening algorithm based on a 100 SNP score. The new diverse 451 score outlined above will enable profiling for risk stratification in diverse populations of European, Asian, and African ancestry.

Eeles's group has started a suite of studies (the PROFILE and BARCODE 1 studies) that are offering intensive screening in studies to men aged 40–69 years who are invited to undergo a DW-MPMRI, prostate biopsy, and have biological samples taken (including a PSA). The entry criteria for PROFILE are individuals with prostates (i) with a family history of at least one first-degree relative (or second if through the maternal line) with prostate cancer < 70 years, or (ii) of African/black Afro-Caribbean origin with the same ancestry in all 4 grandparents, or (iii) with constitutional mutation in a DNA repair gene or polygenic risk score of > 90%.

The BARCODE 1 study has typed 5,000 individuals aged 55–69 years with prostates of European origin in London, United Kingdom, using a saliva sample for 130 risk SNPs, which at that time was only applicable to Europeans. The top 10% of the risk strata were then offered the intensive screening program as in PROFILE.

These studies have reported feasibility data, and the baseline data from BARCODE 1 will be submitted for publication in mid-2024. BARCODE 1 reported that 26% of men offered a saliva test via a general practitioner (GP) letter would take up the test.[152] The PROFILE pilot study reported analysis of 71 SNPs in 100 men from the family history study and at that time these were of European origin; 25 were diagnosed with prostate cancer and 48% had clinically significant disease.[153]

Pashayan's group has modelled potential benefits from polygenic risk stratification of populations for screening with the aim of reducing overdiagnosis[154] and these will need to be tested with real-world data.

Advances have been made in targeted treatments for individuals who are known carriers of pathogenic variants in DNA repair genes and who have metastatic prostate cancer with the use of immunotherapy, platinum agents, and PARP inhibitors showing promise in the research setting. PARP inhibitors have been adopted as standard treatments for men with metastatic disease and a *BRCA1/2* mutation in the United States, Europe, and the United Kingdom. Individuals with pathogenic mutations in the *MMR* genes and metastatic disease are now offered immunotherapy within trials. Therefore, recommendations to include germline testing in individuals with metastatic prostate cancer have been made,[155] which will lead to testing of the patients' unaffected relatives who can then be offered targeted screening.

In summary, there are starting to be international guidelines for targeted prostate cancer screening based on constitutional genetic variation. Although initially these pertain to germline *BRCA* mutations, the results of trials of screening in the next few years will report on the role of more extensive genetic profiles (both rare and common genetic variation) and the optimal screening algorithm. At present, the frequency of PSA testing, the use of MRI and whether some individuals will need to proceed directly to prostate biopsy, in the genetically higher-risk groups, is unknown.

Future of Genetic Information That Is Employed in Clinical Practice

The information provided by a genetic assessment is imperative to decision-making along the prostate cancer journey (**TABLE 1**). Genomic variation influences prostate cancer risk, disease presentation and prognosis, and a patient's response to treatment, including side effects. Understanding and translating this knowledge into a clinical setting can provide patients with significant benefits in terms of patient morbidity and mortality. Prostate cancer patients have only recently begun to benefit from gene-based clinical strategies or "personalized medicine," including risk prediction and metastatic treatment decisions. However, to optimize patient outcomes for *all* men

across *all* stages of disease, further research into genomic predictors of disease and clinical translation of these predictors need to be undertaken. This is particularly critical as prostate cancer incidence is expected to increase due to increased screening in developing countries and aging populations in several western countries, resulting in a significant burden on global healthcare systems.

To ensure personalized medicine continues to evolve and benefit patients, current research is focused on extending the translation of existing gene-based strategies, in addition to generating new knowledge. For example, while the PRS has great potential for informing PSA screening strategies and can be feasibly translated into the clinic[38], several studies have shown that combining rare and common risk variants dramatically improves the discriminative ability of PRS prediction.[51,54,156,157] Clinical trials are also determining whether PARP inhibitors can be extended to carriers of DNA damage repair gene alterations beyond those currently approved, in addition to evaluating PARPi in combination with ARSi.[21,128,158,159] Notably, preliminary data from the latter clinical trials suggest significantly improved rPFS in mCRPC patients with[128,158,159] and without[21] HRR gene alterations, when treated with PARPi in combination with androgen deprivation therapies. These studies have significant implications for PARPi eligibility and when gene-based therapies should be prescribed to optimize survival outcomes in metastatic patients. Importantly, clinical translation of these findings can occur rapidly given a selection of PARP inhibitors and ARS inhibitors are already approved in most countries.

There are also several emerging gene-based therapies that may broaden the scope of patients eligible for personalized therapies. While immune checkpoint inhibitors have proven efficacious in the treatment of other cancers, they have only recently been evaluated in prostate cancer, with mixed results.[160] While early phase 2 trials assessing pembrolizumab appeared promising, several phase 3 trials were halted due to failure to demonstrate an improvement in rPFS and overall survival (OS) compared to standard current therapies for mCRPC.[160] Pembrolizumab was anticipated to be effective in mCRPC patients with increased *PD-L1* gene expression; however, no benefit in outcomes was observed in this subgroup of patients. Instead, a small subset of mCRPC patients with microsatellite instability, mismatch repair deficiencies, and/or a high mutation burden may benefit from this therapy and, as such, the US Food and Drug Administration (FDA) has approved the use of pembrolizumab in these patients. Mixed results have also been observed in clinical trials of protein kinase inhibitors for the treatment of mCRPC.[161] In fact, only the phosphoinositide 3-kinase pathway inhibitor ipatasertib appears promising after randomised phase 2 and 3 trials evaluating ipatasertib in combination with abiraterone.[162,163] In mCRPC patients with PTEN loss, both trials reported significantly improved rPFS after treatment with ipatasertib and abiraterone compared with placebo and abiraterone. Notably, these benefits were not observed in mCRPC patients without PTEN loss.

In order to discover new genomic biomarkers for prostate cancer risk, prognosis, and treatment response, large, diverse, clinical, and genomic resources are required. In recent years, several prostate cancer registries, comprising clinical and genomic patient data linked to patient outcomes, have been formed to achieve this goal.[164–166] The most recent of these, the PROMISE Registry, intends to recruit 5,000 prostate cancer patients over the first 5 years of the study, with follow-up for a subset of 500 patients planned for an additional 15 years.[166] The subset of patients will be selected based on testing positive for germline genetic variants that are considered

pathogenic or likely pathogenic in specific genes of interest, with the intention to identify candidates for recently approved targeted therapies, expand clinical trial data examining specific gene mutations, and understand the effects of targeted treatments in a real-world setting.[166]

It is clear that incorporating genetic testing into the standard clinical care of patients will have significant impact on the clinical care and outcomes of prostate cancer patients. But several challenges need to be addressed to ensure all patients benefit from current and future advances in genetic testing. A study by Beltran and colleagues in 2015 clearly demonstrated a significant "gap" in the translation of genetic information into changes in clinical practice.[167] This study sequenced tumour-normal paired samples from 97 metastatic and mCRPC patients to detect alterations that may inform therapeutic decisions. In total, 94 patients had alterations for which a targeted therapy was available, a targeted therapy was in clinical or preclinical trials, or they were considered cancer drivers and potentially actionable. However, of these 94 patients, only 5 received treatment that was informed by their genetic information.[167] Lack of access to gene-based therapies, whether due to restrictive criteria for clinical trial eligibility or prohibitive costs of off-label therapies, was considered a significant barrier. Other studies have indicated that socioeconomic, regionality, and ethnicity disparities also pose barriers to accessing genetic testing. These issues are being specifically evaluated in the IRONMAN[165] and PROMISE[166] registries through population-wide and, in the case of IRONMAN, international participant recruitment.

With advances in genetic technologies and lessons learned from the COVID-19 pandemic, some barriers associated with genetic testing may be less challenging going forward. Germline genetic material can be easily collected (whether via pathology services or self-administered saliva kits) from patients living outside of metropolitan cities and sent to central processing facilities. Accessing tumour material in mCRPC patients has proven challenging in the past; however, recently, plasma circulating tumour DNA has been established as a minimally invasive source of predictive and prognostic biomarkers, overcoming many of the limitations of tissue-only testing.[168] Costs of massively parallel sequencing are rapidly decreasing. Whole genomes, opposed to current standard genetic testing panels, provide genetic information that can be utilized immediately and in the future, as new risk genes and clinically relevant variants are discovered.[168] Furthermore, noncoding regions of the genome can be interrogated for germline alterations that are important in risk prediction and structural somatic alterations that are associated with aggressive disease and/or are predictors of therapeutic response.

Perhaps one of the greatest challenges to advancing genetic testing is access to genetic providers, particularly genetic counsellors. To address the rising incidence of prostate cancer and aging populations, we will need a rapid and large increase in the genetic provider workforce.[169] This will need to be accompanied with ongoing genomics education of healthcare practitioners, clinicians, and patients, especially as new genetic tests and gene-based therapies become available. These changes will be particularly challenging to implement for men living outside of metropolitan regions and time-poor healthcare providers. However, as we pivoted to phone and video telemedicine and online webinars during COVID, we can do so again to ensure equitable access to genetic testing.

Incorporating Germline Genetics Into Healthcare Systems

Incorporating genomic testing into healthcare has the ability to transform the delivery of care.[170] As a medical discipline, the field of genetics is relatively young, with the American Board of Medical Genetics and Genomics (ABMGG) being recognized by the American Board of Medical Specialties (ABMS) in 1991. ABMGG is responsible for the accreditation, training, and certification of clinical geneticists who complete a 2-year residency, with most having prior training in another area of medicine (Internal Medicine, Family Medicine, or Obstetrics and Gynecology). Physicians trained as clinical geneticists often work in partnership with genetic counsellors who have a 2-year master's degree that involves training in assessing family history and counselling patients regarding the principles related to genetics and human disease. The majority of clinical geneticists are employed in more traditional academic/tertiary medical systems.[171] The number of genetic counsellors trained has nearly doubled since 2009 but the growth of trained clinical geneticists has been more modest, creating more pressure on the field in providing access to genetic services (United States Government Accountability Office [2020] *Genetic Services: Information on Genetic Counselor and Medical Geneticist Workforces*.) As a result, there is increasing importance to educated nongenetics professionals to achieve the goals of personalized medicine and genomics-guided care.[172]

Genetic testing implementation of rare pathogenic mutations

Evidence continues to grow regarding the importance of incorporating hereditary risk into care plans. As mentioned above, historically this has relied solely on family history data, but the negative predictive value of family history remains poor, and there are limitations using family history as a gating mechanism for genetic testing that could impact care. Germline genetic testing for monogenic causes, particularly in oncology, has increasing utility for screening, prevention, and treatment of cancer for which evidence-based guidelines continue to expand testing recommendations.[52,173–175] Furthermore, the Centers for Disease Control and Prevention has designated hereditary breast and ovarian cancer syndrome and Lynch syndrome as tier 1 conditions, demonstrating their importance from a public health perspective.[176] Both of these conditions have implications for prostate cancer.[173]

The evolution of DNA sequencing has scaled our ability to assess hereditary cancer risk. The Human Genome Project provided the first draft in 2001 but the cost was considerably high. The project relied on aligning sequenced bacterial artificial chromosomes (BAC) to produce the human genome sequence. Early clinical testing relied on Sanger sequencing techniques and while accurate was not scalable due to cost and technical limitations. "Massively parallel," so called "next-generation" sequencing (NGS) technology was critical because it allowed for multiplexing of sequencing reactions to create more efficiency and reduce cost. Over a 5-year period, the cost per base of sequencing decreased by 4 orders of magnitude.[177]

NGS has ushered in the modern day approach to "panel testing" where a patient has a cancer panel test performed assessing multiple genes at once. This is critical since clinically determining whether personal or family history

is related to *BRCA2* or *PALB2*, for example, is not possible. Removing the historical gene-by-gene approach to testing has helped with accessibility of genetic information and risk assessment. Panels have become increasingly large over time and efforts by ClinGen and ClinVar to ensure gene-disease associations are valid and ensuring transparency of variant interpretation of labs have been important.[178,179]

Genetic testing in hereditary cancer typically involves sequencing of the exons (and flanking regions) and assessing for structural variations (deletions, duplications, rearrangements). Standards exist for variant interpretation and categories include: pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign (LB), or benign (B). The majority of labs do not report out likely benign/benign variants since they do not confer risk. VUSs remain challenging as there is not enough data, or the data is conflicting, as to whether the variant might increase risk for a condition. The majority of VUSs end up being reclassified as benign over time, thus it is generally recommended not to make medical management decisions based on a VUS.[180,181]

While monogenic risk remains important to assess, it does not capture the entire spectrum of identifiable risk based on genomics. Polygenic risk scores have been developed to address gaps in identified risk.

Genetic testing implementation of polygenic risk scores

Inherited risk, particularly in complex disorders, is often multifactorial and can be influenced by both genetic and environmental factors. Again, as previously mentioned, a PRS is an estimate of this risk and is based on the weighted sum of estimated per-allele affected sizes of SNPs. PRS provides a probability or relative risk for a disease rather than providing an absolute risk for developing a condition over a lifetime. It is a statistical prediction of increased or decreased risk over a patient's empiric personal risk. In addition, PRS has been shown to specifically modify the effects of RPMs.[182] An easy way to conceptualize this is that PRS modifies the penetrance of a RPM. Meaning, if all patients with a BRCA2 mutation collectively have a 3.3-fold higher risk for prostate cancer, individual PRS can modify risk. However, if one of those patients has a PRS of 2.0, then that individual's lifetime risk is 6.6-fold higher. Conversely, if another one of those patients has a PRS of 0.5, then that individual's lifetime risk is only 1.65-fold higher. This information is very useful for counselling patients.

Important points to consider when incorporating PRS into patient care have been previously outlined. There may be a decreased predictive value if the patient is from a population different from the one the PRS was developed, particularly in those of non-white ancestry since early development of most PRSs came from European-based genetic databases. Monogenetic etiologies, if known, should be pursued and not just PRS in isolation.[183] Efforts are ongoing to validate PRS and establish clinical validity across different ancestries.[40]

Genetic counselling

Traditionally genetic counselling is an educational process that has focused on a "nondirectiveness" form of counselling to facilitate autonomous decision-making by patients and not to introduce potential personal bias into the decision-making. The foundation is taking a three-generation pedigree (family history) to better aid

in recognizing patterns suggestive of a particular syndrome that can then guide discussions regarding yield of testing and estimation of risk.

Key points include counselling the patient on the mode of inheritance, typically autosomal dominant with hereditary cancer syndromes, possible outcomes and limitations of testing, strategies to amend risk that may include screening or prevention, and the psychosocial aspects regarding the receipt of knowledge for both the patient and family. Historically this has been performed in a pretesting session to allow for informed consent followed by a post-test results "disclosure" appointment.[184]

While traditional principles remain that include respecting autonomy, privacy, and confidentiality, the era of genomics has ushered in challenges that include an increasing number of variants of uncertain significance and incidental/secondary findings unrelated to the original diagnosis in question being identified. This has led to debate on how genetic counselling should evolve to meet these challenges given the explosion of NGS data.[185–187]

Approaches to facilitating genetic risk assessment

Different workflows have been developed to facilitate hereditary cancer testing uptake and implementation. The predominant model has been in-person genetic counselling, but this is time-intensive and often not cost-efficient.[188]

Health systems have taken population approaches using targeted screening questionnaires in addition to broader "healthy population screening" to improve access.[189–191] Digital tools (platforms/chatbots) are increasingly being used to assist in raising awareness and improving access to genetics.[192–194] Wang *et al.* examined four common workflows: 1) traditional referral, 2) point-of-care scheduling, 3) point-of-care counselling/telegenetics, and 4) point-of-care testing and demonstrated that these can be scalable solutions to improve uptake.[195]

Privacy and security

Historically ethical, legal, and social implications (ELSI) research focused on the negative potential effects on patients or subjects, including psychosocial effects with Huntington's disease being an example that could lead to significant depression, anxiety, or stigmatization and resulted in reluctance of patients pursuing testing.[196,197] Further harms related to health insurance discrimination (coverage decisions or setting of premium rates), obtaining disability and life insurance, and finally employment discrimination have been continued themes of concern by patients and healthcare providers despite the relative paucity of evidence that economic or psychosocial harms have occurred to a significant degree. Passing of the Affordable Care Act the Genetic Information Nondiscrimination Act of 2008 (GINA), 42 U.S.C. § 2000(ff) has provided protections from these concerns with regards to health and employment discrimination. While sporadic cases of discrimination have occurred, the fear of discrimination remains despite the lack of evidence for a ubiquitous problem.[196,198,199]

The wide adoption of NGS technology allows for an abundance of information to be gathered about a person whether through commercial or research sequencing efforts. In the genomics era of medicine, testing and generating sequencing data is not limited to a few highly penetrant genes but rather can encompass the whole genome in healthy or affected individuals. This explosion of data has led to new challenges in providing appropriate consent and the return of results given the potential clinical utility and benefit to the individual that can be context specific as well as indirect benefits for family members.[200]

Implementation Strategies for Genetic Counselling and Germline Testing

Many studies have reported suboptimal referral rates for genetic counselling in the context of hereditary cancer.[201] This is particularly the case for prostate cancer, in which germline genetic evaluation is greatly underutilized. In a nationally representative sample in the National Cancer Institute's Health Information National Trends Survey (HINTS), 52.3% of patients with breast/ovarian cancer versus 1.0% with prostate cancer reported undergoing cancer-specific genetic testing (p=0.001).

A systematic review found that knowledge is the most frequently cited barrier to referral for genetic counselling and genetic testing.[201] For prostate cancer specifically, research has shown critical gaps in provider knowledge including which patients meet criteria for germline genetic evaluation.[202] Digital tools may assist clinicians with targeted family history collection and decision support for genetic counselling referral and/or ordering genetic testing.[203]

Another challenge is public awareness of the link between "breast cancer genes" like *BRCA* with prostate cancer. In the aforementioned HINTS data, the internet was the most common source of information about genetic testing for patients with prostate cancer.[204] However, there is significantly less online activity surrounding genetic evaluation for prostate cancer compared to breast cancer.[205] Some research has been conducted on methods such as podcasts to increase public awareness of prostate cancer genetics.[206]

Even when appropriate referrals are made, barriers to genetic evaluation include the shortage of genetic professionals and long wait times for patients.[207] Numerous studies have been conducted into alternative strategies to provide expedient pretest genetic counselling in prostate cancer. One strategy is for nongenetic providers to provide pretest counselling as part of routine prostate cancer care. For example, in the Germline Genetics in Prostate cancer Study, urologists and oncologists were successfully trained by experts in genetics through a 30- to 60-minute presentation and handouts on current guidelines and the clinical importance of genetic testing.[208] These providers then conducted pretest counselling as part of their clinical encounters, and patients who were found to have a pathogenic variant and/or variant of uncertain significance were then referred to genetic counsellors for post-test counselling. Another strategy is to provide pretest genetic education through digital methods, such as videos or patient-driven webtools.[209,210]

Satisfaction with Genetic Testing

Most available studies reporting patient satisfaction with genetic testing for prostate cancer in the United States do so in the context of studying novel methods of delivering genetic education compared to or in lieu of traditional pre- and/or post-test genetic counselling to improve both access and speed.[211] The multicentre Technology-Enhanced Acceleration of Germline Evaluation for Therapy (TARGET) randomized trial compared a 9-module patient-driven genetic education webtool with traditional pretest genetic counselling.[210] The webtool was non-inferior to genetic counselling for the primary endpoint of decisional conflict and there were no significant differences in satisfaction using an adapted version of the Genetic Counseling Satisfaction Scale.[212] Another large, multisite, randomized controlled trial compared pretest video education (VE) with genetic counselling for men with prostate cancer (n=662). The 8-item Genetic Testing Satisfaction Survey[213] was completed prior to genetic testing and 1 month after results disclosure. Except for one item asking whether the VE/genetic counselling answered all the patient's questions that favoured the genetic counselling arm (p<0.001), there were no significant differences between arms on other aspects of satisfaction after pretest education or results disclosure (p=0.05).[214] In another study of 107 survivors of metastatic and high-risk prostate cancer randomized to streamlined testing where patients were given the option to proceed to genetic testing without pretest genetic counselling versus enhanced usual care where their physician mailed a letter informing them of their eligibility for genetic testing and recommending they schedule a genetic counselling appointment. At 3 months after randomization, the groups did not differ on satisfaction with decision or decision regret.[215]

In a single-arm prospective trial conducted across multiple clinical centres, individuals with advanced prostate cancer were referred by their oncologist for genetic testing for hereditary prostate cancer. Patients (n=501) received pretest education via a printed brochure and video. Average satisfaction ratings were high for pretest education (15.5; SD, 2.2; range, 4–20) and with the decision to undergo genetic testing (17.1; SD, 2.9; range, 4–20). Generally, there were no differences by patient sociodemographic characteristics except for those with beyond a college education reporting lower levels of satisfaction compared to those with a college level or less than college level education.[216] Another study examined oncology-clinician–delivered pretest genetic counselling among 275 patients eligible for genetic testing for hereditary prostate cancer. Patients completed the 12-item Satisfaction with Genetic Counseling Scale[217] after pretest counselling and prior to testing (n=203) also completed the modified 17-item the Royal Marsden Patient Satisfaction Questionnaire.[218] Prior to genetic testing, nearly 90% of respondents indicated being "completely" or "to a great extent" satisfied with various aspects of pretest counselling such as the provider meeting their expectations and being given the right amount of information. After genetic testing, 88% reported that they were pleased to have the test during an existing oncology appointment.[208]

While early findings are encouraging and demonstrate high levels of satisfaction, these studies are primarily focused on non-Hispanic white, English-preferring men with prostate cancer who are receiving care in academic settings. Further study is needed in non-white and non-English–preferring populations (e.g., Spanish-preferring). Also, satisfaction was assessed at relatively early time points in the genetic counselling and testing process and therefore does not include key areas such as support for future medical decision-making and communicating

results to at-risk family members. As such, future studies assessing satisfaction with genetic counselling and testing must include more diverse patients, consider optimal ways to deliver culturally and linguistically concordant genetic services, and assess satisfaction prior to, during, and after genetic testing.

Conclusions

A complete genetic assessment for managing patients along the prostate cancer journey should include three components: family history information, monogenic gene mutations, and a prostate cancer–specific PRS. Evaluation of monogenic gene mutations within DNA repair genes has become routinely included in authoritative guidelines for appropriate patients deemed "high risk." While our current evaluation of identifying "high-risk" patients may be insufficient (e.g., family history information may not be broad enough to capture all patients who would benefit from genetic testing), the results of those men who undergo genetic testing and are found to have mutations within specific genes (e.g., *HOXB13, BRCA2, ATM, CHEK2*, etc.) have potential to influence the timing and frequency of screening. In addition, because of their propensity for developing aggressive tumours, men who are found to have mutations within specific genes (e.g., *BRCA2, ATM, CHEK2, PALB2, NBN, MSH2, MSH6*) may have results that influence treatment decisions including the choice for radical treatment and chemo- or immunotherapy.

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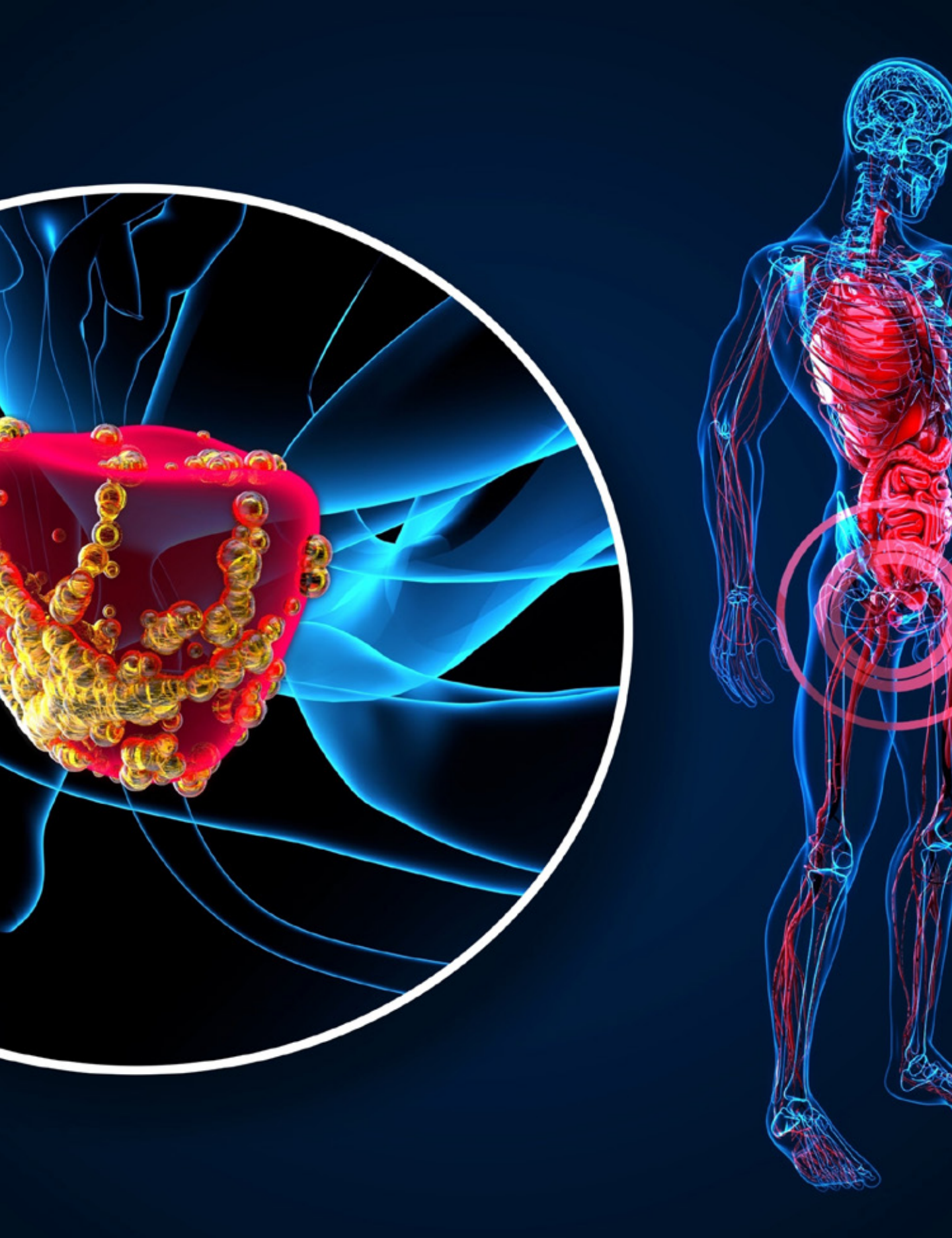

COMMITTEE 6

Prostate Diagnosis and Biopsy Techniques

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Introduction

Biopsy of the prostate gland plays a pivotal role in the diagnostic pathway of prostate cancer (PCa). It provides tissue for histological examination to identify and characterize the tumour itself. However, like every procedure, prostate biopsies carry a risk for complications that can significantly impact patient outcomes. The technical and diagnostic advancements of the past decades such as magnetic resonance imaging (MRI) targeting and the transperineal approach have revolutionized PCa detection and changed the complication profile of biopsies.

Prebiopsy Risk Assessment

Digital rectal examination

Most prostate cancers are located in the peripheral zone and can be detected by digital rectal examination (DRE). In historical series, prostate cancer was detected by DRE alone in 18% of cases, with normal prostate-specific antigen (PSA) levels. However, the rate of DRE abnormalities varies widely depending on the age of onset, and intensity and frequency of screening.[1] A suspicious DRE is associated with a higher risk for undifferentiated tumour (i.e., tumour aggressiveness) and is therefore an indication for prostate biopsy, regardless of the PSA value. In contemporary practices, DRE is still used for local tumour staging (i.e., T stage), although MRI outperforms DRE.[2] The use of DRE alone in the primary care setting has a sensitivity and specificity below 60%, possibly due to inexperience, and can therefore not be recommended to exclude prostate cancer.[3]

PSA

The use of PSA as a serum marker has revolutionized the diagnosis of prostate cancer. However, PSA is not cancer specific, and may be elevated in benign prostatic hypertrophy, prostatitis, and other nonmalignant conditions. A control assay is often recommended due to the intra-individual variability in PSA levels, which is of the order of 20% to 30% of its value. The presence of metastatic disease increases with PSA levels, from up to 15% in men with PSA < 10 ng/mL to 87% in men with PSA > 100 ng/mL.[4] Although there is no formal consensus, the results of two randomized trials on population screening—the European Randomized study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial—indicate that a urology consultation should be considered to assess the value of early individual diagnosis starting at a PSA level of 3 ng/mL.[5,6] This recommendation, however, depends on age, health, family history, and potential germline mutations.

If the PSA level is elevated, it should always be repeated, although the optimal interval for PSA testing is not known.[7] The European Association of Urology (EAU) guidelines recommend to consider a risk-adapted strategy depending on the initial PSA level. Men with an initial PSA level of < 1 ng/mL at age 40 years and < 2 ng/mL at age 60 years have a lower risk for prostate cancer metastasis or death.[8] The interval between retests

may therefore be 2 years for those initially at risk, or 8 years for those not at risk with an initial PSA < 1 ng/mL at age 40 years and PSA < 2 ng/mL at age 60 years and a negative family history.[9] The benefits in terms of long-term survival and quality of life of prolonged PSA retesting (every 8 years) have yet to be proven at a population level. The American Urological Association (AUA) guidelines recommend to offer regular prostate cancer screening every 2 to 4 years to men aged 50 to 69 years.[10]

PSA density

PSA density is defined as the serum PSA level divided by the volume of the prostate, estimated by ultrasound or prostatic MRI. This is a continuous variable, and the higher the PSA density, the higher the likelihood of harbouring high-grade prostate cancer.[11] A PSA density greater than 0.15 ng/mL/cc suggests a greater than 20% chance of having grade group [GG] 2 or higher prostate cancer. Patients with a PSA density below 0.09 ng/mL/cc were found unlikely (4%) to be diagnosed with clinically significant prostate cancer (csPCa).[12]

In clinical practice, PSA density is widely used as a surrogate for detecting csPCa and as a tool to indicate or defer prostate biopsies based on MRI findings. With normal MRI results (Prostate Imaging–Reporting and Data System [PI-RADS] 1–2), the risk for csPCa is very low. A PSA density < 0.15 ng/mL/cc could be used to avoid biopsy in this subgroup.[13] If MRI is doubtful (PI-RADS 3), systematic plus targeted biopsies are sometimes recommended. However, PSA density could once again tip the balance in this indication. In a multicentre retrospective study including 2,512 men with a PI-RADS 3 lesion on MRI, performing biopsies only if PSA density was > 0.2 ng/mL/cc enabled 44% of biopsies to be avoided at the risk of missing 11% of clinically significant cancers.[14] This risk could be less than 5% for a PSA density threshold > 0.10 ng/mL/cc.

Biomarkers

Several serum and urine biomarkers have been developed over the past 20 years to overcome the shortcomings of PSA diagnosis. These biomarkers can be used to better select patients prior to biopsy and avoid unnecessary biopsies.

Several tests measuring a panel of kallikreins in serum or plasma are now commercially available, including the US Food and Drug Administration (FDA)-approved Prostate Health Index (PHI) test (which combines free and total PSA and the [-2]pro-PSA isoform [p2PSA]), and the four-Kallikrein (4K) test (which measures free, intact, and total PSA, and kallikrein peptidase 2 in addition to age, DRE, and previous biopsy status). Both tests aim to reduce the number of unnecessary prostate biopsies in men who have undergone PSA testing.[15,16]

Prostate cancer gene 3 (PCA3) is an overexpressed long noncoding RNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The clinical benefit of the PCA3 score, in addition to the other established factors, has been demonstrated before regarding biopsy decision-making in men with persistent risk for prostate cancer.[17] However, it is rarely used.

The Stockholm3 test is a prediction model that is based on several clinical variables (age, first-degree family history of PCa, and previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free PSA to total PSA, human kallikrein 2, macrophage inhibitory cytokine-1, and *microseminoprotein*-β *)*, and a polygenic risk score for predicting the risk for PCa with International Society of Urological Pathology (ISUP) GG ≥ 2. This test was shown to reduce the percentage of clinically insignificant cancers when used in combination with MRI in a PSA screening population. It also has the potential to decrease the number of multiparametric magnetic resonance imaging (mpMRI) scans required in prostate cancer screening.[18]

The SelectMDX test is similarly based on mRNA biomarker isolation from urine. It assesses the presence of HOXC6 and DLX1 mRNA levels to estimate of the risk for the presence of both PCa on biopsy and high-risk cancer.[19]

The MyProstateScore 2 (MPS2) test is a new urinary test incorporating 18 markers uniquely overexpressed by high-grade cancers relative to low-grade cancers.[20] Clinically, the use of this test could have safely avoided unnecessary additional testing with imaging or biopsy in 35% to 51% of patients while maintaining high sensitivity for high-grade cancers that benefit from early detection. These findings suggest that using the test in patients with elevated PSA levels can reduce the potential harms of prostate cancer screening while preserving its long-term benefits.

The appropriate use of serum and urine biomarkers has the potential to safely limit the proportion of men undergoing additional testing or biopsy, although appropriate comparative studies have yet to be performed. In addition, the widespread use of MRI during the screening process to triage patients prior to biopsy affects the use and usefulness of these biomarkers.

MRI

Advances in prostate MRI over the past two decades have made this imaging modality an important step in the diagnosis of localized prostate cancer. According to EAU guidelines, MRI is recommended before any initial prostate biopsy, [21,22] while AUA guidelines deem it as optional.

Correlation with surgical specimens shows that MRI has good sensitivity for detecting and localizing of ISUP GG ≥ 2 cancers.[23] Three clinical trials have confirmed the added value of prebiopsy MRI in a biopsy-naïve patient population, reducing the number of men undergoing biopsy and decreasing the diagnosis of clinically insignificant prostate cancer (ciPCa).[24–26]

Integrating MRI into the prostate cancer screening process offers a number of advantages. First, the negative predictive value of MRI for detecting clinically significant prostate cancer (ISUP ≥ 2) is greater than 90%, although it is widely variable depending on access, location, equipment, and radiologist. Therefore, a nonsuspicious (PI-RADS 1–2) or doubtful (PI-RADS 3) MRI can help reduce the number of unnecessary biopsies. Second, MRI-targeted biopsy can improve the likelihood of detecting csPCa.[24] Finally, MRI can be integrated into management decisions and prediction of treatment outcomes.

In practice, prostate MRI can be performed on 1.5- or 3-Tesla machines, with an endorectal or external antenna. It should be multiparametric, combining morphological T2 sequences (axial and sagittal) with functional perfusion and diffusion sequences. Contrast injection, always recommended, is now being called into question.[27] The standardized report should include prostate volume measurements and a description of each target (or index) lesion. The percent likelihood of malignancy for each lesion described on MRI is indicated according to the PI-RADS version 2.1 score.[28] This score comprises a five-point scale assessing the likelihood of detecting clinically significant cancer. Ideally, a diagram showing the targets and their location is included. At least two targeted biopsies, in addition to systematic biopsies, are recommended for lesions graded PI-RADS ≥ 3.

Risk calculators

Risk calculators, which combine clinical, biological, and radiological data, are useful for predicting the individual risk of detecting clinically significant cancer at biopsy. Multivariable risk calculators have been developed to stratify patients undergoing prostate biopsy, improving the prediction of ISUP ≥ 2 prostate cancer while reducing unnecessary biopsies and the overdiagnosis of ISUP 1 prostate cancer.

Several tools developed from cohort studies are available online, including:

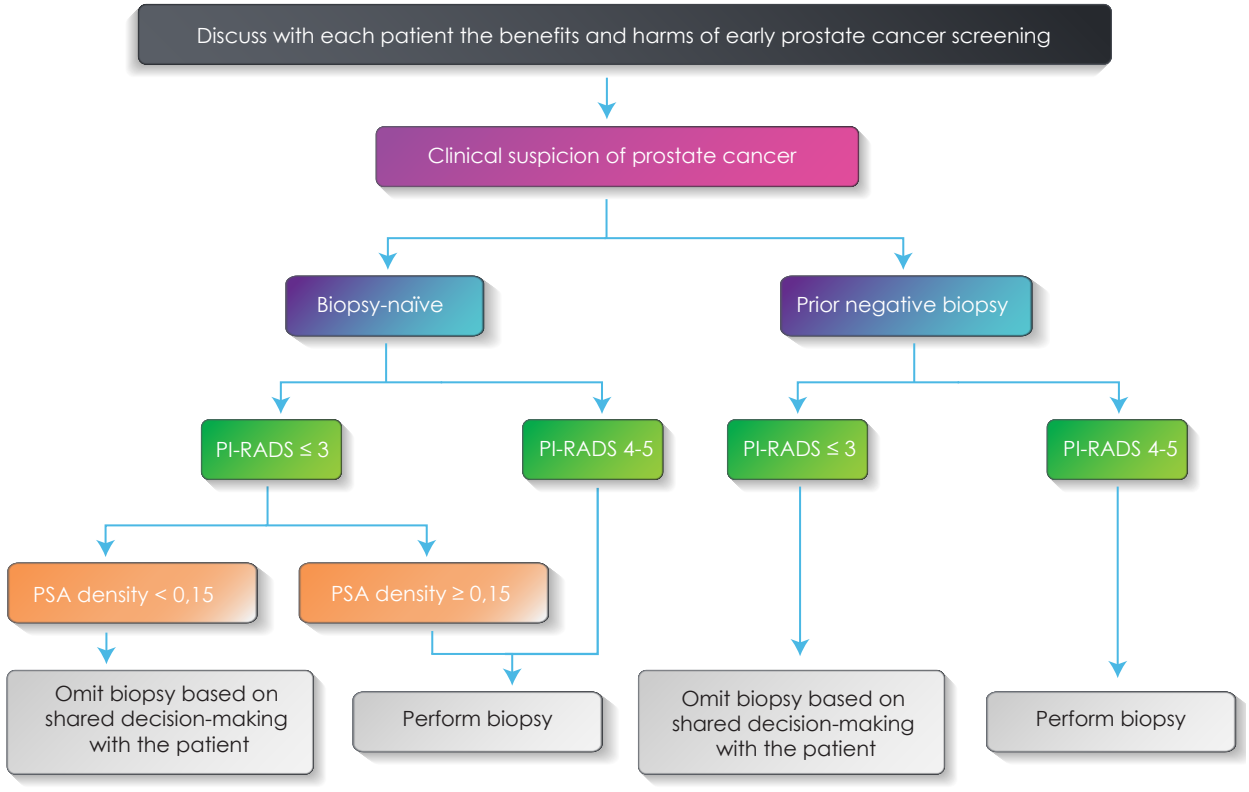
- The ERSPC cohort: ERSPC Risk Calculators
- The PCPT cohort: PCPTRC 2.0
- The Prostate Biopsy Collaborative Group (PBCG) risk calculator: Extended PBCG
- The Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculator (RPCRC-MRI)
- The Prospective Loyola University multiparametric MRI (PLUM) risk calculator
- The prostate cancer risk calculator (PCRC-MRI)

Risk calculators incorporating MRI findings and clinical data are being increasingly used. In a recent study that externally validated and compared the performance of four promising MRI-based prostate cancer risk calculators in independent cohorts from Europe and North America, the authors found better calibration for the RPCRC-MRI and PLUM models.[29]

Algorithm

An algorithm based on prebiopsy MRI is proposed in **FIGURE 1** to inform healthcare providers of one of the strategies that could be used by physicians to detect csPCa. It is not intended to replace the judgment of the physician, who is in the best position to know the patient's risk.

Figure 1. Proposal of biopsy decision-making algorithm based on imaging and clinico-biological characteristics.



Abbreviations: PI-RADS, Prostate Imaging–Reporting and Data System; PSA, prostate-specific antigen.

Prebiopsy Workup

Anticoagulant/Antiplatelet management

An increasing number of older patients receive long-term anticoagulant and/or antiplatelet therapy.[30] However, no specific recommendations exist for peri-procedural antithrombotic therapy management during prostate management.[10,21] Like other vascular organ biopsies, prostate biopsy is considered a high bleeding risk procedure by the European Society of Cardiology (ESC), which suggests a risk-based algorithm for antithrombotic therapy management.[31]

Single-agent antiplatelet therapy (SAPT). Low-dose acetylsalicylate (ASA) can be discontinued in a primary prevention setting. In patients with established cardiovascular disease or with a previous percutaneous coronary

intervention (PCI), low-dose ASA should be continued perioperatively. Adenosine diphosphate signaling ($P2Y_{12}$) inhibitors (ticagrelor, clopidogrel, prasugrel, and cangrelor) prescribed after PCI, or for acute coronary syndrome, stroke, peripheral artery disease, or aspirin intolerance, require a patient-tailored strategy. Options include no interruption, short interruption, switching to ASA, or bridging with intravenous drugs.

Dual antiplatelet therapy (DAPT). Low-dose ASA must not be discontinued, while $P2Y_{12}$ inhibitors should be held for a few days before the procedure based on shared-decision making with the cardiologist (usually, prasugrel for 7 days, clopidogrel for 5 days, and ticagrelor for 3–5 days). In the first month following a PCI, the 3 months after an acute coronary syndrome, or all cases of high risk for stent thrombosis, prostate biopsy should be deferred. Alternatively, after a multidisciplinary benefit-risk evaluation, dual antiplatelet therapy should be bridged with intravenous antiplatelet agents (such as tirofiban, eptifibatide, or cangrelor).

Anticoagulant therapy (ACT) [31]. If a mechanical heart valve is present or in selected high-risk cases (recent stroke within 3 months, antithrombin-3 deficiency, or protein C and/or S deficiency, left ventricular apex thrombus, or atrial fibrillation with a very high stroke risk), bridging oral anticoagulant therapy with unfractionated heparin or low-molecular weight heparin (LMWH) is indicated. In all other cases, interruption of oral anticoagulation is advised, as bridging does not decrease thrombotic risk while increasing bleeding. Warfarin should be interrupted 5 days before biopsy and international normalized ratio (INR) checked before the procedure. Given that prostate biopsy is a high bleeding risk procedure, apixaban, rivaroxaban, and edoxaban should be withheld for 48 hours before the procedure, while the dabigatran interruption interval should be evaluated based on the patient's renal function. Anticoagulation should be restarted as soon as possible after the procedure (usually 24–48 hours); prophylactic LMHW can be considered post-procedure.

Additional considerations. Although prostate biopsy is generally classified as a high bleeding-risk procedure, some evidence suggests that its risk categorization could be downscaled. Saito *et al.* found no grade 3 or higher complications for a 14-core transperineal biopsy in 149 patients who did not interrupt antithrombotic treatment (SAPT 54%, ACT 22%, DAPT 12%, combinations 11%), although urine retention due to clot formation and prolonged hospitalization were more frequent compared to those in untreated patients.[32] Other groups have found no safety signals in continuing antithrombotic therapy for transrectal biopsies.[33] However, Tanabe *et al.* showed that the impact of antithrombotic agents might not be negligible (grade 2 and 3 events were significantly increased in the 341 treated patients compared to 1,476 controls; adds ratio [OR], 2.18; p=0.039).[34] Severe life-threatening bleeding complications are extremely rare but not absent after prostate biopsies.[35] Considering the absence of high-quality evidence, a tailored and conservative approach appears to be a reasonable choice.

Rectal preparation

Rectal preparation before a prostate biopsy is a crucial step for ensuring procedural accuracy (by removing stools and improving the sonic window) and minimizing the risk for complications in the case of a transrectal approach (by reducing presence of bacteria in the rectum). Bowel preparation should consist of a rectal enema, which is equally effective in rectal cleansing and is better tolerated than oral preparations (e.g., polyethylene glycol).[36]

A meta-analysis has shown that when performing a transrectal biopsy, povidone-iodine preparations significantly reduce post-procedural infections (relative risk [RR], 0.5; 95% confidence internal [CI], 0.38–0.65) and hospitalization rates. Therefore, rectal prebiopsy povidone-iodine preparations should be routinely administered; data on chlorhexidine preparation is less robust.[37] When performing a transperineal approach, accurate perineal skin disinfection with an antiseptic solution (such as chlorhexidine or povidone-iodine) is advised.

Anesthesia

Transrectal prostate biopsies (TR-Bx) are classically performed under local anesthesia (LA). A peri-prostatic block with lidocaine injection (not exceeding 45 mg/kg) under TR ultrasound guidance is recommended; this approach enables better pain control than intrarectal lidocaine (or prilocaine) gel instillation alone.[38,39]

Transperineal prostate biopsies (TP-Bx), with systematic and/or MRI-targeted approach, have frequently been performed under general anesthesia (GA). However, numerous studies have established the feasibility and the accuracy of TP-Bx under LA, with similar results to the TR approach, frequently describing a slightly increased peri-procedural pain.[40,41] Accordingly, a meta-analysis has calculated a relative risk of 1.83 (95% CI, 1.27–2.65) for patient pain considered as a procedural complication.[42] A recent systematic review evaluating TP-Bx reported a low rate of procedure abandonment (0.37%) with the pain peak measured at the time of LA administration.[43] Median visual analogue scale (VAS) score during TP-Bx under LA has been reported to be between 2 and 4.7.[44,45] Interestingly, a study has compared TP biopsy performed in LA (peri-prostatic block) and GA (with or without a complementary pudendal block), reporting a higher median Numeric Pain Rating Scale (NRS) pain score during the LA procedure but with a very high overall patient satisfaction (90% would accept the same procedure if necessary) and better use of healthcare system resources.[46]

Technical aspects of local anesthesia for the transperineal approach

The local anesthesia for TP procedures usually involves a cutaneous and subcutaneous perineal injection and a peri-prostatic injection (or other nerve blocks) using 1% or 2% lidocaine, not exceeding a total dose of 45 mg/kg.[44,47] Combinations of different local anesthetics (i.e., bupivacaine, mepivacaine) are also described.[43] Iremashvili *et al.* demonstrated that adding a pudendal block to the periprostatic block is associated with better overall pain control, although with higher scores during the anesthesia phase.[48] Another randomized controlled trial (RCT) showed the superiority of perineal nerve block compared to peri-prostatic block alone for men undergoing a TP procedure, with maximum experienced NRS pain of 2.80 versus 3.95 ($p<0.01$).[49,50] Some groups have advocated for better tolerability of TP procedures using an "access trocar" to reduce the number of punctures of the perineal skin, but comparative studies are lacking.[51]

Also, it is well established that pre-procedural anxiety correlates with higher peri-procedural pain. Some groups routinely use anxiolytic drugs (e.g., oxazepam 10 mg 2 hours prior to the biopsy), while others have explored the use of virtual reality in this setting.[52] However, no formal recommendations can be made in this regard due to the paucity of data.

Antibiotic prophylaxis

Earlier nonrandomized evidence suggested that the TP approach is associated with fewer infections and sepsis when compared to the TR approach. Based on this data, the former should be preferred whenever possible, according to EAU guidelines.[53,54] However, recent RCTs indicate that the approach might be tailored according to MRI lesion location to improve detection rates.[55] Importantly, two RCTs have not shown differences in infection rates between TR biopsy with antibiotic prophylaxis (standard or targeted) and TP biopsy with no (or risk-adjusted) prophylaxis, suggesting the risks associated with TR are comparable and acceptable.[56,57] Accordingly, the AUA guidelines maintain a more nuanced position on this topic, recommending either approach.[10]

Transrectal approach. Level 1 evidence supports the use of antimicrobial prophylaxis when a transrectal biopsy is performed.[58] Fluoroquinolones have long been the first choice for this indication, but their use is now strongly discouraged due to increasing microbial resistance and potential adverse effects, as indicated by the European Medicines Agency. In this context, cephalosporins (ceftriaxone 1 g i.m. or cefixime 400 mg for 3 days) or aminoglycosides (gentamicin 3 mg/kg or amikacin 15 mg/kg) have shown comparable results to fluoroquinolones in RCTs and can be recommended, although conflicting data exists about fosfomycin for this indication.[58] A potential benefit exists for targeted prophylaxis (based on rectal swab or stool cultures) or augmented prophylaxis (using various combinations, including two or three antibiotic classes), when compared to single-agent administration. Therefore, several guidelines suggest targeted and augmented prophylaxis for the TR approach; notably, local resistance patterns and antimicrobial stewardship principles must always be considered when prescribing antibiotic prophylaxis for this procedure.

Transperineal approach. A growing body of evidence suggests antibiotic prophylaxis may not be necessary for TP biopsy, which could be a reasonable option at experienced centres with appropriately informed patients. The NORAPP noninferiority trial did not demonstrate a benefit for cephalosporin-based prophylaxis, with a number needed to treat of 137 to prevent one urinary tract infection.[59] Also, Pirola *at al.* found no differences in patients with or without prophylaxis in terms of infection or bacteriuria rates.[60] The safety of this approach is confirmed by larger prospective cohorts and a meta-analysis.[61,62]

Targeted Biopsies, Systematic Biopsies, or Combination Scheme

Since its initial description by Hodge *et al.* in 1989, transrectal ultrasound (TRUS)-guided biopsy with systematic and blind sampling has been the standard procedure for diagnosing PCa in patients with elevated levels of PSA, abnormal DRE, and/or a previous history of PCa.[63] However, systematic biopsy is associated with poor performance in detecting csPCa, leading to many cases of csPCa being missed, and ciPCa being overdiagnosed, which increases the risk for subsequent overtreatment. In the multicentre PROMIS study, which compared the detection rates of csPCa in patients with clinical suspicion of cancer, TRUS biopsy (involving 10–12 systematic

biopsies) was compared with template biopsy (biopsies taken every 5 mm) after prebiopsy mpMRI.[64] TRUS biopsy demonstrated a sensitivity of 48% in detecting csPCa, with 78% of patients found to have either non-cancerous or ciPCa results. Importantly, utilizing MRI to triage men would have allowed 27% (158/576) of patients to avoid primary biopsy, resulted in 5% fewer diagnoses of ciPCa, and provided information on rates of GG2 or higher or other metrics of potentially clinically meaningful PCa.

Among 158 men with a negative MRI, 17 had csPCa detected by template biopsy. All 17 cases were Gleason grade 3+4 (ISUP grade 2) or less, with core lengths ranging from 6 to 12 mm. Additionally, of the csPCa lesions missed by TRUS biopsy, most were Gleason 3+4 (ISUP grade 2), with a few cases being Gleason 4+3 (ISUP grade 3).

Technological advancements in MRI and prostate biopsy platforms, which enable MRI-targeted biopsies based on suspicious zones identified on MRI, coupled with the increasing expertise of radiologists in interpreting MRI scans, have significantly enhanced the detection of csPCa.[65] Studies comparing MRI with radical prostatectomy (RP) have demonstrated the performance of MRI in detecting and localizing csPCa foci, particularly for tumours larger than 10 mm in size.[66] In a Cochrane meta-analysis comparing MRI to template biopsy, the pooled sensitivity of detecting ISUP grade ≥ 2 cancers was 91%, with a pooled specificity of 37%.[67] However, MRI is less sensitive in identifying ciPCa, detecting fewer than 30% of ISUP grade 1 PCa smaller than 0.5 mL, as identified on RP specimens.[23]

However, MRI is limited in accurately estimating the true tumour volume, as previous studies consistently show that MRI underestimates tumour size.[68,69] Consequently, some authors emphasize the importance of perilesional sampling in combination with MRI-targeted biopsy.[70] They found that most cores containing csPCa were located around the MRI lesion. Moreover, MRI suffers from poor and heterogeneous sensitivity in evaluating the risk for extraprostatic extension (pooled sensitivity for extracapsular extension prediction of 0.57 [0.49–0.64]).[71] Consequently, local staging is more accurately defined when MRI-derived information is included in predictive models.[72]

The PRECISION and PRECISE trials are landmark, multicentre, randomized studies that compared the "MRI diagnostic pathway," wherein MRI-targeted biopsy is conducted only if MRI findings are positive, with the traditional TRUS-biopsy pathway involving 10–12 systematic biopsy cores for all patients suspected of localized PCa.[24,73] These trials unveiled a higher proportion of csPCa detected in the "MRI diagnostic pathway" group, defined as ISUP GG ≥ 2 (38% vs. 26% in the PRECISION trial, and 35% vs. 30% in the PRECISE trial) and a reduction by more than half in the detection of ciPCa (9% vs. 22% in the PRECISION trial, and 10% vs. 22% in the PRECISE trial). These findings have been corroborated by a recently published meta-analysis (27 studies encompassing 13,089 participants) focusing on biopsy-naïve patients with a positive MRI.[74] The analysis revealed that MRI-targeted biopsy detected significantly more ISUP grade ≥ 2 cancers than systematic biopsy across RCTs (risk difference, 11%), prospective cohort studies (risk difference, 18%), and retrospective cohort studies (risk difference, 7%).

The question then arises regarding the continued utility of systematic biopsy. In a systematic review conducted by the Cochrane Collaboration, which analyzed data from 25 studies involving 6,944 patients, and two multicentre prospective studies, the addition of systematic biopsy to MRI-targeted biopsy improved the detection of ISUP grade ≥ 2 by 4.3% to 5.2%, albeit at the cost of overdetecting ciPCa by 10% to 16.7%.[25,26,67] These findings were further validated by a large multicentre European study, which demonstrated additional ISUP grade ≥ 2 findings in 5.6% of patients and ciPCa in 19% of patients.[75] More recently, the GÖTEBORG-2 trial randomized 17,980 patients with PSA levels of ≥ 3 ng/mL into two groups: one undergoing systematic biopsy alongside MRI-targeted biopsy if a suspicious lesion was identified on MRI, and the other group undergoing MRI-targeted biopsy only (with surveillance if MRI was negative).[76] The primary and secondary outcomes focused on the detection of ciPCa (ISUP GG 1) and csPCa, respectively. Overall, systematic biopsy alone detected csPCa in 10 patients, all of whom exhibited favourable features (intermediate-risk and low-volume PCa) and were managed via active surveillance. Notably, omitting systematic biopsy led to a halving in the detection rate of ciPCa (0.6% vs. 1.2%).

As a result, the question arises whether missing csPCa by avoiding systematic biopsy has clinical implications. Arguments in favour of performing systematic biopsy include that some aggressive histological PCa subtypes, such as intraductal and cribriform carcinoma, may have reduced visibility on MRI.[77] Additionally, approximately two-thirds of csPCa foci are missed by MRI, although they generally consist of small and non-index foci. Knowing the presence of csPCa foci outside MRI lesions would thus influence treatment strategies and potentially improve decision-making processes, such as those regarding nerve-sparing surgery and focal therapy.[21]

In contrast, there are several arguments against the addition of systematic biopsy. Methodological issues frequently arise, such as the MRI-suspicious lesion encompassing several systematic biopsy core locations, resulting in unintended additional MRI-targeted biopsies.[78] Moreover, radiological-pathological correlation studies have shown that MRI often underestimates the size and extent of prostate tumours, introducing the concept of perilesional areas.[68,70,79] Consequently, the role of systematic biopsy in detecting non-visible csPCa foci may be falsely exaggerated after excluding cores passing through the MRI lesion and perilesional area. This hypothesis was recently confirmed in a large, multicentre, European study that demonstrated the added value of systematic biopsy taken on the contralateral side of the MRI lesion decreased from 5.8% to 2.8% for the detection of csPCa.[75]

Interestingly, small csPCa foci that are non-visible on MRI may have limited clinical significance. MRI visibility has been correlated with the presence of genes involved in cancer aggressiveness and disease progression.[80,81] A recent study on active surveillance revealed that patients with MRI–non-visible ISUP grade 2 PCa exhibit similar radiological, pathological, and clinical trajectories as those with MRI-visible ISUP grade 1 PCa.[82] Considering this finding, one could hypothesize that MRI-visible and non-visible ISUP grade 2 cancers may not share the same clinical significance.[83] Furthermore, the survival detriment of missing a csPCa lesion on MRI and/or MRI-targeted biopsy may not be as problematic if the patient is regularly monitored, and new biopsies are indicated upon clinical, biochemical, or radiological progression.

Additionally, systematic biopsies are associated with longer procedure times, increased pathologist workload, and a risk for higher patient discomfort, potentially leading to significant costs.[84,85] While active surveillance prevents unnecessary treatment and associated side effects, the substantial amount of ciPCa detected by systematic biopsy incurs non-negligible costs over years of follow-up due to the successive tests and management of patients who experience disease progression.[86,87] Other consequences, such as impact on daily life (e.g., obtaining loans or life insurance) and elevated risk for anxiety or even suicide, are less commonly described but nonetheless significant considerations.

Before advocating for the omission of systematic biopsy, it is crucial to ensure the entire diagnostic process—including the quality of MRI scans and protocols, the interpretation of MRI results by radiologists, and the execution of MRI-targeted biopsies—is as reliable in less experienced centres as in the experienced centres that have participated in international studies. Achieving this requires the involvement of experienced clinicians, optimized equipment, effective interdisciplinary communication among specialists, and standardized workflows.[88] However, it is widely acknowledged that the reproducibility of prostate MRI interpretation, even among experienced readers, remains only moderate, posing a significant challenge to the generalizability of the aforementioned findings.[89]

The widespread adoption of MRI-targeted biopsy has raised concerns about grade migration, as recently suggested.[90] It remains unclear whether the increased detection of csPCa is due to uncovering higher-grade disease that was previously missed by systematic biopsy or if it represents a selective sampling of high-grade areas within an otherwise less aggressive pathology. By focusing on suspicious MRI lesions, MRI-targeted biopsy is more likely to yield a larger number of positive biopsy cores. This not only leads to higher yields of Gleason patterns but also increases the likelihood for greater grade heterogeneity within biopsy samples. While many urologists tend to rely on the worst ISUP grade for treatment decisions, as recommended by the 2014 ISUP guidelines, the ISUP Consensus Conference in 2019 proposed assigning a global grade group for each suspicious MRI lesion, considering perilesional biopsies.[91] A recent study found that implementing the ISUP 2019 recommendations has been associated with a reduction in grade migration induced by MRI-targeted biopsy and has improved accuracy with final specimen assessment.[92] Conversely, another study focusing on the highest-grade component found no compelling evidence to suggest that MRI-targeted biopsy leads to a significant risk for overtreatment, with only a limited risk of downgrading compared to radical prostatectomy specimens.[93]

In conclusion, MRI-targeted biopsy significantly enhances the detection of csPCa, whereas systematic biopsy offers minimal added value for identifying masked PCa foci, likely associated with a favourable prognosis. While systematic biopsy increases the risk of overdetecting ciPCa, it is partially balanced by the growing adoption of active surveillance in such cases. This also emphasizes the necessity for regular self-assessment and expertise within the field to optimize patient outcomes.

Transperineal Versus Transrectal Approach

The past 10 years has witnessed a renewed interest in the transperineal route, mostly due to the threat represented by the rise of antibiotic resistance and an increased awareness on antibiotic stewardship.[94]

Setup and devices

Transperineal biopsies, as originally performed within a saturation strategy, required a resource-intensive setting including a stepper, brachytherapy grid, and general anesthesia. Advances in and evolution of technologies have now made it possible to perform transperineal targeted and systematic biopsies in an outpatient, office-based setting under local anesthesia.[95]

The freehand technique, where the ultrasound probe is not fixed to the table using a stepper or probe holder, allows for a procedure very similar to the transrectal biopsy procedure. Biopsies can be performed using a biopsy guide fixed to the ultrasound probe or using pure cognitive guidance. Coaxial needles, including the PrecisionPoint™ device (BXTA; Burnham, Berkshire, UK), have been proposed to reduce the number of entry points and increase the tolerability of the procedure under local anesthesia.[96] The freehand technique demonstrated similar detection rates when compared to conventional, grid-based biopsies.[97]

Most manufacturers of MRI-ultrasound fusion devices now offer solutions for the transperineal approach, with no significant modification of the workflow. The learning curve for transperineal freehand mpMRI-fusion–targeted biopsies under local anesthesia appears short (50 cases) for the total procedure duration, with a limited effect of the operator's experience on the cancer detection rate.[98]

Biopsy strategy

Previously published data on transperineal prostate biopsy was based mostly on saturation biopsy protocols such as the Ginsburg or Barzell templates, with 28 and 64 biopsy cores obtained. Nowadays, 10–12 cores templates have been proposed, mimicking the widely used transrectal templates, focused on sampling the peripheral zone.[99] Targeted biopsies can be added in the presence of a suspicious MRI lesion, using cognitive or software registration.[100]

Transperineal biopsy results

Reduction of infectious complications

The main driver of implementing the transperineal approach is the attempt to reduce infectious complications. A systematic review and meta-analysis of nonantibiotic strategies to prevent infectious complications after prostate biopsy reported a 45% reduction of the risk for infectious complication with the transperineal approach compared to transrectal biopsies.[37] Furthermore, the very low rate of infectious complications, even when biopsies are

performed without antibiotic prophylaxis, is attractive. In the German-Norwegian binational NORAPP trial, 555 men scheduled for transperineal prostate biopsy were randomized to receive antibiotic prophylaxis or no antibiotic prophylaxis. No sepsis or infection requiring hospitalization was noted in either group, and the rate of urinary tract infections not requiring hospitalization was 1.09% with antibiotics versus 0.36% without.[59]

More recently, two RCTs have provided data on the infection risk after transperineal biopsy compared to the transrectal approach.

In the PERFECT trial, 270 men with PIRADS 4–5 lesions on MRI were randomized to receive systematic plus targeted biopsies using a transrectal approach (with single-dose antibiotic prophylaxis) and a transperineal approach. One grade 3 sepsis was noted in the transrectal group and none in the transperineal group.[55]

The PREVENT trial compared the post-biopsy infection rate among 658 men randomized to receive either transperineal biopsy without antibiotic prophylaxis or transrectal biopsy with targeted prophylaxis. No infection (0%) was reported in the transperineal biopsy arm, versus 4 (1.4%) in the transrectal arm (p=0.059).[57]

Cancer detection rates

Transperineal biopsies were initially developed as a tool for saturation biopsy, involving a high number of biopsy cores performed in the various published biopsy templates. These templates provided high detection rates at the cost of higher rates of urinary retention and detection of ciPCa. New templates with 10–12 systematic biopsy cores have been proposed to align with the number of biopsies performed with the transrectal approach, with expected lower cancer detection rates.[99]

Given the different angle when reaching the prostatic gland, transperineal biopsies are less likely to miss detecting cancer of the apical and anterior areas, which are more likely to be undersampled through a transrectal approach.[101] Conversely, transperineal biopsies may be less effective in targeting very posterior and basal lesions, especially in large prostates.[97] Therefore, different cancer detection rates are anticipated when comparing the two methods.

A first meta-analysis looking at the detection rates of csPCa with the two biopsy approaches reported a higher detection rate with the transperineal approach, especially when the lesion was located in the anterior region.[102]

A recent propensity-matched pair analysis of a prospectively gathered, multicentre, European cohort of 2,602 patients reported a higher detection rate of ISUP ≥ 2 cancer with the transperineal approach (51% vs. 45%; OR, 1.37; 95% CI, 1.15–1.63; p=0.001).[103]

However, in the PREVENT randomized trial, no difference was found in terms of detection of clinically significant cancer (53% transperineal vs. 50% transrectal, adjusted difference 2.0%; 95% CI, –6.0 to 10), which was a secondary objective of the study.[57] These results were recently challenged by the PERFECT trial, which failed to demonstrate the noninferiority of transperineal targeted biopsies compared to transrectal targeted biopsies for the detection of ISUP ≥ 2 cancer (47.2% detection rate for transperineal vs. 54.2% for transrectal biopsies;

p=0.6235). Interestingly, the overall (any grade) cancer detection rate in targeted biopsies was comparable between groups: 71.3% (TP) versus 64.1% (TR; p=0.2209), despite a lower number of biopsy cores performed in the transperineal arm (median, 12 vs. 17), suggesting a possible learning curve of biopsy targeting with the transperineal approach.[57]

Noninfectious complications

Recent RCTs have provided data on the noninfectious complications of transperineal biopsies compared to the transrectal route. Initially, transperineal biopsies were thought to carry a higher risk for acute urinary retention, up to 10% in the PROMIS trial, likely due to the use of more extensive saturation biopsy templates.[64]

With a median of 15 cores performed, the acute urinary retention rate was 0.3% in the transperineal arm of the PREVENT trial, compared to 1.1% in the transrectal arm.[57] Similarly, with a median of 15 cores obtained, the acute urinary retention rate was 1.6% in the transperineal arm of the PERFECT trial, versus 3.1% in the transrectal arm.[55] The rates of bleeding requiring intervention were also lower with the transperineal approach—0% versus 0.4% in PREVENT and 0% versus 0.8% in PERFECT.

Pain scores and procedure duration

The transperineal approach offers several advantages, including reduced infection risk, potential reduction of rectal bleeding risk, and decreased antibiotic use, while maintaining good detection rates, especially for anterior and apical lesions, without increasing the risk for acute urinary retention.

Regarding the tolerance of the procedure when performed under local anesthesia, the median pain level on a numerical rating scale was 3.6 (standard deviation [SD], 2.3) in the transperineal arm versus 3 (SD, 2.1) for the transrectal approach in the PREVENT trial, corroborating previous findings in favour of a slight increase in the per-procedure pain level for transperineal biopsies compared to transrectal biopsies.[41]

Although transperineal biopsy under local anesthesia is generally assumed to be a longer procedure, the difference in duration between the two approaches can be minimized with increased surgeon experience.[104]

Thus, a growing body of evidence suggests TP biopsies offer superior performance in reducing infectious complications, making them the preferred choice when available, according to the EAU guidelines.[105]

Fusion Biopsy Techniques

Targeting of suspicious lesions on mpMRI during prostate biopsy can be carried out using three different techniques: MRI in-bore biopsy, cognitive/visual fusion biopsy, or software-assisted fusion biopsy. So far, there seems to be no significant advantage of one technique over another in detecting csPCa.[106] However, MRI in-bore biopsy is an image-guided technique commonly performed by interventional radiologists and not a fusion technique, *per se*.

Cognitive/visual and software-assisted fusion biopsies can be performed by either a urologist or a radiologist, depending on the country and medical system. Both techniques operate on the same principle: an MRI target within the prostate is identified and transferred onto a real-time ultrasound image of the prostate. The ultrasound is then used to guide the needle to the target. In cognitive/visual fusion biopsy, this process is entirely performed mentally by the operator.

Several systems for software-assisted fusion biopsy are commercially available (**TABLE 1**). The systems vary in tracking mechanisms, image fusion techniques, and additional features. However, all systems follow the same basic steps: initially, the mpMRI is assessed, and the prostate, suspicious lesions, and sometimes additional landmark structures (e.g., urethra or the seminal vesicles) are segmented on T2-weighted images. Most systems provide options for semi-automatic segmentation, where the software suggests segmenting boundaries that the operator then confirms or adjusts.

Following this step, two-dimensional ultrasound images of the prostate are acquired via a coronal or axial sweep. Using manual or semi-automatic segmentation, the three-dimensional (3D) ultrasound volume of the prostate is constructed. The mpMRI and ultrasound data can be fused together to align the images generated by the two different modalities. The process transforms the mpMRI images so that the previously segmented boundaries and target regions align with those of the ultrasound images. This process can be conducted rigidly or elastically. Rigid registration only allows for shifting and rotation of the mpMRI images, preserving the anatomy of the prostate and the location of the segmented lesions. Elastic registration allows for deformation of the image scale within each dimension, perfectly aligning the ultrasound images but potentially altering the anatomy of the gland. Most systems offer both options. Fused images might be displayed side-by-side and/or superimposed.

The actual biopsy process can then begin. Most systems support both the transrectal and the transperineal approaches. During biopsy, the software assists in targeting the region of interest through mapping, tracking, and navigation.[107] Tracking enables real-time visualization of the ultrasound probe and the needle within the previously virtually constructed 3D volume of the prostate, allowing the operator to navigate to the region of interest under complete visualization and monitor the precise location of a biopsy sample. The tracking methods differ between systems and follow a semi-robotic/mechanical, an electromagnetic, or an organ-based tracking principle.

The semi-robotic method tracks the position of the probe through angle sensors located in the robotic arm or mechanical stepper. As the ultrasound probe is manually rotated, the sensors detect mouvements in each of the joints and translate this information into a position in 3D space.[108]

The electromagnetic tracking method requires a magnetic field generator to be placed above the patient to generate a sequentially changing magnetic field. During the procedure, a small sensor attached to the ultrasound probe generates a current in response to the changing magnetic field. The current produced by the sensor is relayed to the fusion device's computer, which determines the location of the probe with respect to the electromagnetic field.[108]

The organ or image-based principle tracks the mouvement of the prostate itself. It identifies and compensates for patient mouvements and prostate deformations.

An overview of the most common commercially available systems for software-assisted fusion biopsy is provided in **TABLE 1**.

TABLE 1 Common commercially available systems for software-assisted fusion biopsy.

Artemis (Eigen Health; Grass Valley, California, USA)	• Semi-robotic/mechanical tracking. • Supports both transperineal and transrectal approaches. • Ultrasound system not integrated. • Prostate and suspicious lesions on mpMRI can be defined and contoured using ProFuse. • The Artemis platform provides applications for focal therapies.
BiopSee® (MedCom; Darmstadt, Germany)	• Semi-robotic/mechanical tracking. • Supports both transperineal and transrectal approaches. • Ultrasound system not integrated. • Prostate and suspicious lesions on mpMRI can be defined and contoured on BiopSee. • Compatible for vector prostate biopsy.
bkFusion (BK Medical; Burlington, Massachusetts, USA)	• Organ-based/operator-dependent tracking. • Supports both transperineal and transrectal approaches. • Allows only rigid fusion. • Integrated ultrasound system. • Prostate and suspicious lesions on mpMRI can be defined and contoured on bkFusion.
KOELIS Trinity® (KOELIS; Grenoble, France)	• Organ-based tracking. • Supports both transperineal and transrectal approaches. • Integrated ultrasound system. • Prostate and suspicious lesions on mpMRI can be defined and contoured on KOELIS Trinity or dedicated software.
UroNav (Philips; Cambridge, Massachusetts, USA)	• Electromagnetic tracking. • Supports both transperineal and transrectal approaches. • Ultrasound system not integrated. • Prostate and suspicious lesions on mpMRI can be defined and contoured using DynaCAD for Prostate.

Abbreviation: mpMRI, multiparametric magnetic resonance imaging.

Biopsy Complications

Infectious complications

Infections such as febrile urinary tract infections, acute bacterial prostatitis, orchitis, epididymitis, and urosepsis are well-known complications of TR biopsies, resulting in hospitalization in up to 6.9% of the cases.[84,85] The TR approach inherently exposes the biopsy channel to fecal flora, significantly elevating the risk for bacterial contamination. Several interventions can lower the rates of infective complications. According to clinical practice guidelines, antibiotic prophylaxis is mandatory before TR biopsies. Rather than fluoroquinolones, empirical aminoglycosides and cephalosporins are currently preferred.[105,109] Notably, when available, rectal swab or stool culture–based antibiogram allows for targeted prophylaxis, which is the treatment of choice.[84,105] Rectal enema with povidone-iodine has also been shown to decrease infective complications, bacteriemia, and bacteriuria (RR, 0.3; 95% CI, 0.21–0.45), and is therefore recommended before TR biopsies.[37,84,85,105,110] Thorough disinfection of perineal skin is recommended before the procedure; however, the role of antibiotic prophylaxis in TP biopsies is questionable, as two meta-analyses have shown no difference in infection rates between TP biopsies with or without peri-procedural chemoprophylaxis.[62,111]

Bleeding complications

Minor bleeding complications such as hematuria, hematoma, hematospermia, and rectal bleeding are common following prostate biopsies, while severe cases are rare, occurring in < 1% of interventions.[85] Various patient- and procedure-related factors, such as prostate size, concomitant anticoagulation treatment, and the number of biopsy cores taken can influence bleeding risk.[84,85] Systematic TR biopsies are associated with a rate of hematuria, hematospermia, and rectal bleeding between 10% to 84%, 1.1% to 93%, and 1.3% to 45%, respectively.[85] The wide variability in observed rates can be attributed to differences in definitions, reporting, and duration of bleeding. Importantly, hematospermia has been found to be affected by the number of biopsy cores taken, while data is controversial regarding hematuria for both TR and TP biopsies.[84,112–114] According to two meta-analyses, TP biopsies are associated with a similar rate of hematuria as TR biopsies.[84,115] Similarly, in the meta-analysis by Xue *et al.*, no difference was found between TR and TP biopsies in hematuria (20.6% vs. 17.1%; OR, 1.14; 95% CI, 0.85–1.53), rectal bleeding (10.2% vs. 1.5%; OR, 4.49; 95% CI, 0.51–39.22), and hematospermia (0.7% vs. 1.2%; OR, 0.59; 95% CI, 0.14–2.47).[116] Minor bleeding episodes are generally self-limiting and do not require any intervention.[84,85] Considering that patients may be receiving anticoagulant and antiplatelet medications, a thorough evaluation of thromboembolic and biopsy-associated bleeding risk, and consultation with the treating physician are necessary before the procedure.[84] Severe hematuria might require bladder irrigation. Serious rectal bleeding can be treated with rectal balloon tamponade, sclerotherapy, or endoscopic or endovascular interventions.[85,117,118]

Urinary retention

Acute urinary retention is a rare and mostly transient complication of prostate biopsies.[84,85] It occurs in approximately 0.4% to 6% and 1.7% to 11% of TR and TP biopsies, respectively.[84,85] Patients with preexisting benign urinary conditions, such as higher prostate volume (OR, 4.45; 95% CI, 2.01–9.84; $p<0.001$), extensive transitional zone, and high International Prostate Symptom Score are at risk of developing retention after biopsies.[84,85,119,120] A meta-analysis by Xue *et al.* showed similar acute urinary retention rates between TR and TP approaches (3.8% vs. 2.4%; OR, 1.39; 95% CI, 0.57–3.37).[116] In line with this, Ploussard *et al.* and Mian *et al.* (OR, 0.96; 95% CI, 0.15–15.34) found no difference between TR and TP approaches in terms of retention rates in two recent clinical trials.[55,56] Importantly, using alpha-blockers as a prophylaxis can mitigate this risk for urinary retention.[84,85,121]

Erectile dysfunction

Erectile dysfunction (ED) following prostate biopsy is a rare complication, although it significantly affects patient quality of life.[84] Importantly, it is typically transient, lasting a maximum of 6 months.[84,122] Due to heterogeneous and low-quality published data, to date it is unclear whether post-biopsy ED is related directly to biopsy with primary nerve trauma, psychological distress caused by the procedure, possible diagnosis of cancer, or all these factors.[84] Notably, among patients undergoing active surveillance, the diagnosis of PCa is associated with anxiety and reduced International Index of Erectile Function (IIEF) domains.[123] In a cohort of 231 men, Fujita *et al.* found repeat biopsies during active surveillance were associated with decreased erectile function (EF).[124] Similarly, Braun *et al.* demonstrated a 1-point/year reduction of IIEF scores in a cohort of 342 men on active surveillance, though the role of aging as a confounder could not be ruled out.[125] Based on a recent meta-analysis and a clinical trial, TR and TP procedures were found to be associated with similar rates of ED, which typically resolved within 6 months of biopsy.[55,122] Prebiopsy counselling of patients may help manage expectations, while post-biopsy support and treatment, if necessary, can assist in recovery.

Conclusion

Prostate biopsies play a pivotal role in the diagnostic pathway of prostate cancer, helping to assess disease characteristics, prognosis, and management strategies. Prebiopsy MRI, MRI-targeting techniques, and the development of the transperineal route have significantly improved the diagnostic process, making it more efficient in detecting clinically significant cancer while reducing unnecessary biopsies, insignificant cancer detection, and infection rates.

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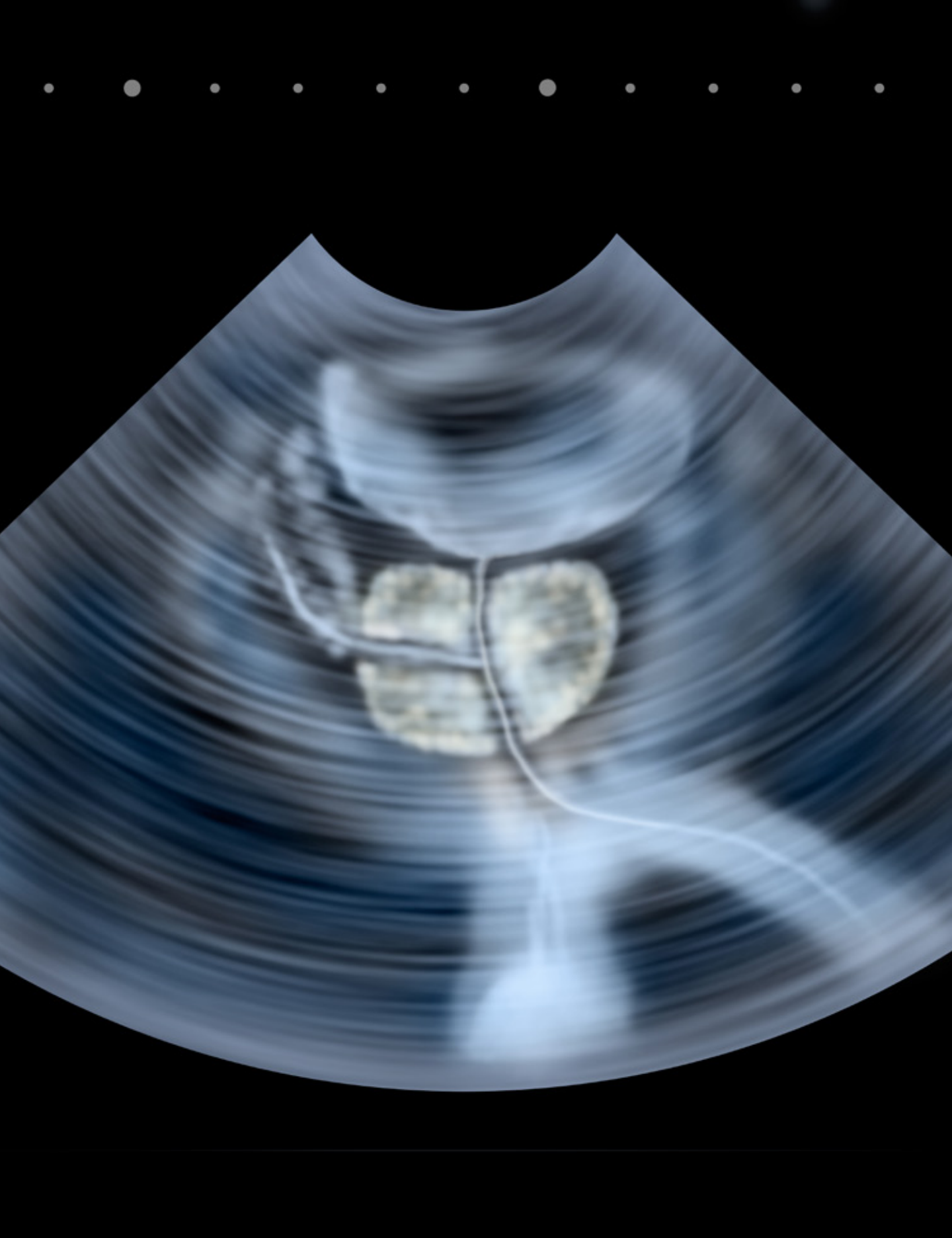
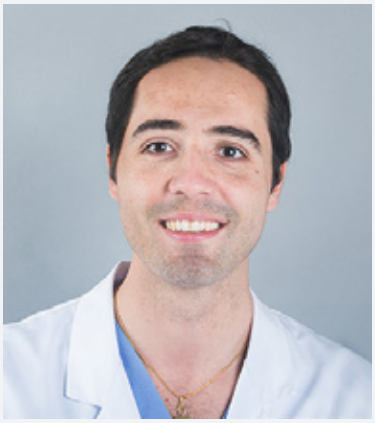


COMMITTEE 7

Imaging for Localized PCa—MRI and MicroUS



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Introduction

The diagnostic pathway for patients with a clinical suspicion of prostate cancer (PCa) has evolved rapidly in recent years. Randomized biopsies, which represented the gold standard for several years, have been gradually replaced by targeted approaches utilizing various imaging modalities to aid in accurate disease characterization. Specifically, multiparametric magnetic resonance imaging (mpMRI) has demonstrated its superiority over systematic biopsies in diagnosing clinically significant PCa (csPca) and reducing the overdiagnosis of clinically insignificant disease. In addition to mpMRI, which is now the diagnostic gold standard, alternative imaging techniques have also been explored. Among these, micro-ultrasound (microUS) has shown promising results, with diagnostic accuracy comparable to that of mpMRI. This chapter aims to summarize the evidence supporting the use of these diagnostic tools in clinical practice and to describe how these technologies can help clinicians optimize the diagnostic workup of PCa patients.

Magnetic Resonance Imaging

Principles of MRI

Imaging of PCa with MRI has traditionally consisted of T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). Technological advances have led to the widespread use of mpMRI, which combines T1WI and T2WI with diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE). These additional sequences enable mpMRI to distinguish indolent PCa from csPCa and play a role in risk stratification and image-guided biopsy.

Image interpretation and PI-RADS score

Multiparametric MRI of the prostate includes various anatomical and functional imaging parameters, each focusing on specific aspects of the prostate gland.

T2-weighted imaging

T2WI delivers a precise anatomical view of the zonal architecture with excellent soft tissue contrast. The peripheral zone in a normal prostate exhibits hyperintense T2 signal due to its abundant glandular ductal tissue, while the transition zone appears heterogeneously hypointense with higher cellular density.[1] PCa, characterized by high cellularity and low water content, typically exhibits a low T2 signal. However, conditions like prostatitis, scars, irradiation, hormonal treatments, and post-biopsy hemorrhage can mimic PCa on T2WI.

Diffusion-weighted imaging

DWI illustrates water molecule motion in tissues, linked to tissue cellularity. A region with restricted diffusion, like PCa, appears hyperintense on high-b-value sequences and hypointense on the corresponding apparent

diffusion coefficient (ADC) map. Current DWI protocols recommend the dedicated acquisition of the highest b values (usually 1,400 s/mm^2 and 2,000 s/mm^2 for 1.5-T and 3-T scanners, respectively) for optimal results.[2] PCa, with increased cellularity and glandular tissue destruction, results in lower water diffusivity and ADC values compared to normal tissue.

Dynamic contrast-enhanced imaging

DCE imaging, generated post-injection of a contrast agent (usually Gadolinium), evaluates both intensity and dynamics of contrast enhancement in prostatic tissue. Despite debate due to increased costs and potential side effects of Gadolinium, DCE imaging proves valuable in cases of equivocal T2WI and DWI, and for evaluating local recurrence after treatment.[3,4] PCa exhibits early wash-in and early wash-out compared to nonmalignant tissue.

Prostate Imaging–Reporting and Data System (PI-RADS) score

A significant challenge in prostate mpMRI has been establishing a standardized reporting system.

Dickinson and colleagues initiated a 5-point Likert MRI-based scale in 2011[5] and the Prostate Imaging–Reporting and Data System (PI-RADS) versions 1, 2.0, and 2.1 followed in subsequent years.[6–8]

Each lesion receives a score ranging from 1 to 5, indicating the likelihood of clinically significant cancer:

- PI-RADS 1: Very low (the presence of clinically significant cancer is highly unlikely)
- PI-RADS 2: Low (clinically significant cancer is unlikely to be present)
- PI-RADS 3: Intermediate (the existence of clinically significant cancer is uncertain)
- PI-RADS 4: High (clinically significant cancer is likely to be present)
- PI-RADS 5: Very high (clinically significant cancer is highly probable)

The PI-RADS guidelines do not provide management recommendations since these decisions rely on various factors such as prostate-specific antigen (PSA) levels, clinical history, the radiologist's expertise, and patient preferences. However, biopsy is typically recommended for PI-RADS 4 or 5 lesions, whereas PI-RADS 1 or 2 findings usually do not warrant biopsy.

At present, PI-RADS v.2.1 is widely used, though some experienced radiologists prefer the subjective Likert scoring system, emphasizing flexibility in considering additional parameters beyond the rigid PI-RADS criteria.

Multiparametric vs. biparametric MRI

Biparametric MRI (bpMRI) and multiparametric MRI (mpMRI) differ in the number of imaging sequences used to create detailed images of the prostate gland: mpMRI uses three sequences: T2-weighted imaging, diffusion-weighted imaging (with its ADC map), and dynamic contrast-enhanced imaging, while bpMRI uses only the first two sequences and omits the use of contrast agents.

Studies have shown that bpMRI can be a faster, cheaper, and safer alternative to mpMRI for detecting csPCa. At least one study comparing the diagnostic accuracy of bpMRI and mpMRI for detecting csPCa found that the two techniques had comparable accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Another study also found that bpMRI and mpMRI had similar diagnostic accuracy when considering PI-RADS scores 3, 4, and 5 as suspicious.[9–12]

However, some studies suggest that mpMRI may still be preferred in certain scenarios. Current guidelines still recommend the use of mpMRI over bpMRI in a wide range of clinical scenarios. Additionally, some studies suggest that mpMRI may be more effective at detecting csPCa in patients with PSA levels between 10 ng/mL and 20 ng/mL.[13] Overall, both bpMRI and mpMRI have their advantages and disadvantages, and further research is needed to determine the most effective approach for detecting csPCa, including the upcoming PRIME trial.

MRI and diagnosis of PCa

Biopsy-naïve patients

Systematic transrectal ultrasound (TRUS) of the prostate biopsy has historically been shown to underestimate the final Gleason grade of tumours upon histological examination after radical prostatectomy. This can result in inaccurate risk assessment and selection of treatment options. Additionally, TRUS biopsy often identifies more cases of low-risk clinically insignificant PCa, leading to overdiagnosis and imposing psychological stress on patients, sometimes resulting in overtreatment. Conversely, mpMRI has demonstrated promising outcomes in diagnosing, localizing, risk stratifying, and staging csPCa, even in biopsy-naïve men.

In a randomized prospective study reported by Panebianco *et al.*,[14] 186 of 355 (52%) of men following an initial negative systematic TRUS biopsy had csPCa on MRI-targeted biopsy. In another study, Haffner *et al.* reported a cancer detection rate of 54% in the systematic biopsy arm versus 63% in the MRI imaging arm.[15] Other single-centre studies have also shown detection of more csPCa following MRI compared to systematic biopsy, thereby improving the biopsy performance for PCa detection.[15–18]

Van der Leest *et al.* in 2018 performed a head-to-head comparison of TRUS-guided systematic prostate biopsy versus mpMRI-guided biopsy in biopsy-naïve men with elevated PSA levels in a single-arm, prospective, multicentre trial.[19] The MRI pathway resulted in a similar detection rate of csPCa compared with systematic biopsy (159/626 [25%] vs. 146/626 [23%]), with significantly fewer insignificant PCas detected (88/626 [14%] vs. 155/626 [25%]). In men with negative MRI, csPCa was detected in only 3% (10/309) on immediate systematic biopsy. However, a limitation of this study was that since systematic biopsy and MRI-targeted biopsies were obtained in all participants, the performance of one test may have been affected by the other, complicating the assessment of each test's unbiased performance in isolation. In fact the authors mention that "focal saturation" by adding perilesional cores to the MRI-targeted biopsies would have improved detection of csPCa in the MRI-targeted samples by 7%. In another similar single-arm, multicentre study, 13 (14%) of csPCas were detected by systematic biopsy only, 19 (20%) by MRI-targeted biopsy only, and 62 (66%) by either technique. The study

concluded that obtaining a mpMRI before biopsy in biopsy-naïve patients can improve the detection of csPCa but does not avoid the need for systematic biopsy.[20]

More recently, two level 1 evidence studies have exhibited the benefit of MRI-targeted biopsy over systematic biopsy in the detection of clinically significant PCa. The PRECISION trial (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) prospectively assessed in biopsy-naïve men whether multiparametric MRI, with targeted biopsy of MRI lesions when present, was noninferior to standard 10- or 12-core transrectal ultrasonography–guided biopsy in the detection of clinically significant PCa in men with a clinical suspicion of PCa (elevated or rising PSA and/or abnormal digital rectal exam [DRE]).[21] The results of the trial showed that over a quarter of the men were able to avoid a biopsy following MRI. Additionally, targeted biopsy of the MRI sites resulted in the detection of more clinically significant PCas (≥ grade group [GG] 2), with fewer cores compared to the standard systematic transrectal prostate biopsy. At the same time, fewer clinically insignificant PCas were detected in the MRI arm.

In a similar two-arm randomized controlled trial (RCT) conducted across five Canadian academic health sciences centres, 226 participants were randomized to the systematic biopsy arm and 227 to the MRI arm. In the study by Klotz *et al.*, 83 of 221 (38%) participants in the MRI arm had a negative MRI result (PI-RADS ≤ 2) and avoided biopsy. CsPCa was detected in 67 of 225 (30%) of participants in the systematic biopsy arm and 79 of 227 (35%) participants in the MRI arm. GG 1 clinically insignificant PCa detection in the systematic biopsy arm was 22% compared to 10% in the MRI arm.[22] In a 2-year follow-up to the initial RCT, Klotz *et al.* in 2023 reported that including MRI for patients in both arms of the PRECISE trial resulted in no difference in the detection of csPCa between the MRI and systematic biopsy arms, even though 38% of men in the MRI arm avoided the initial biopsy.[23]

Based on the results and the evidence of the studies above, most guidelines now recommend the use of mpMRI before prostate biopsy, acknowledging the benefits of mpMRI in improving the detection and localization of csPCa.[24]

Repeat biopsy setting

Detection of csPCa is a quality-of-care concern, and the diagnostic pathway for PCa is distinct from that of nearly all other solid organ cancers.[25] Historically, prostate biopsies have been performed in a randomized fashion using transrectal ultrasound (TRUS). This approach has been shown to be quite inaccurate. When diagnostic uncertainty persists, men often need to undergo repeat biopsies.[26] In this more nuanced scenario, mpMRI has become a crucial tool for assessing the risk for csPCa in men who present with elevated PSA levels or other clinical indications, such as an abnormal DRE. According to a Cochrane systematic review, mpMRI boasts a sensitivity of 0.91 for detecting csPCa (defined as International Society of Urological Pathology [ISUP] grade ≥ 2), although its specificity is limited to 0.37.[27] A recent systematic review further indicates that the percentage of csPCa is 6%, 12%, 48%, and 72% for PI-RADS scores of 2, 3, 4, and 5, respectively.[28] Additionally, a Likert scoring system, based on subjective radiologist assessments without predefined criteria, has shown a specificity of 0.77 and a sensitivity of 0.94 for PCa diagnosis.

Grivas *et al.* recently reported results of a systematic review of the literature to investigate the proportion of PCa detected at repeat biopsy (either clinically significant or any cancer) and the characteristics of these cases in patients with negative initial prostate biopsies despite positive initial mpMRI.[29] Of 2,344 identified records, 1,179 were screened after removing duplicates. Of these, 33 articles were reviewed in full, and nine studies were ultimately included.

Their key findings from the included studies show a wide range of detection rates for PCa and csPCa:

- For PI-RADS 3 lesions, the detection rate for PCa ranged from 0% to 80%, and for csPCa from 2.5% to 22%.
- For PI-RADS 4 lesions, the detection rate for PCa ranged from 15.4% to 86%, and for csPCa from 7.7% to 45%.
- For PI-RADS 5 lesions, the detection rate for PCa was up to 87.5%, and for csPCa up to 50%.

The study confirmed that patients with higher initial PI-RADS scores had higher detection rates for PCa. For patients with PI-RADS 3 lesions, clinical follow-up with PSA and repeat mpMRI at 6–12 months is recommended. For PI-RADS 4 lesions, clinical follow-up and repeat MRI to guide biopsy decisions are suggested, while for PI-RADS 5 lesions, a standard repeat biopsy is recommended. The findings highlight the importance of reevaluating initial mpMRI results and considering follow-up strategies involving repeat imaging and biopsies in high-risk cases.

On the other hand, serum and urinary biomarkers also hold promise, offering the potential for a noninvasive test that might help men decide whether to avoid a repeat biopsy. However, the UK National Institute for Clinical and Health Excellence (NICE) recently found that two biomarkers, the prostate health index and PCA3, were less accurate and cost-effective compared to an imaging-based pathway.[30] Other biomarker panels, such as the 4-kallikrein panel and a PSA density > 0.20, have shown good performance characteristics and are undergoing further evaluation.[31]

Active surveillance

Over the past decade, the landscape of PCa management has experienced a significant shift toward the widespread adoption of active surveillance (AS) as a viable strategy. This approach is gaining momentum among patients diagnosed with low- to intermediate-risk PCa, especially those with a life expectancy surpassing 10 years. The primary goal of AS is to delicately balance the avoidance of treatment-related side effects while preserving oncological efficacy. This delicate equilibrium is maintained by intervening with appropriate treatment only when there is evidence of higher-risk disease.[32]

The incorporation of mpMRI into AS has garnered substantial attention. This imaging technique has evolved into a standard tool for selecting candidates for AS due to its remarkable NPV for csPCa. Essentially, a patient with a negative mpMRI and favourable biopsy findings may be recommended to pursue AS. Beyond its NPV, mpMRI during AS plays a pivotal role in identifying patients who might benefit from additional biopsy. It not only enhances the precision of targeted biopsy but also contributes to a reduction in complication rates. Emerging evidence even suggests that mpMRI can uncover cases within AS where PCa was initially undersampled during the biopsy process.[33]

For the repeated use of mpMRI during AS, the crucial factor lies in proper image acquisition. The PI-RADS guidelines provide clarity in this regard, indicating that both 1.5-T and 3-T magnets can deliver reliable scans when acquisition parameters are optimized. The growth, alteration, or emergence of lesions on mpMRI can be indicative of true pathological progression. This insight prompts the exploration of MRI-led AS, wherein biopsy triggers are based solely on mpMRI findings. This is a paradigm that is met with controversy but holds the promise of potential benefits.[34]

The year 2015 marked a pivotal moment in recognizing challenges in reporting serial mpMRI scans during AS. The European School of Oncology Task Force convened in Milan to formulate the PRECISE recommendations. The PRECISE score, a 1-to-5 scale estimating the likelihood of radiological progression during AS based on serial mpMRI, has demonstrated reproducibility and agreement levels comparable to other scoring systems. Its application aims to identify AS patients who require timely intervention and simultaneously reduce surveillance intensity for those exhibiting radiological regression or stability. This dual objective holds the promise of alleviating the overall burden on individuals and healthcare systems.

Moving forward, the imperative for better evidence on the use of mpMRI in AS becomes increasingly clear. Rigorous randomized controlled trials or prospective multicentre studies are warranted to establish thresholds for radiological progression, optimal intervals for MRI, and triggers for initiating treatment. Robust data analysis across diverse cohorts is essential for determining the clinical significance of radiological changes over time. The new version of the PRECISE recommendations (PRECISE v.2) is expected soon, and future research should focus on the best methods for measuring lesion size on MRI scans and identifying criteria that reflect significant disease changes on serial MRI.[35]

MRI and staging of PCa

Accurate locoregional staging of PCa at diagnosis is a crucial component of guiding subsequent management strategies and preventing overtreatment or undertreatment. The tumour-node-metastasis (TNM) staging system is used to describe the extent of PCa spread beyond the prostate, with T describing the primary tumor, N describing the regional lymph nodes, and M describing distant metastases. T3a disease indicates that extraprostatic extension (EPE) is present, T3b disease indicates that seminal vesicle invasion is present, and T4 disease indicates that PCa has spread to adjacent structures, including the rectum, bladder, or pelvic wall.[36]

Current strategies for staging PCa primarily rely on serum PSA values, DRE, and Gleason score, which can underestimate the true disease stage. The presence of extracapsular extension and seminal vesicle invasion is associated with a higher risk for biochemical recurrence after definitive therapy, due to the increased likelihood of positive surgical margins and nodal metastases, respectively.[36] Accurate identification of extraprostatic disease on mpMRI can allow for more precise surgical planning, which can reduce the incidence of positive surgical margins on final pathology.[36] Moreover, while the mainstay approach to managing T3a disease consists of either surgery or brachytherapy, management of T3b disease typically consists of a multimodal approach combining long-term androgen deprivation therapy with definitive therapy.[37]

Therefore, accurate localization of seminal vesicle invasion and regional invasion on mpMRI can enable treating clinicians to tailor management to each individual patient's disease burden. In a study of 532 patients who underwent mpMRI prior to MRI/US fusion biopsy and radical prostatectomy, the addition of mpMRI to standard clinical nomograms improved the predictive ability of organ-confined disease, extraprostatic extension, seminal vesicle invasion, and lymph node involvement.[38] In another meta-analysis of 75 studies investigating the accuracy of mpMRI for local PCa staging, mpMRI had a sensitivity and specificity of 0.57 and 0.91 and 0.58 and 0.96 for the detection of extraprostatic disease and seminal vesicle invasion, respectively.[39] Therefore, while mpMRI has high specificity for local PCa staging, a negative mpMRI does not exclude the presence of extraprostatic disease.

Multiple scoring systems have been developed to evaluate the possibility of extraprostatic extension on mpMRI, including the European Society of Urogenital Radiology score, the Likert scale, tumour contact length, and EPE grade.[2,6,40,41] A retrospective analysis compared these criteria for predicting extraprostatic extension and highlighted the value of the EPE grade, which relies on both quantitative and qualitative mpMRI parameters and depends less on reader experience.[42] Most recently, the capsular enhancement sign on DCE was demonstrated to be a highly specific predictor of extraprostatic extension in a study of 146 patients who underwent mpMRI prior to radical prostatectomy.[43] Further research is necessary to establish the most sensitive and specific parameters for detecting extraprostatic extension on mpMRI.

A hypointense signal on T2WI, restricted diffusion on DWI, and early enhancement on DCE can indicate seminal vesicle invasion, as well as invasion to adjacent structures.[36] Currently, the identification of nodal metastases on mpMRI is limited by the restricted field-of-view on mpMRI compared with whole-body imaging modalities. Furthermore, using size alone to separate malignant from benign lymph nodes can lead to both false positives (due to enlargement from inflammatory changes) and false negatives (due to micrometastases that do not meet size criteria).[36] Therefore, PCa patients have historically undergone computed tomography (CT) and nuclear medicine bone scans to stage nodal and distant metastases. However, novel imaging modalities, including prostate-specific membrane antigen positron emission tomography (PSMA PET), have shown promising results. In a study of 764 men with intermediate-to high-risk PCa who underwent a PSMA PET scan prior to radical prostatectomy, the sensitivity and specificity for the detection of pelvic nodal metastases was 0.40 and 0.95, respectively.[44] These results suggest that PSMA PET has high specificity for the detection of pelvic nodal disease, although it may miss smaller pelvic nodal metastases. Therefore, a negative PSMA PET does not exclude the presence of nodal disease.

MRI: benefits and pitfalls

MRI has emerged as a validated tool in the diagnosis and management of localized PCa. Its superior soft tissue contrast and functional capabilities compared to other imaging modalities offer both benefits and drawbacks in this context, warranting careful consideration.

Benefits

MRI's multiplanar views and high tissue contrast enhance the detection of clinically significant cancer and can identify cancer missed by traditional TRUS biopsy. MRI can be used to guide biopsies, including in-bore and MRI-ultrasound image fusion, reducing unnecessary biopsies and improving diagnostic accuracy. Its

superior localization and staging facilitate risk stratification, helping to select between definitive treatment or active surveillance. MRI also informs radiotherapy planning by defining tumour volumes and adjacent critical structures, enabling precise targeting and dose optimization. This leads to improved treatment efficacy while minimizing side effects. Additionally, MRI is useful for surveillance and treatment monitoring, detecting local recurrence earlier than serum PSA alone.[45,46]

Pitfalls

The exquisite sensitivity of MRI can lead to the detection of clinically insignificant lesions that may never progress to clinically relevant cancer. This raises concerns about unnecessary biopsies, anxiety, and potential overtreatment with associated morbidity. Balancing the benefits of early detection with the risks for overdiagnosis requires personalized decision-making. Additionally, MRI is more expensive and resource-intensive compared to standard imaging modalities such as ultrasound. This limits its accessibility, particularly in resource-constrained settings. Furthermore, technical limitations and expertise required for interpretation can pose challenges in less experienced hands. Image features of benign and malignant lesions overlap, leading to variable performance in different scenarios. Moreover, some men cannot undergo MRI because of implanted medical devices or claustrophobia, and even those who can safely undergo MRI may have conditions such as hip prostheses or rectal distention that compromise image quality, limiting the utility and cost-effectiveness of prostate MRI. Finally, the long-term benefits of MRI for localized prostate cancer have yet to be proven.[21]

MicroUS

Principles of micro-ultrasound

Transrectal ultrasound of the prostate is traditionally performed with the conventional 6-9 MHz curved linear endocavity transducer. The ability of ultrasound to provide a real-time image of the prostate capsule has been critical for image-guided procedures such as the application of reliable local nerve block for anesthesia, as well as for the spacing of the systematic biopsy itself. Unfortunately, while the internal prostatic tissue can be detected, the sensitivity for targeted sampling is low.[47] These transducers offer a -6dB resolution of 210 μm axially, which is insufficient for visualizing the prostatic ductal architecture.

In order to visualize the prostatic ductal architecture, a new ultrasound transducer and system were developed based on recent advances in the field of preclinical ultra-high frequency ultrasound.[48,49] A resolution of 70 μm was selected in order to optimally visualize the prostatic ducts (averaging 100 μm), while still permitting an imaging depth covering the full prostate. This system was first tested clinically in men undergoing radical prostatectomy and compared to whole-mount pathology, where it demonstrated superior sensitivity and specificity to conventional ultrasound.[50] More recent work by Pensa *et al.* using image processing algorithms to automatically count and measure prostate ducts in whole-mount slices confirms the original hypothesis that microUS visualizes approximately 95% of the prostatic ducts while conventional ultrasound resolves only 15%.[51]

High-frequency ultrasound transducers are not unheard of and have been developed for other applications such as intravascular ultrasound (IVUS); however, these transducers would not be suitable for the prostate due to their low number of elements, high element spacing, and limited bandwidth. In practical terms, this would result in a small field of view and visualization of only the shallowest areas within the peripheral zone. MicroUS was made possible by novel transducer designs with many individual elements packed at extremely high density. Furthermore, the individual elements are specially tuned to have wide bandwidth, allowing high sensitivity and improved penetration depth compared to traditional designs. This has allowed for imaging of the full length of most prostates and the full height of all prostates while maintaining the 70-micron resolution required for high sensitivity.

The technical principles enabling visualization of the prostatic tissue architecture have led to new clinical principles related to interpretation of the images. Unlike with conventional ultrasound, cancer on microUS demonstrates a range of appearances that were first described by Ghai *et al.* in 2016 as part of the Prostate Risk Identification using MicroUS (PRI-MUS) protocol.[52] This work was extended to the anterior and transition zones of the prostate, with subsequent validation demonstrating equally robust cancer detection to the peripheral zone.[53]

Image interpretation and PRI-MUS score

MicroUS enables visualization of prostate cancer through unique acoustic features. The high frequency of microUS enables 70-micron resolution, allowing visualization equivalent to low magnification microscopy. To understand microUS imaging requires a histologic foundation.

The peripheral zone, transition zone, central zone, and anterior fibromuscular stroma all appear uniquely on microUS. Cancers may arise from any portion of the prostate, but traditionally occur as benign glands condensing into cellularly dense tumours. The cancer distribution is skewed toward the peripheral zone (77%), transition zone (20%), and central zone (3%).[54] The anterior fibromuscular stroma does not produce primary adenocarcinoma; however, this zone can be invaded by tumours originating from the anterior transition zone or peripheral zone.[55]

The PRI-MUS protocol identifies distinct acoustic patterns within the peripheral and transition zones indicative of prostate cancer.[52] Despite the protocol's validity, it is difficult for a urologist to rotate the probe, visualize all anatomic zones simultaneously, and identify cancerous acoustic patterns during a rectal examination.

We suggest utilizing an anatomic progression to arrive at the PRI-MUS score and reduce missed tumours. First, evaluate the anterior prostate (above the urethra). The highest prevalence of anterior cancer will reside in the anterior apical horn of the peripheral zone and the apical transition zone.[55] Anterior zone cancers have no visible ducts, have hypoechoic background stroma, and are longer rather than have a tall shape. Large-volume tumours may demonstrate irregular borders or finger-like projections down into the normal stroma. A visual clue may also be the loss of hyperechoic fat above the visible tumour. Importantly, all anterior tumours lack ducts and have hypoechoic stroma. These features alone reach a high-risk PRI-MUS classification.[53] Larger anterior tumours have irregular borders and loss of anterior fat.

Benign anterior tissue also has a classic appearance and can aid in differentiation from cancer. Benign prostatic hyperplasia (BPH) nodules look akin to Easter eggs sitting on ends. BPH nodules are taller rather than long and have hyperechoic components and occasional internal ducts or cysts. The capsule of a BPH nodule is smooth and will cast a "V"-shaped shadow posteriorly.

After evaluating the anterior prostate for cancer, focus on the central zone. As only 3% of cancers occur in the central zone, the evaluation is to identify the midline and verumontanum, adjust the ultrasound depth, and distinguish a hypoechoic background. The posterior evaluation strategy mirrors the anterior. First look for large patulous ducts in the peripheral zone. The absence of large patulous ducts is indicative of no cancer, and the area is labelled PRI-MUS 1. Small but visible ducts indicate PRI-MUS 2. The absence of ducts means that the lesion is at least PRI-MUS ≥ 3, suggesting cancer transformation from a benign duct into a condensed cancerous phenotype that is visible on microUS. Ducts should be visualized on the highest resolution setting, with a 3-cm penetration depth, which ensures complete visualization of the peripheral zone. If it's challenging to determine the presence of ducts, apply pressure on the probe to see whether the ducts open and close. If the ducts do not change, then the area is more concerning for cancer.

Lesions without ducts and a hyperechoic background relative to the central zone are classified as PRI-MUS 3. A mixed or mottled echogenic background usually indicates PRI-MUS 4. An isoechoic or a hypoechoic background relative to the central zone typically indicates PRI-MUS 5. The anterior prostate will cause irregularities in the adjacent benign tissue, prostate capsule, or transition zone.

Finally, there are a handful of unique acoustic considerations. In areas with prior bleeding or inflammation, small calcifications can cause a "starry-night" pattern, where bright calcifications contrast against a dark backdrop. However, this pattern can sometimes be a false positive, such as when calcifications around the urethra are benign. In general, prioritize looking for other PRI-MUS 4 indications. Lesions that lack ducts, exhibit hypoechoic stroma, and show a starry-night pattern are likely indicative of cancer. These characteristics aid in identifying potentially malignant areas during prostate evaluation.

In summary, start by checking for ducts. Where ducts are absent, evaluate tissue echogenicity relative to the central zone; darker tissue suggests a higher likelihood of cancer. Large tumours often cause irregular borders regardless of their location within the prostate.

MicroUS and diagnosis of PCa

Biopsy-naïve patients

As already pointed out in the section on the principles of microUS, the high resolution up to 70 μm enables examiners to visualize potential cancerous lesions in real time. This information can be used with or without mpMRI imaging either to counsel men regarding the need for a prostate biopsy or to perform targeted biopsies. In most trials reporting the cancer detection rate of microUS and PRI-MUS scoring, men had an initial mpMRI with

a PI-RADS lesion ≥ 3. Therefore, the data must be interpreted as an additional imaging to mpMRI. Nonetheless, the data provides an initial indicator of the performance of high-resolution ultrasound.

The first prospective multisite trial was published in 2021 by Hofbauer *et al.* using a blinded PRI-MUS scoring system in men with a PI-RADS lesion ≥ 3 and an indication for prostate biopsy. In this cohort, 71% of men had a primary prostate biopsy. MicroUS detected 97% of men with clinically significant prostate cancer when compared to mpMRI.[56] In conclusion, the trial showed a noninferiority of microUS compared to MRI targeting.

Lughezzani *et al.* in a large Italian series was able to show similar detection rates of PRI-MUS scoring compared to PI-RADS. For men with an initial prostate biopsy, the sensitivity was 86.5% and the NPV was 71.4%, which may also reflect that this was the first larger series published on microUS.[57]

In a prospective analysis of 94 men with a primary biopsy between 2019 and 2020, microUS detected 67% of the lesions found in the previously performed mpMRI. When combining the targeted biopsies with MRI and microUS, the additional systematic biopsies found no further clinically significant cancer.[58]

In two meta-analyses that included 1,125 and 1,759 men, the performance of microUS echoed the results seen with mpMRI, but the analysis also included men with repeat biopsies.[59,60] Overall, being able to visualize the target lesion in addition to incorporating MRI/microUS fusion seems to increase the precision of targeted biopsies.

When comparing targeted microUS–guided biopsies to a 3D organ–based fusion platform (KOELIS®; Meylan, France), there was no difference in cancer detection in a prospective trial of 80 men.[61] Beyond the visualization of the MRI lesion by microUS, Wiemer *et al.* demonstrated in a mixed cohort that high-resolution ultrasound detected an additional 17% of significant prostate cancers and 9% of high-risk cancers missed by the MRI-targeted approach.[62] This analysis also highlighted that a targeted-only approach for all microUS lesions and MRI lesions combined would have achieved results similar to the currently standardized MRI-targeted plus systematic biopsies. This would result in a lower number of cores taken without hampering the rate of significant cancer detection.

Overall, the current mpMRI pathway leads to a detection of significant cancer in around 40% of men biopsied, despite higher overall cancer detection rates. This is mostly related to the low yield of significant prostate cancer in men with PI-RADS 3 lesions. The overall cancer detection rate of PI-RADS 3 is around 30%. Adding microUS to the pathway provides the option to counsel men in this unclear scenario toward or against prostate biopsy. If no suspicion was documented by microUS only, no significant cancers would have been missed and therefore 27% of men could have been spared a biopsy.[63] Larger series are needed to validate these findings, but the initial trend shows the potential of the technology to be used as a triage tool before prostate biopsy and for targeted biopsy once it is indicated.

In the published series so far, which mostly included MRI preselected cohorts, the potential of microUS is promising. The true potential will be demonstrated by the currently ongoing OPTIMUM trial comparing microUS to the mpMRI pathway.[64] The trial will include 1,200 men with an indication for prostate biopsy based on either PSA values or DRE. The three-arm design will compare microUS alone or in combination with mpMRI against the current mpMRI standard arm. Since all men included will undergo prostate biopsy as per protocol, the true NPVs of both imaging modalities will be evaluated. Although the primary endpoint is noninferiority of microUS compared to mpMRI in the detection of significant prostate cancer, this trial will also assess whether microUS has the potential to be used as a screening tool alongside the current clinical parameters. Besides the potential benefit over the MRI arm, the number to beat will be the 30% of men who are spared prostate biopsy in the mpMRI pathway as presented by Drost *et al.* in a Cochrane meta-analysis in 2019.[27]

Repeat biopsy setting

With the wide adoption of the mpMRI pathway, the number of men undergoing repeated biopsy sessions (mostly repeated systematic biopsies) has been reduced consistently. The initial mpMRI trials included mostly men with previous systematic biopsies and clearly showed the benefit of the imaging pathway, which has led to the clear recommendation in the guidelines. In regard to microUS, we have to therefore separate its use in men with previous negative systematic biopsies without mpMRI imaging from men with a negative MRI-targeted biopsy. Only a few studies report the outcome of men with a negative MRI-targeted biopsy, and there currently is no recommendation by the guidelines as how to further manage these men.

Where does microUS fit in the management of men with a negative MRI-targeted biopsy? The high resolution of microUS enables the examiner to visualize old biopsy channels, especially in the peripheral zone. These biopsy "artifacts" usually measure 0.4 mm in size and can be seen even years after a previous biopsy.

Especially in a short-term scenario after a negative targeted biopsy, the added knowledge of the sample sites, in combination with the PRI-MUS scoring, can be used to counsel men. If a visible lesion does not show a sampling or biopsy channel, a repeat microUS-targeted biopsy may be warranted. There is currently little data published on this detailed topic. Beatrici *et al.* published a retrospective analysis on 304 men with a previously negative MRI-targeted biopsy. When compared to mpMRI, microUS detected 17.1% of clinically significant prostate cancer versus 14.5%.[65] Furthermore, microUS had a higher sensitivity (91.2% vs. 77.2%) and NPV (66.7% vs. 45.8%) in detecting or ruling out significant cancer. Even with the potential biases from a single-centre retrospective trial, there is clear potential to visualize suspicious lesions with microUS in the repeat biopsy setting. The series that included both primary and repeat biopsy men were included in two large meta-analyses that showed no statistically significant difference in the performance of microUS compared to mpMRI.[59,60] Further trials and analyses are needed to evaluate not only the full potential of microUS but also the risk for overdiagnosis.

Another scenario is men under active surveillance who are planned for a repeat biopsy. In a series of 100 men, microUS could have avoided 18 biopsies with no upgrading where no lesion was seen but would have been missed 4 cases with ISUP upgrading.[66] In a cohort of 128 men under active surveillance, microUS performed comparably to mpMRI in detecting ISUP ≥ 2.[64] In this unblinded series, the NPV of microUS was 97% compared to 91% for mpMRI.

Active surveillance

As previously mentioned, AS has become the preferred strategy for managing men with low-risk prostate cancer.[68–70] The proportion of men with low-risk prostate cancer managed by AS has significantly increased over the past decade.[71] When patients are selected and followed carefully, development of prostate cancer metastases and evolution to prostate cancer mortality are relatively rare. In one study of 1,818 men with low-risk PCa who were followed in AS for many years, only 4 men died from PCa.[72] However, the rate of definitive treatment in these men was 36% at 5 years and 48% at 10 years.

MRI-guided prostate biopsy has become the new gold standard to help eliminate men upfront who are destined to require active treatment and, during active surveillance, identify those remaining men who progress.[73,74] Several studies have compared high-resolution microUS to MRI during active surveillance.[75,76] These studies show that microUS compares favourably with MRI, detecting similar amounts of Gleason grade group ≥2 prostate cancers. The sensitivity of PRI-MUS ≥ 3 lesions for grade group ≥ 2 is between 94% and 97%. Furthermore, the concept of a "double negative" exists, when a patient has had both a negative MRI and microUS. In one study, no patients upgraded to Gleason grade group ≥ 2 if both the MRI and microUS were negative.[75] However, prospective, multicentre trials are needed to further validate the accuracy of microUS in active surveillance. The ongoing multicentre study MicroUS In Cancer—Active Surveillance (MUSIC-AS) is a prospective, paired, diagnostic trial comparing detection of Gleason grade group ≥ 2 at confirmatory biopsy that will provide high-level evidence for the utility of microUS in the active surveillance setting.

MicroUS and staging of PCa

Local prostate cancer staging or "T-staging," is classically based on DRE findings. The accuracy of MRI in determining extracapsular extension and seminal vesical invasion has been previously studied. Recently, the ability for microUS to determine local staging of prostate cancer has been assessed.[77] In men undergoing radical prostatectomy with whole mount pathology, preoperative microUS evaluations focused on the following criteria: visible breach of the prostate capsule; capsular irregularity or bulging; obliteration of the prostatic-seminal vesicle angle; presence of a hypoechoic halo, and capsular contact length ≥ 15 mm. Visible breach, a capsular bulge, presence of a hypoechoic halo, and obliteration of the prostatic-seminal vesicle angle were all found to be associated with non–organ-confined disease.[78] Furthermore, the greater the number of factors identified, the higher the likelihood of T3 disease. Based on microUS imaging findings, a nomogram has been created for the prediction of extracapsular extension.[79]

A limitation to staging using microUS is the inability to stage pelvic lymph nodes or bony pelvic structures, as can be done for prostate MRI. Finally, further work is required to determine accuracy of predicting tumour margins and the volume of intraprostatic tumours as measured by microUS.

MicroUS: benefits and pitfalls

As with many new imaging technologies, microUS has certain benefits over existing technologies that make it attractive in particular clinical scenarios. However, like any new imaging technology, it also has pitfalls that must

be understood in order to use the technology effectively. In this section, we describe the key technical benefits of the technique, along with scenarios where they may translate into clinical benefits. Similarly, we describe several known pitfalls, how they can disrupt clinical management, and how they can be managed.

Key benefits

The principal benefit of microUS is its ability to visualize areas suspicious for prostate cancer in real time. This ability is unique among current prostate imaging technologies, which generally require a separate patient visit for imaging. Many studies concur that microUS compares well with mpMRI.[57,58,60,62,80,81]

MicroUS is able to visualize the detailed anatomy of the prostate. In addition to detailed tracing of the prostate capsule, surrounding vessels, facial planes, musculature, and neurovascular supply, the walls and lumen of the ejaculatory duct are generally visible. Needle scars from prior biopsy procedures have been reported after more than 2 years. This anatomical detail, combined with the precise visualization of lesions, can potentially lead to improved planning for both focal therapy and surgical approach.[79,82]

Clinical scenarios

Patient ineligible for MRI: There are several relative contraindications to mpMRI that are particularly prevalent in the population at risk for prostate cancer. These include implanted devices such as pacemakers, hip replacements (4%),[83] impaired kidney function (12%), and claustrophobia (3–5%)[84]. These men should not have to settle for the high false negative rate of a systematic biopsy, and microUS provides a clear and simple way to ensure they receive an accurate diagnosis.

Equivocal or negative MRI: Biopsy yield is reduced in men presenting with equivocal or negative MRI, even in cases where there is continued suspicion based on abnormal DRE, PSA, or other liquid biomarkers. In these cases, MRI/US fusion biopsy does not add value. Use of microUS, on the other hand, appears to provide information independent of MRI, and these men may benefit from further risk stratification and targeted biopsy with microUS.[85] In one study on the MRI-negative population, detection of clinically significant cancer with microUS was 47% higher than with conventional ultrasound.[86] MicroUS therefore serves as a tool complementary to MRI in the diagnostic pathway for detection of csPCa.

Real-time therapy guidance: While it is possible to perform near-real-time–guided therapy in MRI (for example, using MRI thermometry, combined with laser or ultrasound ablation), microUS guidance enables these procedures to be performed faster and easier. Therapies using laser, cryotherapy, high-intensity focused ultrasound (HIFU), and steam have all demonstrated feasibility under microUS guidance. This is particularly attractive because of the rapid visualization of the growing ablation zone, lesion borders, and critical structures with microUS, which may allow for finer control of treatment margins.

Known pitfalls

As with all ultrasound procedures, the primary pitfall for the novice operator is artifacts such as air bubbles, reverberations, and edge shadowing. More importantly, calcifications within the prostate, particularly in men with significant *corpora amylacea* may make visualizing the deeper or anterior structures more challenging in some cases. However, microUS has a smaller imaging plane compared to conventional ultrasound, which means that the shadowing tends to obscure a narrower band of tissue.

It is traditionally assumed that lesions in the anterior part of the prostate, particularly in men with very large glands, would be a pitfall for microUS. This was likely true until recently, as recent technological updates have resulted in improved deep imaging. Leveraging these improvements, Schaer *et al.* conducted a study on the ability of microUS to identify anterior cancers in prostates of any size, which demonstrated the same accuracy as in the posterior part of the prostate.[53] This surprising result suggests that anterior prostate cancers and larger prostates may not be a true limitation of the technology.

The real-time nature of the technique suggests the potential for inter-reader variability. This has not been adequately assessed, although the original PRI-MUS validation by Ghai *et al.* demonstrated fair-to-moderate correlation between readers.[52] Inter-reader variability in the anterior part of the prostate was similar, with a higher Fleiss kappa but lower Cronbach alpha score.[53] Expert consensus on the technique suggests that a revision to the PRI-MUS protocol will likely be required to reduce variability due to the similarity of many of the patterns involved.

Conclusions and Future Perspectives

In recent years, there has been a paradigm shift in the diagnostic pathway for patients with suspected csPCa. Multiparametric MRI followed by a targeted biopsy has indeed emerged as the gold standard diagnostic modality, capable of maximizing the diagnosis of csPCa while minimizing the overdiagnosis of clinically significant PCa. Biparametric MRI may be a faster and less expensive alternative, particularly in the screening setting, although further evidence is needed to validate its use in clinical practice. Other imaging modalities have also been extensively evaluated. Among these, microUS has shown a potential role as an alternative diagnostic tool and may represent an effective modality in the diagnosis of PCa, especially when mpMRI is not available or cannot be performed. Further evidence from randomized controlled trials is awaited. Both MRI and microUS may benefit from the implementation of artificial intelligence algorithms, which could further enhance their diagnostic capabilities while limiting operator dependence.[87,88]

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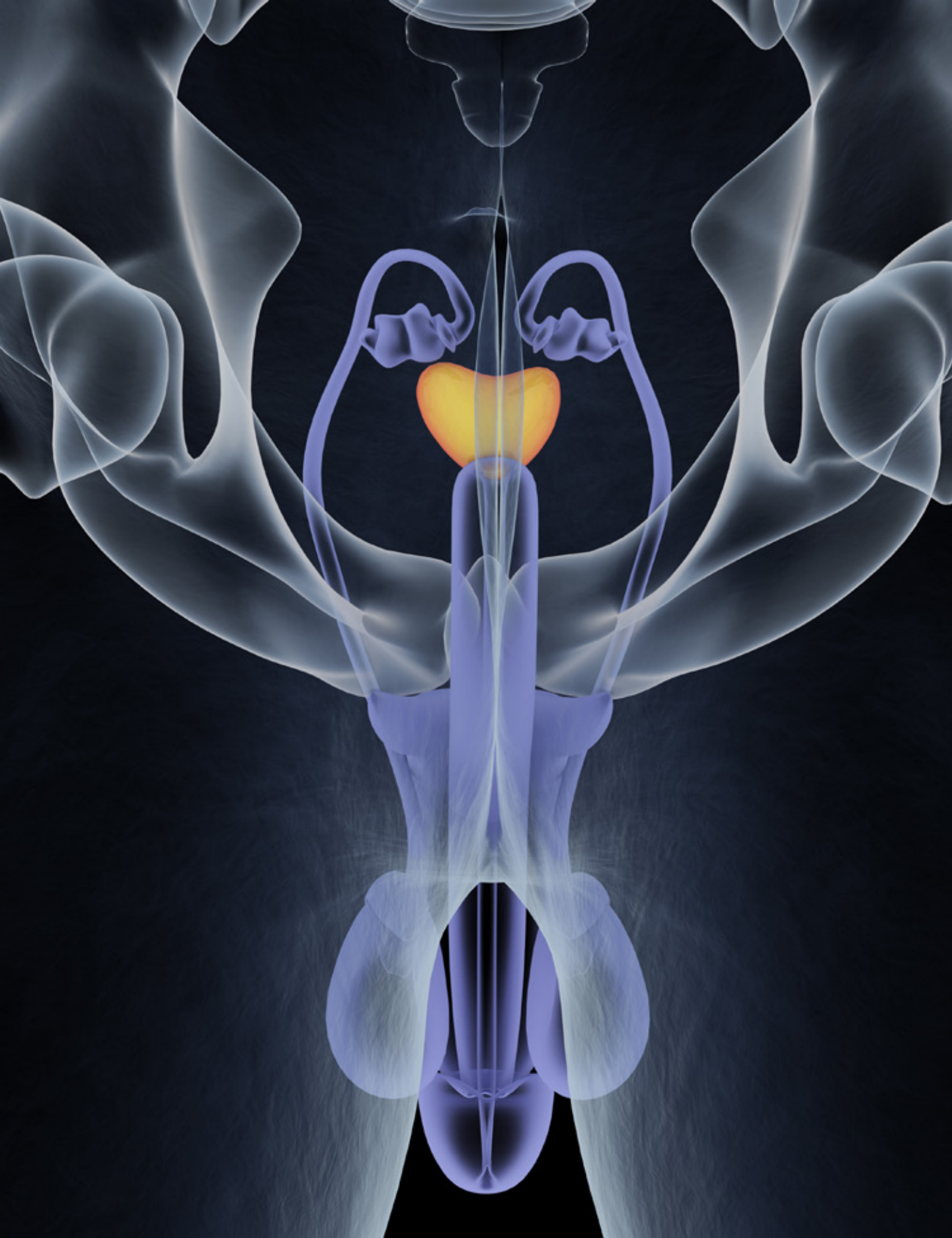

COMMITTEE 8

PSMA PET Scans: Performance and Role in Localized Disease

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Introduction

Prostate cancer (PCa) is the second most diagnosed cancer and one of the leading causes of cancer-related mortality in men worldwide.[1,2] The incidence of PCa has been progressively increasing due to factors such as an aging population and widespread uptake of prostate-specific antigen (PSA) testing.[1,3] One criticism that PSA screening has faced is the risk for increased detection of clinically insignificant PCa (ciPCa).[4] The European Association of Urology (EAU) Guidelines define ciPCa as PCa that does not cause harm, while clinically significant PCa (csPCa) is defined as PCa that may result in morbidity or mortality.[5] This distinction is crucial to avoid unnecessary side effects associated with overtreatment of ciPCa.

The diagnosis of PCa often involves prostate biopsies, preferably with imaging guidance. The current imaging modality of choice is magnetic resonance imaging (MRI). The PRECISION trial compared MRI-guided biopsy against ultrasound-guided biopsy and demonstrated that the addition of MRI increased the detection rate of csPCa from 26% to 38%, while reducing detection of ciPCa from 22% to 9%.[6] However, the use of MRI may result in an increase in the number of unnecessary biopsies while potentially missing some csPCa.[7] There is further room to improve the detection of csPCa while reducing the detection of ciPCa, therefore, newer imaging modalities are being explored.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is upregulated in PCa cells, making it an ideal target for molecular imaging due to its limited expression in benign prostatic tissue.[8] The introduction of PSMA positron emission tomography (PSMA PET) scans has undoubtedly changed our diagnosis and management of PCa (**FIGURE 1**). Following the ProPSMA trial, PSMA PET scans have replaced conventional imaging modalities (abdomen and pelvis computed tomography [CT] and whole-body bone scan [WBBS]) for staging.[9,10] The EAU guidelines recurrently recommend PSMA PET scans only for selected PCa patients with concerns of recurrence or staging of International Society of Urological Pathology grade group (ISUP GG) ≥ 3.[5] Although there is no role for PSMA PET scans for staging of ISUP GG 2 PCa, there may be a role for its use in evaluating localized intraprostatic PCa. There is emerging evidence for the use of PSMA PET scans for evaluation of intraprostatic lesions, and it has been shown to improve our detection of csPCa.[11] This book chapter aims to provide a comprehensive overview of the clinical applications and performance of PSMA PET scans in localized PCa.

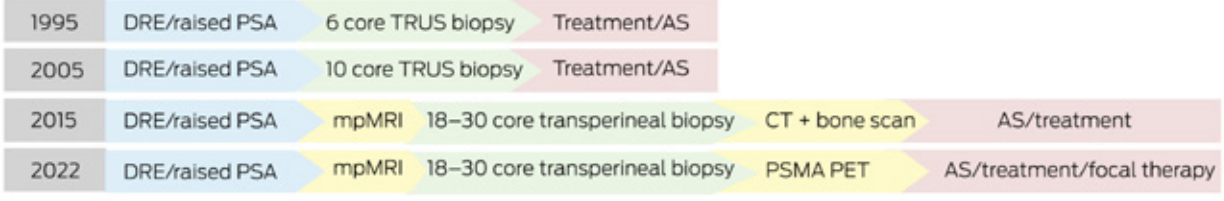
Types of PSMA Tracers

The first PSMA agent, Ga-PSMA-11, was introduced in the late 1990s, with clinical use emerging in 2012.[12,13] PSMA distinguishes itself from the most widely used PET tracer, F-FDG, which has limited utility in PCa due to the low glycolytic rate of many PCa tumours.[14] Since then, various PSMA tracers have been developed and labelled with isotopes such as ^{68}Ga and ^{18}F. A comparison of advantages and disadvantages of different tracers is described in **TABLE 1**. These tracers all have unique diagnostic attributes, biodistribution, and therapeutic potentials.

The majority of publications have focused on Ga-68–labelled PSMA PET imaging tracers, such as [^{68}Ga] Ga-PSMA-11 and [^{68}Ga]Ga-PSMA-I&T, primarily due to their early development and the operational advantages they offer.[15] However, the F-18–based tracers are theoretically advantaged in imaging resolution and diagnostic performance compared to Ga ligands due to the physical properties of a longer half-life and lower positron energy.

Despite multiple comparative studies, there remains a lack of consensus on the superiority of one PSMA tracer over others.[15,16] In clinical practice, the choice of radiopharmaceutical may likely largely depend less on a tracer's physicochemical differences (e.g., background uptake, renal excretion, hepatic metabolism) but rather on availability, local reporter expertise, cost, and regulatory approval.

FIGURE 1 Change in the diagnostic pathway of prostate cancer over time.



Abbreviations: AS, active surveillance; CT, computed tomography; DRE, digital rectal exam; mpMRI, multiparametric magnetic resonance imaging; PSA, prostate-specific antigen; PSMA PET, prostate-specific membrane antigen positron emission tomography; TRUS, transrectal ultrasound.

PSMA-Based Imaging Modalities

PSMA PET/CT and PSMA PET/MRI are two principal imaging modalities leveraging PSMA tracers for detecting PCa (**TABLE 2**). The PET scanner detects gamma rays from the radiotracer within the body, highlighting areas with increased radiotracer uptake. This is then fused with either CT or MRI images to offer a comprehensive view of both the metabolic activity and anatomical correlation.[17]

PSMA PET/CT is a less expensive modality, has less image artifacts from metal or motion, and has faster image acquisition when compared with MRI. Although PSMA PET/MRI is not as readily available, it offers superior soft tissue delineation, with lower radiation exposure compared to PET-CT, which significantly improves prostate region resolution.

Both PET CT and MRI face challenges like tracer trapping in non-target tissue, the PSMA flare phenomenon, and patient radiation exposure from radiotracers.[18] For example, urinary excretion, the primary elimination pathway for most PSMA PET tracers, can complicate the interpretation of imaging results due to radiotracer activity in the ureters. Strategies such as the use of diuretics, delayed phase imaging, and dual-point or dynamic PET imaging have been employed to mitigate these challenges.[19–21]

TABLE 1 PMSA Tracers: Advantages and Disadvantages

PSMA tracer	Advantages	Disadvantages
[68Ga] Ga-PSMA-11	• First PSMA tracer approved, subsequently the most evidence and experience in its use. • Demonstrates a substantial impact on clinical management across both recurrent and primary prostate cancer scenarios.	• Relatively shorter half-life limits distribution capabilities. • Potential for high urinary bladder uptake, complicating prostatic imaging.
[68Ga]Ga-PSMA-I&T	• Theranostic capabilities allowing for both diagnostic imaging and targeted therapy.	• Limited availability and experience outside of research settings compared to PSMA-11. • Limitations related to the radionuclide's shorter half-life.
[18F]F-DCFPyL	• Lower positron range and longer half-life than Ga-68–labelled tracers, offering potential for better image resolution and wider distribution capabilities.	• Higher cost and complexity of production compared to Ga-68–labelled tracers. • High accumulation in the urinary tract, which can complicate prostatic imaging.
[18F]F-PSMA-1007	• Low urinary excretion, facilitating clearer imaging of the prostate and pelvic region. • Longer half-life of F-18 allows for centralized production and broader distribution.	• Possible higher hepatic uptake, potentially complicating the assessment of liver metastases. • The high sensitivity might detect more lesions of benign origin, potentially leading to interpretative challenges.
[18F]F-rhPSMA-7.3	• Incorporates the radiohybrid (rh) concept, potentially combining advantages of different PSMA ligands. • F-18 labelling offers advantages in terms of distribution and imaging quality.	• Newer tracer with less extensive clinical validation compared to others. • Potential for detection of non-prostate cancer–related PSMA expression, requiring careful interpretation.

Abbreviation: PSMA, prostate-specific membrane antigen.

TABLE 2 PSMA PET/CT Versus PSMA PET/MRI Comparison

Feature	PSMA PET/CT	PSMA PET/MRI
Availability	Widely available/well established.	Less widely available but growing in clinical use.
Cost	Generally more cost-effective than PET/MRI.	Higher initial cost and maintenance.
Radiation exposure	Higher level of ionizing radiation due to the CT component.	Still involves exposure to radiation from the radiotracer, but overall radiation dose is lower than PET/CT.
Anatomical detail	Provides good anatomical detail with CT.	Superior soft tissue contrast with MRI, offering exceptional detail of the prostate gland and adjacent structures.
Soft tissue contrast	Limited soft tissue contrast compared to MRI.	Superior soft tissue contrast, offering exceptional detail of the prostate gland and adjacent structures.
Scan duration	Shorter scan times, making it more convenient for patients.	Longer scan duration due to comprehensive MRI protocols.
Multiparametric imaging	Limited to anatomical and metabolic imaging.	Enables multiparametric imaging (combining various MRI techniques with PET).

Abbreviations: CT, computed tomography; MRI magnetic resonance imaging; PET, positron emission tomography; PSMA PET, prostate-specific membrane antigen positron emission tomography.

Methods of Reporting Localized Prostate Cancer on PSMA PET Scans

Standardized reporting of PSMA-ligand scans is crucial in PCa diagnosis, to ensure report quality and reproducibility for clinical decision-making and research. PSMA PET scans distinguish between malignant and benign lesions using quantitative measures such as standardized uptake values (SUV) and tumour-to-background ratios (TBR), and qualitative analyses such as visual interpretation of images and lesion morphology.[17] The SUV is a measurement of relative concentrations of PSMA uptake, with maximum SUV (SUVmax) representing the highest uptake in a region of interest.

The PRIMARY Score is a 5-category scale developed based on the ^{68}Ga PSMA tracer to evaluate intraprostatic lesions. The aim is to standardize reporting and identify csPCa by combining anatomic site patterns and SUVmax.[22] The criteria of PRIMARY score are detailed in **TABLE 3**. A high PRIMARY score of 3 to 5 demonstrates an 88% sensitivity, 64% specificity, 76% positive predicting value (PPV), and 81% negative predicting value (NPV) in detecting csPCa. Validation study showed that when comparing the PSMA PET scan–based PRIMARY score against the mpMRI-based Prostate Imaging–Reporting and Data System (PI-RADS) score, the PRIMARY score had higher interrater reproducibility.[23] But both reporting systems have similar diagnostic performance.

TABLE 3 PRIMARY Score Classification

PRIMARY score	Description	Clinical implication	Proportion of men with csPCa based on original study
Score 1	No significant PSMA uptake pattern or low-grade activity only.	Likely benign; very low likelihood of csPCa.	8.5%
Score 2	Diffuse uptake in transition or central zone.	Low likelihood of csPCa.	27%
Score 3	Focal transition zone activity above background activity (visually at least twice).	Intermediate likelihood of csPCa.	38%
Score 4	Focal peripheral zone activity of any intensity.	High likelihood of csPCa.	76%
Score 5	SUVmax > 12 in any zone.	Very high likelihood of csPCa.	100%

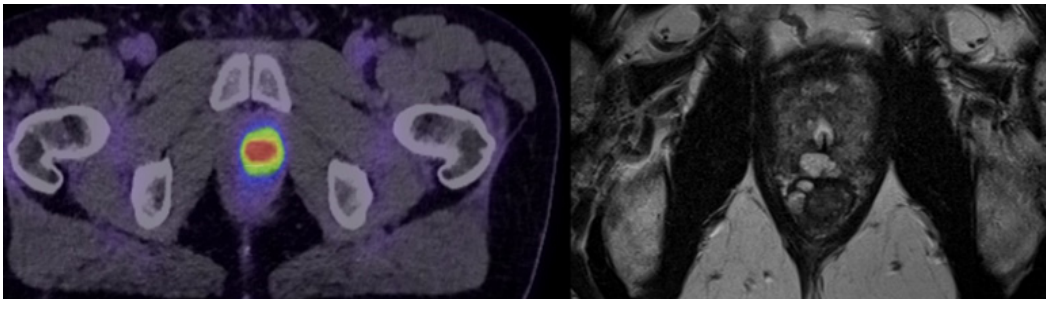
Abbreviations: csPCa, clinically significant prostate cancer; PSMA, prostate-specific membrane antigen; SUVmax, maximum standardized uptake values.

Clinical Applications and Performance of PSMA PET Scans in Localized Prostate Cancer

PSMA PET scans for primary diagnosis of prostate cancer

Previous meta-analysis demonstrated that PSMA PET/CT can detect localized PCa with sensitivity between 0.71 to 0.84, and specificity of up to 0.92.[24,25] Given the moderate sensitivity, PSMA PET/CT may miss some intraprostatic lesions. There appears to be no significant difference in terms of sensitivity and specificity of detecting localized PCa when comparing PSMA PET/CT to multiparametric MRI (mpMRI).[25] PSMA PET/MRI appears to have a higher diagnostic accuracy of detecting localized PCa when compared with PSMA PET/CT (97% vs. 86%).[26] These findings are limited by the fact that most existing studies are retrospective in nature. In low- to intermediate-risk PCa, PSMA PET scans identified MRI occult lesions in 12.3% to 29% of patients (**FIGURE 2**), of which up to 10% may harbour underlying unfavourable pathology.[27] PSMA PET scans may be a useful tool for improving risk stratification during active surveillance, but further studies are needed.

FIGURE 2 Example of MRI occult lesion seen on transverse imaging, which manifested as PSMA-avid lesions on 18F PSMA PET/CT (left) but identified as PI-RADS 2 lesions on mpMRI (right).



Abbreviations: CT, computed tomography; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; PI-RADS, Prostate Imaging–Reporting and Data System; PSMA, prostate-specific membrane antigen.

Identifying clinically significant prostate cancer

The identification of csPCa may be more clinically relevant, as it is crucial for distinguishing between patients who are suitable candidates for active surveillance and those who require active treatment. Higher-grade PCa has been shown to have higher PSMA expression, which correlates with the SUV on PSMA PET scans.[28] Although there is no consensus on the optimal SUVmax to differentiate csPCa from ciPCa, previous studies have proposed cutoffs between 5.4 and 8.[29] One limitation of some existing studies is the use of prostatectomy histopathology as a reference point. Since prostate biopsies only represent a small proportion of PCa being sampled, it is not uncommon to observe histopathological upgrading during the examination of prostatectomy specimens.[30] It is also worth noting that 5% to 10% of PCa may be PSMA negative.[31]

The PRIMARY trial is a landmark study that explored the use of PSMA PET/CT as an initial diagnostic tool in biopsy- and MRI-naïve patients with clinical suspicion of PCa, indicated by abnormal PSA levels or digital rectal examination (DRE) findings.[32] It demonstrated that the addition of PSMA PET/CT to MRI as compared with MRI alone improves the NPV (91% vs. 72%) and sensitivity (97% vs. 83%) of detecting csPCa (ISUP GG ≥ 2). In the PRIMARY trial, an SUVmax of 12 appeared to have 100% specificity and 100% PPV in detecting csPCa, independent of MRI findings. However, in the presence of a PI-RADS 4 or 5 lesion on MRI, an SUVmax of 8.7 showed 100% specificity and 100% PPV for csPCa. PSMA PET/CT appears to be a useful adjunct in the MRI-triaged population. Further studies are needed, but the findings of the PRIMARY trial raise the question of whether prostate biopsies can be safely avoided in patients without any imaging evidence of csPCa.

Local staging

Extraprostatic extension (EPE) is defined as the presence of PCa in tissue beyond the confines of the prostate gland, such as the neurovascular bundle or peri-prostatic adipose tissue.[33] Post-prostatectomy, the histological evidence of PCa extending beyond the confines of the prostate is described as pT3a and above in the tumour, lymph node, and metastasis (TNM) staging system.[34] Accurate preoperative detection of EPE on imaging is critical for treatment planning and informed consent, influencing decisions on nerve-sparing prostatectomy or the requirement for a wider excision margin. The presence of EPE also indicates a worse oncological prognosis such as the risk for biochemical recurrence (BCR).[35] PSMA PET/MRI demonstrates higher diagnostic accuracy as compared to PSMA PET/CT in the detection of EPE (77% vs. 73%) and seminal vesicle invasion (SVI) (90% vs. 87%).[26] Additionally, PSMA PET/MRI showed higher sensitivity than mpMRI in detecting EPE (78.7% vs. 52.9%) and SVI (66.7% vs. 51.0%) during initial staging of intermediate- to high-risk PCa.[10] The existence of SVI has also been linked to reduced overall survival (OS) and increased rates of BCR.[36]

PSMA PET scans peri-prostatectomy

A meta-analysis found that the increased diagnostic accuracy of PSMA PET/CT over conventional imaging during primary staging resulted in a change in clinical management in up to 28% of patients.[24] The improved detection of lymph node involvement and metastatic disease leads to a "stage migration" among patients who would have traditionally undergone prostatectomy in the era of conventional imaging. While long-term follow-up data is lacking, early results have shown that PSMA PET scans improve post-prostatectomy oncology outcomes by decreasing the risk for BCR by up to 42%.[37]

Prior to prostatectomy, patients undergo prostate biopsies for diagnosis, which may delay time to surgery. Prostate biopsies can occasionally cause complications such as urinary retention, hematuria, rectal bleeding, or sepsis.[38] Additionally, patients who undergo multiple prostate biopsies may have worse functional outcome post-prostatectomy, possibly due to scar tissues limiting nerve sparring intraoperatively.[39] Some recent studies have suggested a biopsy-free method for identifying candidates for prostatectomy, utilizing preoperative risk stratification through the combination of elevated PSA, abnormal DRE, and clinically concerning imaging (PSMA

PET/CT and mpMRI).[40,41] Given the relatively low morbidity associated with prostate biopsies and the lack of large prospective randomized controlled trials, PSMA PET scans should not replace pre-prostatectomy biopsies at this stage.

During post-prostatectomy follow-up, PSMA PET/CT can detect residual PCa in patients experiencing persistent elevation of PSA levels and identify local recurrence within the prostatic fossa in cases of BCR.[42–44] The combination of MRI with PSMA PET/CT further enhances the detection of local recurrence.[45] Detection rates in both scenarios depend on the patient's PSA level. According to the EAU guidelines, PSMA PET/CT is recommended as a staging tool when PSA levels rise above or persistently remain above 0.2 ng/mL, particularly if the results are anticipated to influence treatment decisions.[5]

PSMA PET scans in radiotherapy

Gross tumour volume (GTV) is frequently measured on imaging to ascertain the extent and size of PCa. It holds significant implications for treatment delivery and guides treatment intensity in both radiotherapy and focal therapy. PSMA PET scans outperform mpMRI in estimating GTV, demonstrating higher sensitivity (75.7% vs. 64.7%), specificity (87.1% vs. 86.4%), and Area Under the Receiver Operating Characteristic Curve (AUROC) (0.889 vs. 0.852).[46]

Higher-grade PCa is known to be more resistant to radiotherapy and linked to higher rates of local recurrence.[47] An appropriate increase in radiation dose has been previously shown to improve oncological outcomes.[48] PSMA PET scan's ability to predict higher-grade PCa appears promising in guiding radiotherapy dose escalation. A study conducted by Eade *et al.* showcased the effectiveness of PSMA/MRI-guided focal boost within stereotactic body radiation therapy (SBRT), demonstrating promising efficacy with minimal toxicity and low decision regret.[49]

In post-radiotherapy follow-up, MRI serves to identify local recurrences, assist in target biopsy, and guide local salvage therapy.[50] However, it may underestimate the extent of local recurrence.[51] PSMA PET/CT appears to be comparable to MRI in detecting local recurrences post-radiotherapy but offers the added benefit of lymph node and distal metastasis detection.[52,53] Concordant findings on both PSMA PET/CT and MRI are a strong indicator of local PCa recurrence. Currently, the EAU guideline recommends PSMA PET/CT as a staging tool in patients with PSA recurrence after radiotherapy only if they are suitable for curative salvage therapy.[5]

Salvage radiotherapy (SRT) to the prostatic fossa is a viable option for selected patients experiencing PSA-only recurrence (i.e., BCR without distant metastasis).[5] PSMA PET/CT enables accurate staging to rule out distal metastasis before initiating SRT. PSMA PET scans may also help identify the site of local recurrence and tailor radiation dosimetry.[54] Additionally, PSMA PET scans may be predictive of responsiveness to SRT.[55] Previous studies have shown that PSMA PET/CT influences treatment decisions in patients with BCR; however, there is a lack of data regarding its impact on long-term outcomes.[54]

PSMA PET scans in focal therapy

Focal therapy aims to target small foci of low and selected intermediate-grade PCa while preserving surrounding healthy tissue. MRI is often performed prior to identify the size and location of PCa. The addition of PSMA PET scans may help improve patient selection for focal therapy by excluding csPCa and identifying MRI occult lesions.[27]

Post-focal therapy follow-up involves repeat MRIs and prostate biopsies. However, MRI may be confounded by post–focal therapy artifacts. Theoretically, PSMA PET scans should be able to detect recurrent PCa without being hindered by treatment artifacts and could be a valuable tool for post–focal therapy follow-up.[56] However, there is a lack of studies evaluating the use of PSMA PET scans in focal therapy.[57]

PSMA PET scans in theranostics

Theranostics is a term derived from the combination of "therapy" and "diagnostics." It refers to a field of medicine that combines diagnostic techniques with therapeutic interventions. Given PSMA tracers' high affinity to PCa cells, there is growing interest in modifying the tracers into therapeutic isotopes to treat PCa.[58] After identification of metastatic deposit with PSMA PET scans, therapeutic radiopharmaceuticals labelled with β(lutetium-177 or yttrium-90) or α(actinium-225)-emitting isotopes are given. In metastatic castration-resistant PCa, Lutetium-177 [177Lu]Lu-PSMA-617 has shown to result in more than 50% decrease in PSA levels and improvement in OS.[59] Given the high rates of BCR after prostatectomy in high-risk PCa, the LuTectomy trial explored the use of [177Lu]Lu-PSMA-617 in localized PCa.[60,61] It was demonstrated that in men with high-risk features (e.g., PSA >20 ng/mL, or ISUP GG 3-5) with high PSMA expression on PSMA PET/CT, two cycles of [177Lu]Lu-PSMA-617 prior to prostatectomy were well tolerated with minimal side effects, did not compromise surgical safety, while delivering targeted doses of radiation to tumour-affected tissues. Further studies in this area will be interesting to determine whether theranostics can reduce the long-term risk for BCR in localized PCa.

PSMA PET scans for prognostication

Increased uptake of PSMA tracer in PCa has been linked to traditional prognostic indicators such as higher Gleason scores, higher ISUP GG disease, and lower BCR-free survival after prostatectomy.[62,63] As described above, PSMA PET scans are effective for local staging, with the detection of adverse surgical pathology (e.g., EPE and SVI) serving as unfavourable prognostic indicators.[64] PSMA PET/MRI has been shown to be comparable to Memorial Sloan Kettering Cancer Center (MSKCC) and Partin nomograms for prediction of extracapsular extension (ECE) and SVI.[65] The ability to predict GTV is also important, as it has been previously shown to be an independent predictor of mortality from PCa and OS.[66] Due to the rarity of aggressive subtypes of PCa, such as neuroendocrine and ductal tumours, which have distinct underlying tumour biology, there is limited published research on the role of PSMA PET scans in these subtypes.[67,68]

Future Directions

The incorporation of new imaging modalities in diagnostic pathways leading to a "stage migration" has implications for the way PCa is risk stratified.[69] There is a need for more prospective studies to provide data regarding long-term oncological outcomes of patients whose management decisions were influenced by PSMA PET scans.

Due to the low risk of developing metastatic disease, in low-risk and some intermediate-risk PCa there is no role for PSMA PET scans as a staging modality.[5] However, PSMA PET scans may help improve risk stratification of these patients for active surveillance.[27] Further studies are needed to elucidate the best way to incorporate PSMA PET scans into active surveillance. The CONFIRM trial is an ongoing study evaluating the use of PSMA PET scans prior to confirmatory biopsy.[70] One of the study endpoints is to determine which group of patients with high-risk features (such as ISUP GG 2 disease or ISUP GG 1 disease with elevated PSA, high-volume disease, or clinically significant MRI findings) will benefit the most from a PSMA PET scan.

Another area of interest being explored is how PSMA PET/CT could potentially help patients avoid unnecessary biopsies. The PRIMARY II trial is an ongoing study that compares three groups of biopsy-naïve patients with clinical or MRI suspicion of csPCa. The experimental group will be subdivided into two comparison groups: patients with positive PSMA PET/CT who will undergo targeted biopsies and patients with negative PSMA PET/CT who will undergo PSA monitoring only. The third group serves as a control arm, with patients undergoing template transperineal prostate biopsies only.[71]

Conclusion

The current guidelines recommend the use of PSMA PET scans for detection of recurrent PCa or for pretreatment staging of ISUP GG ≥ 3. However, emerging evidence suggests that PSMA PET scans may also be beneficial as a tool for primary diagnosis and local staging of PCa, particularly when used in combination with mpMRI. The integrated PSMA PET/MRI system appears to outperform PSMA PET/CT in terms of local staging, but further studies are needed.

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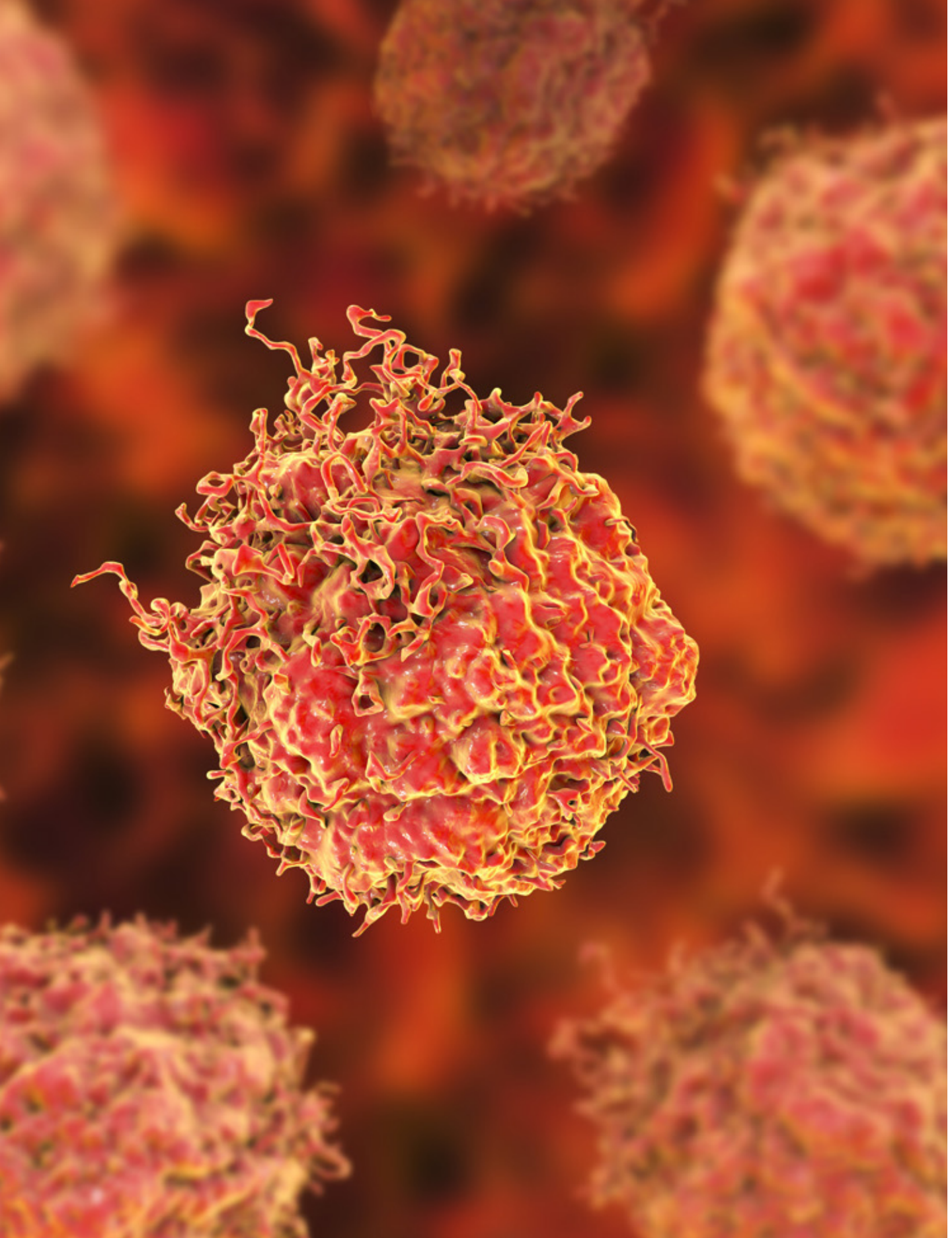

COMMITTEE 9

Liquid- and Tissue-Based Biomarkers in Prostate Cancer

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Table of Contents

Introduction

Prostate cancer (PCa) is the second most prevalent malignancy, and the sixth leading cause of cancer-related death among men, placing an extensive socioeconomical burden on modern healthcare systems.[1] Since the birth of modern medicine, the development of predictive and prognostic biomarkers aiming to optimize and guide early detection and disease management of PCa has been the focus of translational research endeavours. As a result, several commercially available liquid- or tissue-based markers have been introduced in clinical practice aiming to guide decision-making related to prediagnosis, active surveillance, and treatment (**TABLE 1**). The real value of a biomarker depends on its ability to impact the course of the disease. For example, prostate-specific antigen (PSA) is probably one of the most well-known and widely utilized tumour markers worldwide, with a unique facility ranging from diagnosis to treatment-related follow-up of PCa patients. However, despite the ever-evolving collection of biomarkers, most of them never get translated to everyday clinical practice, due to their poor efficacy, lack of validation, or unfavourable cost-effectiveness. In the era of personalized medicine, being familiar with the applications, efficacy, and limitations of available tests is of high importance for the clinician. In this chapter, we focus on the most important clinically validated liquid- and tissue-based biomarkers aiding decision-making in various stages of localized PCa.

Biomarkers Guiding Diagnosis

Blood-based markers

Prostate-specific antigen

Prostate-specific antigen (PSA) is a serine protease enzyme, a member of the tissue kallikrein family, that is secreted by both prostate epithelial cells and malignant prostatic tissue into blood, urine, and semen.[2] It was first isolated from the prostate in 1979 by Wang *et al.* and established as a biomarker for PCa in 1986 by Stamey *et al.*[3–5] Consequently, in 1986, PSA was approved by the US Food and Drug Administration (FDA) for the purpose of disease monitoring and in 1994 as a diagnostic tool.[5] Since then, it has been one of the most widely used biomarkers worldwide, despite its numerous limitations including high false-positive rates and poor specificity for prostate cancer diagnosis.

Importantly, PSA is not tumour specific, as many benign processes such as inflammation, benign prostatic hyperplasia (BPH), trauma, and sexual intercourse may lead to elevated PSA levels. It is strongly associated with prostate size and age of the patient and affected by hormonal agents such as finasteride and dutasteride.[6] Moreover, due to the variety and instability of the isoforms of PSA in the serum, reliably measuring the analyte is particularly challenging for laboratory medicine.[7] Considering these disadvantages, it is not surprising that defining a clear, generalizable cutoff value, capable of predicting PCa is not possible, which makes the interpretation of PSA levels challenging and individualized. Historically, a PSA level of 4 ng/mL was widely accepted as the cutoff

to predict the presence of prostate cancer.[8–10] However, 20% of patients with PCa have a PSA level lower than 4 ng/mL, and applying this PSA cutoff in prostate cancer screening leads to unnecessary biopsies, overdetection, and overtreatment.[11,12] Based on the results of the European Randomized study of Screening for Prostate Cancer (ERSPC), discrimination at a PSA level of 3 ng/mL is the most widespread cutoff and therefore recommended in early detection by the European Association of Urology (EAU) guidelines.[13] Considering the strong correlation of PSA with age, age-specific PSA cutoffs can also help clinical decision-making such as biopsy selection and re-invitation for screening.[14] Based on EAU guidelines, men with a PSA level of > 1 ng/mL at 40 years and with a PSA level of > 2 ng/mL at 60 years are considered at risk, and therefore should be offered a 2-year follow-up interval for screening. Contemporary prostate cancer screening strategies use PSA as a primary screening tool but are followed by a reflex test, such as prostate magnetic resonance imaging, other biomarkers, or risk calculators to refine patient selection for prostate biopsy. However, the use of PSA in the early detection of PCa is unquestionable.

To overcome the inherent limitations of PSA, several other PSA-based metrics have been employed, including the ratio of free to total PSA, PSA density (PSAD), PSA doubling time, and PSA velocity, particularly for PSA levels ranging from 3 ng/mL to 10 ng/mL. However, due to the performance and growing global uptake of magnetic resonance imaging (MRI) of the prostate, only PSAD can provide additional diagnostic value in the PCa diagnostic pathway. PSAD is the ratio of serum PSA level to the prostate volume and is a strong predictor of clinically significant disease (above 0.15 ng/mL/cc).[15,16] PSAD is used extensively in PCa risk calculators, with elevated PSAD values indicating the need for prostate biopsy even in the case of negative MRI results; however, accurately measuring the prostate volume can be challenging.[17]

Prostate Health Index

The Prostate Health Index (PHI) is a three kallikrein-based immunoassay, combining total PSA, free PSA, and [-2]proPSA into a single score aiming to lower biopsy indications and improve clinically significant prostate cancer detection. It was approved by the FDA in 2012 for men over 50 years who have normal rectal exams and PSA levels between 2 ng/mL and 10 ng/mL. PHI has been proven to offer better diagnostic accuracy than total PSA or free to total ratio.[18,19] Moreover, PHI has shown to be able to predict high-grade disease, and a strong ability to avoid unnecessary biopsies, overdetection, and overtreatment.[18,19] In the study by Tosoian *et al.* using PHI could avoid up to 38% of unnecessary biopsies while missing 2% of significant cancers.[20] Notably, PHI does not depend on age or prostate volume, highlighting its value in PCa detection.[18]

Integrating PHI in predictive models and nomograms in combination with MRI results is a promising option to enhance the accuracy of detecting PCa, especially in patients considering repeat biopsies.[21] Adding PHI to multiparametric MRI (mpMRI) results has been shown to improve the prediction of clinically significant PCa (area under the curve [AUC], 0.75) compared to mpMRI or PSA alone (AUC, 0.64 and 0.69), with PHI using a cutoff of 35 showing an exceptional negative predictive value of 97%.[21]

4K score

Similar to the PHI, the 4K score comprises four kallikrein assays including free PSA, intact PSA, total PSA, and human kallikrein 2 (hK2), and additionally integrating clinical variables (age, digital rectal examination [DRE], previous biopsy) to predict clinically significant PCa. Several studies have shown its utility in improving PCa diagnostics with reducing unnecessary biopsies and overdiagnosis.[22–24] In the ERSPC cohort, incorporating the 4K score with PSA and age significantly improved predictive accuracy (AUC, 0.78 vs. 0.70).[22] In a prospective cohort of more than 1,000 patients, compared to the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) 2.0 model, the 4K score had higher AUC (0.82 vs. 0.74, $p<0.0001$) in predicting significant disease.[25] A comparative analysis of the 4K score and PHI was conducted in a populated-based cohort study of 531 men with PSA 3–15 ng/mL by Nordström *et al.*[26] The two tests performed similar in predicting both any-grade PCa (4K score: AUC, 69; PHI: AUC, 70.4) and high-grade PCa (4K score: AUC, 71.8; PHI: AUC, 71.1).[26]

The 4K score has been evaluated in the repeat-biopsy setting as well.[27] In an ERSPC cohort of 925 men, Gupta *et al.* found higher accuracy of the 4K score than either PSA and DRE alone (AUC, 0.68 vs. 0.58, $p<0.001$) in detecting PCa on repeat biopsy.[27] For the prediction of high-grade disease, the 4K score outperformed clinical factors alone (AUC, 0.87 vs. 0.76, $p=0.003$).[27]

Despite the weak level of evidence, both the PHI and 4K score are acknowledged by EAU, American Association of Urology (AUA), and the National Comprehensive Cancer Network (NCCN) as promising markers in the early detection of PCa. These tests are capable of improving the balance between the harm and benefits associated with early detection of PCa, with enhancing aggressive PCa detection and reducing unnecessary biopsies in men with PSA levels between 2 ng/mL and 10 ng/mL. However, the costs of the tests and lack of established cutoff values can make their integration into clinical practice challenging.

Stockholm3

The Stockholm3 (STHLM3) test is a complex prediction model integrating several clinical variables (age, family history of PCa, previous biopsy), serum markers (total and free PSA, human kallikrein 2, macrophage inhibitory cytokine-1, microseminoprotein-β), and a polygenic risk score for predicting clinically significant PCa.[28,29] In combination with MRI, it has been shown to decrease detection of clinically insignificant PCa and the number of MRI scans in population-based screening.[28,29] A microsimulation study has shown the test to be cost-effective in the Swedish health system.[30,31]

Urine-based markers

Progensa Prostate Cancer Antigen 3

Prostate cancer antigen 3 (PCA3) is a noncoding RNA molecule that is overexpressed in prostate cancer cells compared to benign epithelial tissue.[32] It can be measured in urine sediments collected after prostate massage

during DRE, using the Progensa assay, and its expression has been shown to be unaffected by prostate size or PSA levels in the blood.[32,33] To date, Progensa is the only FDA-approved urine-based test to aid decision-making in the primary and repeat-biopsy settings. The study of 463 patients by Haese *et al.* showed that higher PCA3 scores were associated with higher rates of a positive repeat biopsies (39% vs. 22%; $p<0.0001$).[34] Moreover, the mean PCA3 score was significantly higher in men with a positive compared to those with negative biopsy (63.8 vs. 35.5; $p<0.0001$).[34] Importantly, PCA3 was found to be independent of PSA level, prostate volume, and patient age.[34] A prospective validation trial of 859 patients by Wei *et al.* aimed to assess the diagnostic accuracy of PCA3 both in the initial and repeat-biopsy settings.[35] The authors demonstrated a positive predictive value (PPV) of 80% upon initial and a negative predictive value (NPV) of 88% at repeat biopsy.[35] In a prospective study of 106 patients, PCA3 was shown to be strongly correlated with tumour volume and grade, and therefore to be potentially capable of enhancing patient selection for active surveillance (AS).[36]

Considering the favourable predictive utility of the test in various clinical settings, clinical practice guidelines support the use of urinary PCA3 to risk stratify patients both in the primary and repeat-biopsy settings.

ExoDx Prostate (Intelliscore)

ExoDx Prostate Intelliscore (EPI) is a novel, currently investigational, urine-based predictive assay, based on measuring mRNA-containing exosomes secreted by tumour cells diagnostic for high-grade PCa.[37] As the test does not require a prostate massage upfront sample collection, it is noninvasive and offers convenience for both patients and clinicians. In the study by McKiernan *et al.*, incorporating EPI into the standard of care improved discrimination between high-grade and low-grade or benign disease (AUC, 0.73 vs. 0.63; $p=0.001$).[37] Moreover, using EPI resulted in a 27% decrease in number of biopsies at the cost of missing 5% of high-risk PCa.[37]

Michigan Prostate Score

The Mi Prostate Score (MiPS) assay utilizes the combination of PCA3 and a fusion of the TMPRSS2 and ERG genes.[38] The gene fusion is present in 50% of PCa cases and is a strong indicator of PCa.[39] The largest validation trial of the assay to date, by Tomlins *et al.*, assessed the ability of the MiPS in predicting PCa and high-grade PCa in 1,225 patients.[38] The predictive model incorporating TMPRSS2:ERG assay had a higher AUC than PSA level in predicting both any-grade PCa (0.693 vs. 0.585) and high-grade PCa (0.729 vs. 0.651), outperforming models utilizing PCA3 or PSA alone.[38]

The association between ERG overexpression and biochemical recurrence after radical prostatectomy has been studied in a cohort of 1,180 men by Pettersson *et al.*[40] While TMPRSS2:ERG or ERG overexpression was associated with tumour stage at diagnosis, the authors found no correlation of the test with biochemical recurrence, highlighting its limited diagnostic value in this setting.[40]

The Mi Prostate Score has no FDA approval and is therefore currently considered as an investigational tool by clinical practice guidelines.

SelectMDx

The SelectMDx test is based on the combination of mRNA levels of the two genes HOXC6 and DLX1 in the urine, obtained after prostate massage, and clinical parameters such as age, family history, previous negative biopsies, and DRE findings.[41] The test is capable of predicting both the presence of PCa and high-risk disease.[41] In the multicentre trial of 310 patients by Maggi *et al.*, SelectMDx outperformed prostate MRI both in terms of sensitivity (86.5% vs. 51.9%) and specificity (73.8% vs. 88.3%) in predicting PCa.[42] However, it has been shown to have similar performance to MRI in detecting clinically significant PCa.[42] Interestingly, SelectMDx has been shown to be a valuable tool after an initial negative Prostate Imaging–Reporting and Data System ([PI-RADS], 1–3) MRI, as it led to a 45.8% decrease in the number of biopsies.[42] In a study by Hendriks *et al.*, SelectMDx was found to avoid unnecessary biopsies in 38% of biopsy-naïve men but at the cost of missing 10% of high-grade PCa.[43] Notably, the most promising diagnostic role of the test was for MRI selection of patients in case of limited MRI resources, which is supported by a recent cost-effectiveness analysis.[43,44] Interestingly, a recent study assessing a cohort of patients with PSA values between 3 ng/mL and 10 ng/mL found the diagnostic accuracy of SelectMDx, ERSPC+DRE, and MRI to be similar in detecting clinically significant PCa.[45] Moreover, the combination of the test and MRI had the highest NPV (93%) of the diagnostic strategies assessed. Despite these results, the added value of SelectMDx in the MRI era remains unclear.[45]

Tissue-based markers

ConfirmMDx

Epigenetic changes related to PCa are thought to have a "field effect", therefore hints of PCa can be observed in otherwise morphologically normal tissue adjacent to tumour tissue.[46] This is utilized by ConfirmMDx® (MDx Health; Irvine, California, USA), a molecular test using methylation profiling of three known epigenetic markers of PCa: *GSTP1*, *APC*, and *RASSF1* relative to *ACTB*.[47,48] The assay was developed to aid decision-making of patients with prior negative biopsy in the repeat-biopsy setting, and is based on formalin-fixed, paraffin-embedded (FFPE) prostate tissue obtained during biopsy.[47] The DOCUMENT and MATLOC trials followed by two meta-analyses combining their cohorts by Partin and Van Neste *et al.* validated ConfirmMDx in the repeat-biopsy setting.[47–50] The two study cohorts comprising 803 men had negative first biopsy of which all the cores were profiled using the test, followed by a repeat biopsy within 30 months.[49,50] ConfirmMDx was found to have a negative predictive value, sensitivity, and specificity of 89.2%, 64.8%, and 63.8% to detect any PCa, respectively.[50] Moreover, high methylation intensity was predictive of high-grade disease (odds ratio [OR], 6.44; 95% confidence interval [CI], 2.57–16.13; $p<0.001$) and was the best performing factor to identify men with occult, high-grade PCa based on residual tissue of a prior negative biopsy.[49,50] In a preliminary field observation study, Wojno *et al.* found that ConfirmMDx has the potential to decrease repeat biopsy rates by 10 fold; however, no prospective randomized trials have confirmed the utility of the test in clinical practice.[51] Interestingly, despite that NCCN guidelines consider ConfirmMDx as a useful tool in the repeat-biopsy setting, current EAU guidelines do not mention the utility of the test at all.[52,53]

Available Assays for Guiding Active Surveillance or Definitive Treatment

Prolaris

Prolaris® (Myriad Genetics, Inc.; Salt Lake City, Utah, USA), is a combination of Cancer of the Prostate Risk Assessment (CAPRA) risk score and a cell-cycle progression (CCP) score (range, -3 to +3) based on a mRNA-based gene panel, consisting of 15 housekeeping genes and 31 genes involved in proliferation.[54] The mathematical combination of CAPRA and CCP score results in the cell-cycle risk (CCR) score, with higher values conferring more aggressive disease.[55] The present state of knowledge confirms that the assay is a robust prognosticator of biochemical recurrence, metastasis-free survival, and cancer-specific survival. The panel was developed by Cuzick *et al.* and tested in 366 patients, with 337 patients undergoing radical prostatectomy, and in patients with clinically localized PCa diagnosed through transurethral resection of the prostate (TURP), respectively.[54] In the prostatectomy cohort, CCP score was found to be a predictor of biochemical recurrence (BCR) (hazard ratio [HR], 1.77; 95% CI, 1.40–2.22; $p<0.001$); in the in the TURP cohort, it was found to predict prostate cancer–specific mortality (HR, 2.57; 95% CI, 1.93–3.43; $p<0.001$) with a median follow-up of 9.8 years.[54] Since then, the test has been validated by several groups.[55–59] In the study by Bishoff *et al.* the CCP score was found to be a strong predictor of both BCR (HR/CCP unit, 1.47; 95% CI, 1.23–1.76; $p=4.7\times10-5$) and metastatic disease (HR/CCP unit, 4.19; 95% CI, 2.08–8.45; $p=8.2\times10-6$) in a cohort of more than 550 patients.[56] Cuzick *et al.* found that the CCP score combined with the CAPRA score was highly predictive of prostate cancer–specific survival (HR, 2.17. 95% CI, 1.83–2.57; $p\leq1\times10-20$).[55] In a cohort of 1,062 men who underwent definitive treatment for PCa, CCP score was shown to be predictive of metastatic disease at 10 years (HR/CCP score, 2.21; 95% CI, 1.64–2.98; $p=1.9\times10-6$).[57] Recently, Tward *et al.* found CCR score as a promising tool in patient selection for multimodal treatment in a cohort of 718 intermediate- and high-risk PCa patients.[59]

Importantly, the Prolaris test with CCP score has shown to directly affect real-life clinical decision-making. In the study by Shore *et al.*, utilizing Prolaris changed 47.8% of treatment decisions, with 72.1% and 26.9% reduction and intensification of treatment, respectively.[60]

Despite the limitations arising from the lack of large randomized controlled trials assessing the efficacy of Prolaris, the assay is recommended by NCCN for low-risk, favourable intermediate– and unfavourable intermediate–risk, as well as high-risk patients with a 10-year life expectancy as an initial risk stratification tool in the pretreatment setting.[53] In contrast, current EAU guidelines do not recommend the routine use of the test for all-comers, but for selected men such as those with favourable intermediate–risk PCa who are candidates of AS.[52]

Oncotype DX Genomic Prostate Score

Oncotype DX Genomic Prostate Score® (Genomic Health; Redwood City, California, USA), or GPS for short (scale, 0–100), is dedicated for men with very low–risk, low-risk, and favourable intermediate–risk NCCN risk

category PCa to help patient selection for immediate or deferred treatment.[53] It is based on expression analysis of five housekeeping reference genes and 12 genes involved in different biological pathways associated with PCa recurrence and metastatic potential: proliferation (*TPX2*), androgen signalling (*AZGP1, KLK2, SRD5A2, RAM13C*), cellular organization (*FLNC, GSN, TPM2, GSTM2*), and stromal response (*BGN, COL1A1, SFRP4*).[61]

In 2014, Klein *et al.* conducted a complex, three-stage study for predicting adverse pathology (primary Gleason pattern 4 or any pattern 5 and/or ≥ pT3) in patients eligible for AS.[62] Using decision curve analysis, a greater net benefit was observed for a model composed of GPS and CAPRA than for any single clinical variable.[62] In a study of 402 NCCN very low–risk, low-risk, and intermediate-risk patients by Cullen *et al.*, the GPS increase per 20 units was associated with BCR.[63] In the two low-grade (3+3 and 3+4) cohorts, the GPS was validated and established as an independent predictor for adverse pathology.[63] Similarly, in the cohort of 215 men undergoing AS by Kornberg *et al.*, a higher GPS (per 5 units) was associated with biochemical recurrence (HR, 1.10; 95% CI, 1.00–1.21; p=0.04) and adverse pathology (HR, 1.16; 95% CI, 1.06–1.26; p<0.01).[64] Interestingly, in a multicentre study of 432 patients undergoing AS, Lin *et al.* did not find an association between GPS scores and either upgrading upon biopsy (p=0.48) or adverse pathology (HR, 1.85; 95% CI, 0.99–4.19; p=0.066) when adjusting for multiple clinical variables.[65] However, the clinical utility of the assay was subsequently confirmed in patients undergoing mpMRI-guided biopsy followed by radical prostatectomy (RP).[66] Of the 134 patients, 44% and 56% underwent primary and repeat biopsy, respectively. In the full study cohort, analyzing very low– to intermediate NCCN-risk patients, GPS, but not PI-RADS and UCLA MRI classifications, was found to be an independent predictor for adverse pathology.[66] Notably, the inclusion of imaging data did not improve the diagnostic accuracy of GPS (AUC, 0.79).[66]

The impact of GPS testing on decision-making was analyzed by Eure *et al.* in patients qualifying for both AS and immediate treatment.[67] Patients with, compared to without, GPS test results were more likely to undergo AS by 22% (55% relative difference) and stay on AS at 1 year (55% vs. 34%).[67] Notably, 96% of physicians and 92% of patients confirmed the usefulness of the genomic assay.[67]

A cost-effectiveness analysis in the US identified that utilization of GPS led to decreased aggregate healthcare costs (average, $2,286 per patient, including the cost of the GPS of $4,520) for men with NCCN very low–risk and low-risk PCa in the first 180 days.[68] Moreover, GPS was considered useful and informative in decision-making in 90% of cases.[68]

According to the NCCN guidelines, Oncotype DX can be considered after positive biopsy for additional risk stratification of very low–risk, low-risk, and favourable intermediate–risk PCa patients with at least a 10-year life expectancy.[53]

ProMark

ProMark (Metamark; Cambridge, Massachusetts, USA) is a protein-based panel for quantitatively assessing 12 proteins related to PCa aggressiveness, with a multiplex immunofluorescence assay of prostate tissue samples.[69] Based on the assay, a risk score (range, 0–1) is given.[69]

A refined 8-protein assay was tested and validated in a cohort of 381 and 276 patients by Blume-Jensen *et al.*, respectively.[70] The endpoints were "favourable" (Gleason ≤ 3+4 and organ-confined disease ≤ T2) and "non-favourable" (Gleason ≥ 4+3 or non–organ-confined disease T3a, T3b, N, or M) pathology.[70] A favourable (≤ 0.33) risk score was able to predict favourable pathology in NCCN very low– and low-risk patient groups and low-risk D'Amico groups with 95%, 81.5%, and 87.2% accuracy, respectively.[70] A non-favourable a risk score (> 0.8) was able to predict unfavourable pathology with a 76.9% accuracy across all risk groups.[70] Importantly, the test was able to differentiate between favourable and unfavourable pathology (AUC, 0.68; $p<0.0001$; OR, 20.9), as well as GS-6 and non–GS-6 histology (AUC, 0.65; $p<0.0001$; OR, 12.95) in the validation cohort.[70]

ProMark is mentioned as a promising tool in the patient selection for AS; however, it is currently not recommended for clinical use by the EAU guidelines.[52] The latest version of NCCN guidelines do not mention ProMark.[53]

Decipher—after prostate biopsy

The Decipher® (GenomeDx Biosciences, Inc., Vancouver, British Columbia, Canada) is a 22-RNA genomic classifier (GC) test, which was initially developed to predict early metastasis after RP.[71] The GC risk score is a continuous value between 0 and 1 and is based on genes contributing to cellular differentiation, adhesion, motility, cell cycle, androgen signalling pathway, and immune modulation.[72] Every 0.1 increase in GC score represents a 10% increase in metastatic risk, and a score of > 0.6 is considered high risk for disease progression.[73] Currently, its broad clinical utility has been confirmed and extended to adverse pathology, distant metastasis, biochemical recurrence, and survival prediction based on biopsy specimens expanding its usage to AS and irradiation therapy.[73,74]

In the study by Klein *et al.*, GC accurately predicted 10-year metastasis post-RP in biopsy samples.[73] The score was related to the primary Gleason pattern ≥ 4 (OR, 1.52) and rapid metastasis (OR, 1.93), but not pT3 disease (OR, 1.08).[73] The utility of biopsy as a source of tissue for Decipher test was then validated in a large, multicentre study by Nguyen *et al.*, who confirmed biopsy-based GC as an independent predictor of 5-year metastasis irrespective of primary therapy (RP or external beam radiation therapy (EBRT) ± androgen deprivation therapy [ADT]).[75] Low, intermediate, and high GC scores were associated with 0%, 0%, and 9.4% 5-year prostate cancer–specific mortality, respectively.[75]

Herlemann *et al.* studied the association between biopsy-based GC score in men with NCCN very low–risk, low-risk, and favourable intermediate–risk men and adverse pathology findings (GG 3–5, ≥ pT3b, lymph node invasion) upon RP.[76] Decipher results were found to be different in patients with and without adverse pathology findings upon RP (0.38 vs. 0.30, $p=0.016$).[76] Moreover, in the favourable intermediate–risk group, patients with Decipher score of > 0.6, but not those with a score of ≤ 0.6, were more likely to harbour advanced disease compared to men with very low–risk or low-risk PCa (OR, 6.83; $p<0.001$).[76]

The impact of Decipher on everyday practice has been evaluated by Zaorsky *et al.* in a study based on the Surveillance, Epidemiology, and End Results (SEER) database of men with PCa.[77] Clinical characteristics and

outcomes of 8,927 patients who underwent GC test were studied.[77] In the real-world setting, the uptake of AS or watchful waiting (WW) was higher among patients tested with GC (OR, 2.21; 95% CI, 2.04–2.38; $p<0.001$).[77] Moreover, in patients with NCCN low-risk or favourable intermediate–risk PCa, higher GC was associated with higher likelihood of local treatment (OR, 4.79; 95% CI, 3.51–6.55; $p<0.001$).[77] In the multicentre, real-world cohort of 855 patients on AS, Vince *et al.* confirmed a strong correlation of higher Decipher scores with time to curative treatment (HR, 2.51; 95% CI, 1.52–4.13; $p<0.001$).[78]

Both the NCCN and EAU recommendations concerning Decipher upon initial risk assessment are similar to Prolaris. The assay is recommended for low-risk, favourable intermediate–risk, and unfavourable intermediate–risk, as well as high-risk patients with a 10-year life expectancy as an initial risk stratification tool in the pretreatment setting by NCCN.[53] However, due to the lack of large prospective trials, EAU guidelines do not recommend the routine use of the test—but only for selected men such as those with favourable intermediate–risk PCa who are candidates for AS.[52]

Available Assays for Guiding Adjuvant therapy

Decipher—after radical prostatectomy

Decipher was initially developed to predict early metastasis after RP, based on tissue obtained during surgery by Erho *et al.*[72] In the nested case-control study with a long follow-up (median, 16.9 years), a high GC score (> 0.5) was associated with shorter prostate cancer–specific survival (median, 2.9 years vs. 6.9 years) and overall survival (OS) (median, 2.5 years vs. 4.98 years) after developing metastasis.[72] In another study including 260 post-RP intermediate- and high-risk patients of whom 99 developed metastasis and did not receive any adjuvant therapy, Ross *et al.* identified the GC score as an independent predictor of metastasis.[79] The GC score correlated with BCR, metastasis, and prostate cancer–specific survival but was not associated with overall survival.[79] Den *et al.* evaluated the association between GC score and 5-year metastasis-free survival in intermediate- to high-risk patients treated with post-RP adjuvant or salvage radiotherapy.[80] Among men with a score ≥ 0.4, those who were treated with salvage radiotherapy had greater risk of developing metastasis (23%) than those undergoing adjuvant radiotherapy (6%).[80]

Cooperberg *et al.* analyzed the association between the post-RP GC, CAPRA-S scores, and the prostate cancer–specific mortality in 185 high-risk patients (median follow-up, 6.44 years).[81] Both the GC and CAPRA-S were identified as independent predictive factors.[81] A high GC (≥ 0.6) was associated with an estimated incidence of metastasis in 30% and a CAPRA-S score ≥ 6 was associated with a 13% incidence at 10 years, respectively.[81] The authors developed a combination of genomic and clinical scores (GCC), with the aggregate metastasis incidence reaching 45%. It should be noted that no improvement in AUCs was identified (GCC 0.78 vs. GC 0.78 or the CAPRA-S 0.75).[81] An important individual patient-level meta-analysis of Spratt *et al.* in 855 men undergoing RP confirmed the independent utility of GC in predicting metastasis (HR, 1.30; 95% CI, 1.14–1.47; $p<0.001$).[82]

Recently, several ancillary studies of high-quality trials tested the risk-stratification capability of Decipher.[83] In the patient cohort of 226 patients after RP with biochemical recurrence from the SAKK 09/10 randomized controlled trial (RCT) (median follow-up, 6.3 years), GC was shown to be associated with both biochemical (HR, 2.26; 95% CI, 1.32–3.98; p=0.003) and clinical progression (HR, 2.99; 95% CI, 1.55–5.76; p=0.001).[83] Moreover, in the ancillary study of the phase 3 RCT NRG/RTOG 9601 study, GC results (per 0.1 unit) were independently associated with distant metastases (HR, 1.17; 95% CI, 1.05–1.32; p=0.006), prostate cancer–specific mortality (HR, 1.39; 95% CI, 1.20–1.63; p<0.001), and OS (HR, 1.17 95% CI, 1.06–1.29; p=0.002).[84] In the phase 3 NRG Oncology/RTOG 01-26 study assessing primary prostate radiation of intermediate-risk patients, Decipher was assessed based on prostate biopsy.[85] After a median follow-up of 12.8 years, GC score (per 0.1 unit) was associated with disease progression (HR, 1.12; 95% CI, 1.00–1.26; p=0.04), biochemical failure (HR, 1.22; 95% CI, 1.10–1.37; p<0.001), distant metastasis (HR, 1.28; 95% CI, 1.06–1.55; p=0.01), and prostate cancer–specific mortality (HR, 1.45; 95% CI, 1.20–1.76; p<0.001).[85] Notably, 4% and 16% of GC low-risk and high-risk patients had distant metastasis at 10 years, respectively.[85] In the meta-analysis of Nguyen *et al.*, GC was obtained from initial prostate biopsy in three phase 3 studies assessing definitive irradiation (RTOG 9202, 9413, 9902).[86] At a median follow-up of 11 years, GC score (per 0.1 unit) was independently associated with distant metastases (HR, 1.29; 95% CI, 1.18–1.41 p<0.001), prostate cancer–specific mortality (HR, 1.28; 95% CI, 1.16–1.41; p<0.001), and OS (HR, 1.12; 95% CI, 1.05–1.22; p<0.001).[86]

The effect of GC on decision-making has been evaluated in several studies.[87] For example, adjuvant and salvage radiotherapy were modified by the results of GC in 43% and 53% of cases, respectively.[88] In the PRO-IMPACT study, a cohort of patients who underwent RP and were considered for either adjuvant (n=150) or salvage (n=114) radiotherapy, 37% of high-risk PCa patients were advised to intensify their treatment, after obtaining their GC results.[89] A recommendation to remain in the observational protocol was increased in the low-risk Decipher score group in the salvage arm (63% to 74%).[89] In the study by Zaorsky *et al.* assessing the SEER database, high GC scores were associated with the use of radiation after prostatectomy (OR, 2.69; 95% CI, 1.89–3.84).[77]

Based on the growing body of evidence on the outstanding prognostic and predictive utility of Decipher, current NCCN guidelines state that GC can be considered as part of counselling for risk stratification in patients with after radical prostatectomy.[53] However, the EAU guidelines do not recommend routine testing, although they acknowledge the clinical utility of the test.[52]

Decision-making tools based on artificial intelligence

Artificial intelligence (AI) tools aiding clinical decision-making have been extensively studied recently.[90,91] The multimodal deep learning model by Esteva *et al.* was developed and trained on histopathologic data of 5,654 patients (median follow-up, 11.4 years) from five phase 3 RCTs assessing radiotherapy for localized PCa (NRG/RTOG-9202, 9408, 9413, 9910, and 0126) on six binary outcomes (5- and 10-year distant metastasis, biochemical failure-free survival, 10-year prostate cancer–specific survival, 10-year overall survival).[91] In a validation cohort of patients (20% of participants from each trial), the model outperformed NCCN risk stratification in terms of prediction of all the outcomes (relative improvement in AUC ranging from 9.2% to 14.6%).[91] In a further study,

Spratt *et al.* used an AI-based predictive model based on digitalized histology images and data from four phase 3 RCTs (NRG 9202, 9413, 9910, and 0126).[90] The model was validated on the data of 1,594 NCCN intermediate-risk PCa patients from NRG/RTOG 9408 study (median follow-up, 14.9 years). The AI-based prediction model was able to accurately discriminate between patients who can benefit from treatment intensification with ADT.[90] These results underline the outstanding efficacy and abundant number of clinical implications of AI-based models in decision-making during the work-up of localized PCa.

Single-Analyte Prognostic/Predictive Markers in Localized Prostate Cancer

Ki-67

Ki-67 is a nuclear protein that has been widely used as a marker for proliferation in oncology. It is quantified by immunohistochemistry (IHC) and reported as the percentage of cells stained positively, which reflects the proliferation status of the tumour.[92] Theoretically, Ki-67 has potential for both during biopsy and post-RT risk stratification.[92]

In as study of 451 men, Tollefson *et al.* showed that Ki-67 expression was associated with local or systemic progression and prostate cancer–specific death (median follow-up, 12.9 years).[92] Every 1% increase in Ki-67 expression was associated with a 12% increased risk for cancer-specific death after RP.[92] Fisher *et al.* confirmed Ki-67 as a significant predictor of PCa-related mortality (HR, 2.78; CI, 1.42–5.46; p=0.008) in a cohort of patients who underwent RP.[93]

Ki-67 evaluation in RP specimens has been studied since 1996. Bettencourt *et al.* found that men with higher Ki-67 had earlier progression and a lower 5-year recurrence-free survival rate.[94] More recently, in a cohort of 1,004 patients, Tretiakova *et al.* found that Ki-67 (per 1% increase) provided independent prognostic value for recurrence-free (HR, 1.04; p=0.008), overall (HR,1.07; p=0.02), and disease-specific survival (HR, 1.10; p=0.02).[95] Mathieu *et al.* analyzed the RP specimens of 3,123 patients and showed Ki-67 to be a strong predictor of biochemical recurrence (HR, 1.19; p=0.019).[96]

Despite its promising prognostic utility, Ki-67 is not recommended for clinical use in NCCN guidelines and not mentioned in the EAU guidelines.[52,53]

PTEN

Phosphatase and tensin homolog (PTEN) is a tumour suppressor gene located on chromosome 10 that has been shown to suffer loss-of-function mutations in up to two-thirds of prostate cancer cases.[97] Generally, PTEN loss can be detected with fluorescence in situ hybridization (FISH) or IHC in tumour tissue.

In a study by Murphy *et al.*, PTEN loss was shown to be associated with both volume and grade (low-volume International Society of Urological Pathology [ISUP] 1: 2% vs. ISUP ≤ 2: 46%).[98] Moreover, Lotan *et al.* found higher rates of PTEN loss in patients who upgraded from biopsy upon prostatectomy, compared to those who did not (18% vs. 7%; p=0.02).[99] Among Gleason 3+4 PCa, PTEN loss at biopsy has also been shown to remain associated with an increased risk for non–organ-confined disease (HR, 2.46; 95% CI, 1.34–4.49; p=0.004).[100]

PTEN loss has also been tested as a prognostic biomarker. In a study of 902 men with localized PCa who underwent RP, markedly decreased PTEN staining was associated with a higher risk for biochemical recurrence (OR, 1.67; 95% CI, 1.09–2.57; p=0.02).[101] In line with this, Murphy *et al.* showed that among ISUP ≤ 2 PCa, PTEN loss was associated with higher recurrence rates (80% vs. 55%).[98]

Due to the lack of large prospective studies, similar to Ki-67, testing for PTEN loss is not recommended by the NCCN guidelines and not mentioned by the EAU guidelines.[52,53]

TMPRSS2:ERG gene fusion

The fusion of TMPRSS2 and ERG gene is a well-described mutation in PCa and is present in 50% of cases.[39] The presence of the fusion gene was associated with an inferior 8-year OS (25% vs. 90%; p<0.001) in a WW cohort of 445 patients.[102] Moreover, it was found to correlate with PCa-specific mortality (cumulative incidence ratio, 2.7; 95% CI, 1.3–5.8; p<0.01).[103] Based on two meta-analyses, TMPRSS2:ERG is not associated with biochemical recurrence or prostate cancer–specific mortality.[104,105]

Testing for TMPRSS2:ERG gene fusion from PCa tissue is not mentioned by either the EAU or the NCCN guidelines.[52,53]

Future Perspectives

There is an urgent need to integrate biomarkers into everyday clinical practice due to their potential to enhance diagnostic accuracy, prognostic evaluation, and treatment response predictions. This includes combining biomarkers with current algorithms and novel emerging imaging techniques, such as prostate MRI and prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT). Despite a growing body of knowledge and evidence, considerable challenges remain in optimizing risk stratification and patient selection in different PCa-related settings.

Compared to novel imaging methods such as mpMRI and PSMA PET/CT, liquid- and tissue-based biomarkers are progressing at a slower pace. The supporting evidence for the use of most of the novel markers is currently weak, primarily due to poor study design or low statistical power of the studies. Meanwhile, cutting-edge technologies such as next-generation sequencing (NGS) and AI-based deep learning models are rapidly evolving and poised

to significantly influence clinical practice. However, comprehensive, large-scale, multicentre, prospective trials are necessary to properly evaluate the prognostic and predictive performance, cost-effectiveness, and impact on clinical decisions of any biomarker.

TABLE 1 Overview of Biomarkers in Prostate Cancer

Clinical indication	Test	Stage of management	Description	Relevant reviews	Sample used for test	Cost
Prediagnosis	Prostate-specific antigen (PSA)	Initial and repeat biopsy	Total PSA	[106,107]	Serum	$10–100
	Prostate Health Index (PHI)	Initial and repeat biopsy	Total and free PSA, [-2]proPSA	[106,108]	Serum	$72–130
	4K score	Initial and repeat biopsy	Total, free, and intact PSA, human kallikrein 2	[106,108]	Serum	$760
	Stockholm3 (STHLM3)	Initial biopsy	Total and free PSA, human kallikrein 2, macrophage inhibitory cytokine-1, microseminoprotein-β, polygenic risk score	[106,109]	Serum	$243
	Progensa Prostate Cancer Antigen 3 (PCA3)	Initial and repeat biopsy	PCA3 noncoding RNA	[106,108]	Post-DRE urine	$200–450
	ExoDx Prostate (Intelliscore)	Detection of HG PCa on initial biopsy	ERG, PCA3, SPDEF Exosomal mRNA	[106,108]	First-catch urine (no DRE)	$600
	Michigan Prostate Score (MiPS)	Detection of any-grade and HG PCa on initial and repeat biopsy. Currently investigational.	TMPRSS2:ERG, PCA3 mRNA normalized to urine PSA mRNA, serum PSA	[106,108]	Post-DRE urine, serum	$780
	SelectMDx	Detection of HG PCa on initial and repeat biopsy	HOXC6, DLX1, KLK3 mRNA	[106,108]	Post-DRE urine	$300
	ConfirmMDx	Detection of any-grade and HG (GS > 7) PCa on repeat biopsy	Methylation intensity of GSTP1, APC, and RASSF1, relative to ACTB	[106]	Negative biopsy tissue	$2,000

Abbreviations: DRE, digital rectal examination; FFPE, formalin fixed paraffin embedded; GPS, Genomic Prostate Score; GS, Gleason score; HG, high grade; NA, not available; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; PTEN, phosphatase and tensin homolog; RP, radical prostatectomy.

TABLE 1 Overview of Biomarkers in Prostate Cancer *(Cont'd)*

Active surveillance vs. Treatment	Prolaris	Post-biopsy confirmed NCCN low- to high-risk patients	46 gene mRNA assay (31 cell cycle progression, 15 housekeeping) CCP score (-3 to +3)	[106,108]	FFPE from biopsy or RP tumour tissue	$3,400
	Oncotype DX	Post-biopsy confirmed NCCN low- to favourable intermediate–risk patients	17 gene mRNA assay (12 PCa related, 5 reference) GPS (0–100)	[106,108]	FFPE from biopsy tumour tissue	$4,000
	ProMark	Post-biopsy confirmed NCCN low- to favourable intermediate–risk patients	Quantitative analysis of 12 proteins then converted to a score between 0 to 1	NA	FFPE from biopsy tumour tissue	$3,900
	Decipher—post-biopsy	Post-biopsy confirmed NCCN low- to high-risk patients	22 gene mRNA panel (all PCa related) GC score (0–1)	[74,106]	FFPE from biopsy tumour tissue	$4,250
Adjuvant treatment intensification	Decipher—post-RP	Post-RP risk stratification	22 gene mRNA panel (all PCa related) GC score (0–1)	[74,106]	FFPE from RP tumour tissue	$4,250
	Artificial intelligence	Post-biopsy risk stratification before radiation	Deep learning-based model using histopathological data (digital image)	NA	FFPE from biopsy	NA
Evaluation of tumour aggressiveness	Ki-67	Predicting tumour aggressiveness (biopsy/post-RP)	Nuclear protein used as a proliferation marker, which can be measured using immunohistochemistry	[110]	FFPE from biopsy or RP tumour tissue	NA
	PTEN	Predicting tumour aggressiveness (biopsy/post-RP)	A tumour suppressor gene located on chromosome 10	[111]	FFPE from biopsy or RP tumour tissue	NA
	TMPRSS2:ERG	Predicting tumour aggressiveness	Fusion of TMPRSS2 and ERG genes	[104,105]	FFPE from biopsy or RP tumour tissue	NA

Abbreviations: DRE, digital rectal examination; FFPE, formalin fixed paraffin embedded; GPS, Genomic Prostate Score; GS, Gleason score; HG, high grade; NA, not available; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; PTEN, phosphatase and tensin homolog; RP, radical prostatectomy.

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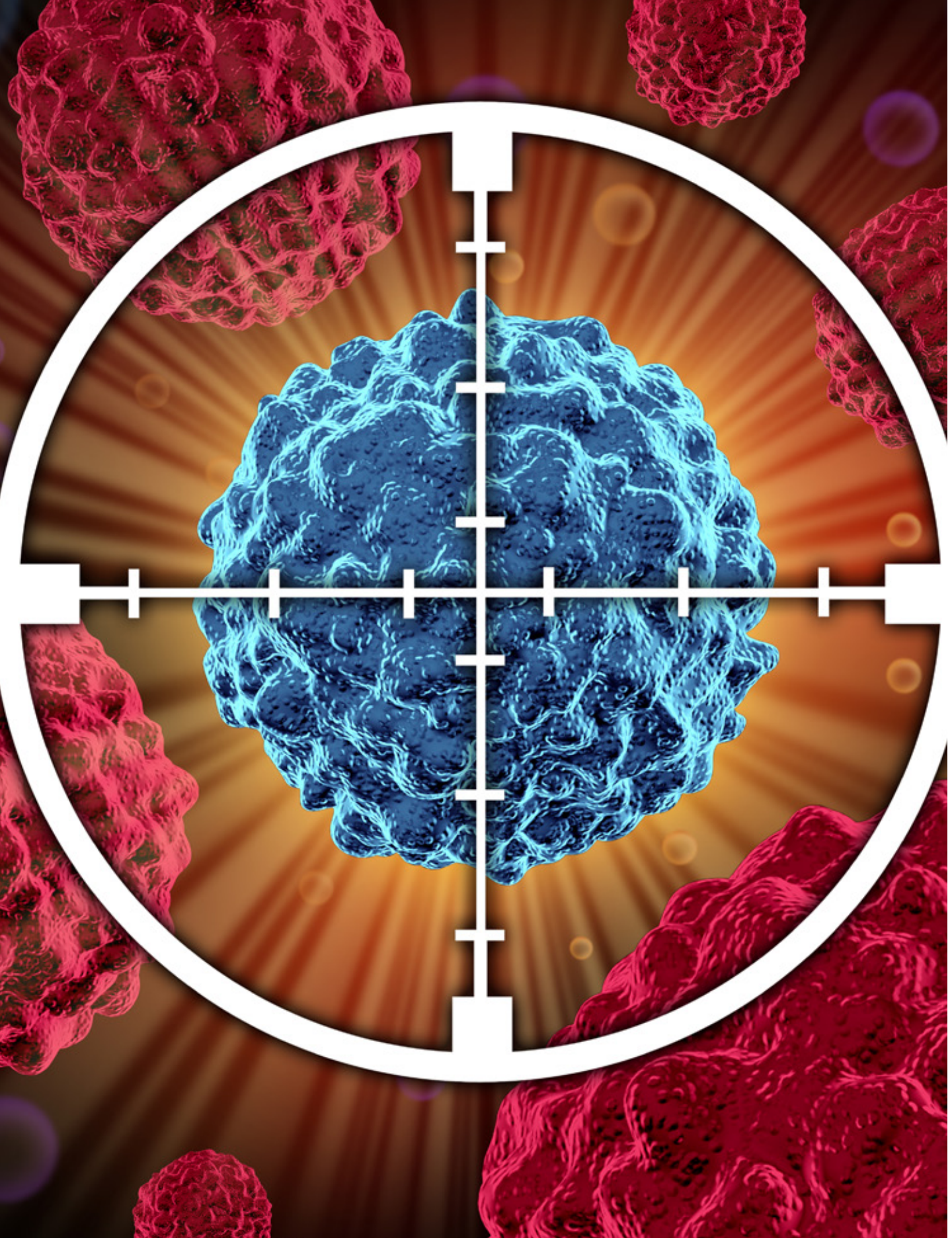

COMMITTEE 10

Advances in Robotic-Assisted Radical Prostatectomy: Outcomes, Benefits, Challenges, and Future Directions

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Introduction

Robotic-assisted radical prostatectomy (RARP) has revolutionized the surgical management of prostate cancer (PCa) over the past two decades. By combining robotic technology with minimally invasive techniques, RARP offers several advantages over traditional open surgery, including reduced blood loss, shorter hospital stays, and faster recovery times. This chapter explores the evolution of RARP, its current outcomes, benefits, challenges, and future directions, focusing on its role in managing intermediate- and high-risk prostate cancer.

Advances in RARP Technology

Robotic platforms

Since the first RARP procedure performed by Dr. Mani Menon in 2000, the Da Vinci™ Surgical System (Intuitive Surgical; Sunnyvale, CA, USA) has been instrumental in the field of RARP.[1] The discussion in this chapter focuses primarily on the Da Vinci Surgical System, as most publications to date have centred on this platform. Advancements in robotic technology have been pivotal in enhancing the precision and outcomes of RARP. The development of robotic platforms, such as the Da Vinci Surgical System, has led to significant improvements in instrumentation, ergonomic design, and integrated imaging technologies. These advancements enable surgeons to perform intricate surgical maneuvers with enhanced dexterity and precision, contributing to improved oncological and functional outcomes.[2,3]

Several new robotic platforms have been developed in recent years, with Hugo™ RAS (Medtronic; Minneapolis, MN, USA) emerging as one of the frontrunners.[4] The Hugo RAS system differs by having modular robotic arms and an open surgical console with pistol grip controls and a flat three-dimensional (3D) display screen.[4] Preliminary comparative studies have shown Hugo RAS to be safe with similar operative and functional outcome.[5,6] However, further studies are needed to evaluate long-term oncological outcomes. Other upcoming platforms include the Senhance™ Surgical System (TransEnterix Surgical, Inc.; Morrisville, NC, USA)[7] and the Versius® Robotic Surgical System (CMR Surgical Ltd.; Cambridge, UK).[8]

Single-port systems

The Da Vinci™ single-port (SP) robot was developed to minimize the number of incisions, allowing for a less-invasive procedure. This single-port technique is also referred to as single-incision or single-site surgery.[9] It gained US Food and Drug Administration (FDA) approval in 2018 and consists of a single-port trocar that houses a flexible camera and three biarticulated arms.[10] Similar to other multi-armed robotic systems, RARP can be performed using the Da Vinci SP robot via an extraperitoneal, transperitoneal, transperineal, or transvesical approach.[10] Systematic reviews have found that the Da Vinci SP platform offers advantages such as less blood loss, better cosmetic outcome, shorter length of hospital stay, and less postoperative pain.[9] However, due to its novelty, the Da Vinci SP platform lacks long-term functional and oncological data.

Advances in Intraoperative Imaging for RARP

Intraoperative transrectal ultrasonography

Transrectal ultrasonography (TRUS) is a widely used imaging modality among urologists and is often easily accessible. Robotic consoles enable the simultaneous display of the operative field and TRUS images. TRUS enables intraoperative identification of the prostate contour and PCa nodules.[11] Intraoperative use of TRUS during RARP has been shown to reduce rates of positive surgical margins.[12] With advancements such as TRUS with Doppler and 3D reconstruction, the intraoperative utility of TRUS may be broadened for better identification of neurovascular bundles and extraprostatic extensions (EPEs).[13]

Intraoperative fluorescence imaging

Intraoperative fluorescence imaging involves the use of fluorescent dyes to highlight specific tissues or structures, aiding surgeons in real-time identification of structures and improving surgical precision. Ganzer *et al.* demonstrated that oral 5-aminolevulinic acid (5-ALA) could improve detection of positive surgical margins intraoperatively.[14] Similarly, Mangano *et al.* showed that intravenous indocyanine green (ICG) improves identification of neurovascular bundles.[15] The combination of ICG with radioactive 99mTc-nanocolloid has also been used to identify lymph nodes intraoperatively.[16] These techniques are limited by the availability of the specialized cameras required to detect the fluorescent dyes.

3D Models and augmented reality

Preoperative imaging is crucial for surgeons to understand prostatic anatomy, predict the presence of EPE, and assess the suitability for nerve-sparing procedures.[17] However, it does not offer any real-time correlation during RARP and is still largely dependent on the surgeon's visual interpretation. 3D-printed patient-specific prostate cancer models has been shown to improve visualization of complex anatomy and are useful in nerve-sparing RARP.[18] Augmented reality (AR) involves the use of preoperative imaging such as magnetic resonance imaging (MRI) or TRUS to develop a virtual 3D model that is then superimposed onto the surgeon's surgical field in real time. AR appears promising in reducing positive surgical margins and enabling real-time identification of the index lesion to guide the extent of nerve sparing.[17,19] However, due to the risk for anatomical mismatch, this technology needs further development for mainstream integration.

Advances in Perioperative Management of RARP

Preoperative education is crucial for achieving patient satisfaction. Enhancing traditional verbal and written educational materials with interactive multimedia tools and preoperative patient-specific 3D-printed prostate models has been shown to improve patient understanding and satisfaction.[18,20–22]

With advancement in RARP, routine use of a postoperative prophylactic drain tube could be safely omitted.[23] Additionally, there has been a growing trend toward same-day discharge (SDD) following RARP, with large trials showing favourable results.[24,25] For SDD to be feasible, surgeries need to be scheduled as the first or second case of the day to ensure sufficient postoperative monitoring time, careful patient selection, thorough preoperative education, well-defined postoperative protocols, and close collaboration with anesthetists and nursing staff.[24,25] Usage of reduced pneumoperitoneum and minimizing bladder and bowel mobilization seem to increase the likelihood of achieving SDD.[26]

Advances in RARP Techniques

Surgical approaches

The magnification and ability to access narrow spaces have facilitated the development of various surgical approaches. Among the most common are the transperitoneal and extraperitoneal approaches. In transperitoneal prostatectomy, ports are inserted into the peritoneal cavity, allowing access to the seminal vesicles through a posterior retrovesical transperitoneal approach. Alternatively, the bladder can be dissected away from the anterior abdominal wall to access the space of Retzius via an anterior transperitoneal approach.[27] In contrast, the extraperitoneal approach involves creating a space between the *rectus abdominis* muscle and its posterior sheath using a dilating balloon. Ports are then placed in this extraperitoneal space, followed by further development of the space of Retzius.[28]

Additional techniques include the transvesical and transperineal approaches. In the transvesical approach, ports are directly inserted into the bladder. After making an incision at the bladder neck, the procedure mirrors that of an anterior transperitoneal approach.[29] With the introduction of the Da Vinci SP robot, the transperineal approach is being considered. Access to the prostatic fossa is achieved through a transverse perineal incision.[30]

Retzius-sparing RARP

The Retzius-sparing approach involves the preservation of the endopelvic fascia and anterior bladder wall during prostatectomy, which helps to maintain the integrity of the supportive structures around the bladder and urethra. By sparing these structures, surgeons aim to reduce surgical trauma to the pelvic floor and minimize disruption to the continence mechanism.[31]

The anatomical preservation provided by Retzius-sparing techniques helps maintain the integrity of the external urethral sphincter and pelvic floor musculature, essential for urinary continence. By minimizing disruption to these structures, surgeons can mitigate the risk for postoperative stress urinary incontinence (SUI) and improve patients' early recovery of urinary control.[32]

Retzius-sparing techniques appear to have multiple benefits to postoperative urinary function. Previous systematic reviews have demonstrated earlier return to urinary continence, higher continence rates, and reduced number of postoperative pads required.[33–35] Postoperative sexual function recovery rates appear to be similar to conventional RARP.[36]

However, one of the key concerns with Retzius-sparing RARP is the risk for positive surgical margins.[33,34] Successful implementation of Retzius-sparing techniques requires meticulous patient selection based on preoperative assessment of prostate size, tumour location, and anatomical considerations. Surgeons with expertise in robotic surgery and nerve-sparing techniques play a crucial role in achieving optimal functional outcomes while maintaining oncological efficacy.

Despite its benefits, Retzius-sparing RARP presents technical challenges related to anatomical complexity and surgical proficiency. Studies emphasize the importance of comprehensive training and ongoing quality assurance to minimize complications and optimize patient outcomes.[37]

Hood-sparing RARP

In Hood-sparing RARP, anterior tissues such as the detrusor apron, endopelvic fascia, and puboprostatic ligaments are preserved during prostate dissection.[38] This technique aims to support the external urethral sphincter and was developed to reduce high rates of positive surgical margins (PSMs) while maintaining anterior pelvic anatomy similar to the Retzius-sparing technique. Preliminary results show promising outcomes, with patients achieving early recovery of urinary continence and maintaining long-term continence rates.[38,39]

Indications for RARP

Primary treatment of localized prostate cancer

RARP is primarily used for treating localized intermediate-, high-risk, and very high–risk PCa. The outcomes discussed in the following sections of this chapter will focus on this patient population. Optimal patient selection is crucial in maximizing the benefits of RARP in intermediate- and high-risk prostate cancer patients. Guidelines from international urological societies, including the European Association of Urology (EAU) and the American Urological Association (AUA), emphasize the importance of preoperative risk stratification based on prostate-specific antigen (PSA) levels, Gleason score, and clinical staging.[40–42]

Salvage RARP

Salvage RARP (sRARP) is reserved for PCa recurrence after radiotherapy or focal therapy. It should be performed only in highly selected patients with low comorbidity, good life expectancy, and absence of distal metastatis.[43] sRARP after radiotherapy (RT) is associated with a higher likelihood of adverse events (AEs) compared to primary

surgery because of the risk for fibrosis and poor wound healing due to radiation.[44] Patients who undergo sRARP are at higher risk of developing anastomotic stricture and rectal injury than those who undergo primary RARP.[43] Absorbable hydrogel rectal spacers (SpaceOAR) are being investigated to determine whether they can prevent rectal injury and assist in the dissection of Denonvilliers' fascia in sRARP. When compared to open salvage prostatectomy, sRARP has reduced anastomotic stricture rates, estimated blood loss, and length of hospital stay.[44] Oncological outcomes of sRARP appear similar to those of open salvage prostatectomy.[45]

Cytoreductive RARP

RARP in patients with metastatic PCa is currently investigational but appears to be safe with some survival benefit.[46] However, existing trials are limited by heterogeneous inclusion criteria, varied imaging modalities, and different outcomes.[47] In the current era of prostate-specific membrane antigen (PSMA) positron emission tomography (PET; PSMA PET) imaging, a new subset of patients with oligometastatic PCa is being identified, which may have been missed using previous conventional imaging techniques such as computed tomography (CT) of the abdomen and pelvis and whole-body bone scan (WBBS).[42] These patients would have traditionally underwent prostatectomy in the era of conventional imaging. Preliminary findings of cytoreductive RARP in oligometastatic PCa appear promising as a multimodal approach; however, further research into the role of RARP in this group of patients is needed.[48]

Outcomes of RARP

Operative outcomes

When compared to open prostatectomy, RARP reduces the length of hospital stay and need for blood transfusion.[49] There appears to be little to no difference in terms of postoperative pain and surgical complications.[49] The dexterity provided by robotic systems has facilitated the development of new suturing techniques for vesico-urethral anastomosis. Anastomoses have progressed from approximation sutures to continuous sutures under direct vision, allowing for watertight anastomoses. Compared to conventional non-barbed sutures, unidirectional barbed sutures significantly reduce anastomosis time, operative time, and posterior reconstruction time. However, there are no differences in postoperative leak rates, length of catheterization, or continence rates between the two techniques.[50]

Oncological outcomes

Longitudinal cohort studies and population-based analyses by Spahn *et al.*[51] report sustained oncological efficacy with RARP, including low rates of biochemical recurrence and favourable cancer-specific survival rates in intermediate- and high-risk prostate cancer patients. In patients with high-risk and very high–risk PCa, oncological outcomes are comparable to below those seen in high-risk PCa.[52] These findings highlight the evolving standard of care provided by RARP in aggressive prostate cancer management.

Research comparing RARP with open surgery consistently demonstrates comparable oncological outcomes, including biochemical recurrence-free survival and cancer-specific survival rates.[49,53] Long-term studies[54,55] highlight the effectiveness of RARP in achieving negative surgical margins and minimizing disease recurrence, particularly in intermediate- and high-risk prostate cancer patients.

Functional outcomes

Preservation of urinary continence and erectile function is critical in prostate cancer surgery. Meta-analyses and prospective studies consistently demonstrate encouraging functional outcomes with RARP compared to open surgery, attributed to advanced nerve-sparing techniques and reduced surgical trauma.[2,54] These findings underscore the potentially significant quality-of-life benefits associated with RARP.

Early systematic reviews showed little to no difference in terms of urinary and sexual quality-of-life outcomes.[49] However, an updated meta-analysis of prospective studies demonstrated that RARP improved nerve-sparing and postoperative erectile function recovery compared to open prostatectomy.[54] Despite these findings, the updated meta-analysis still showed no difference in postoperative urinary continence.

Benefits of RARP

Patient-centred benefits

Patients undergoing RARP experience reduced postoperative pain, shorter hospital stays, and faster return to daily activities compared to open surgery. Enhanced patient satisfaction and improved quality-of-life outcomes are consistently reported in prospective studies and patient surveys, underscoring the patient-centred advantages of RARP.[56]

Surgeon-centred benefits

Surgeons benefit from improved ergonomics and enhanced 3D visualization provided by robotic systems, which mitigate fatigue and enhance procedural efficiency. Structured training programs and simulation-based learning have played a crucial role in accelerating the learning curve for robotic surgery, ensuring proficient surgical performance and optimal patient outcomes.[55]

Healthcare system benefits

Adoption of RARP has demonstrated cost-effectiveness through reduced hospital stays, decreased perioperative complications, and optimized resource allocation within healthcare systems. Economic evaluations and health outcomes research consistently support the financial viability of RARP as a preferred surgical approach for prostate cancer management.[57]

Challenges and Limitations

Despite its advantages, RARP presents challenges related to equipment costs, training requirements, and the potential for perioperative complications.[58] Some studies emphasize the importance of structured training programs and ongoing quality assurance measures to mitigate these challenges and optimize patient outcomes.

Debates regarding the oncological equivalence of RARP compared to open surgery continue, particularly concerning long-term cancer control outcomes and the adequacy of surgical margins. Multicentre studies and systematic reviews[59,60] contribute to the ongoing discourse on the clinical efficacy and safety of RARP across different patient cohorts.

Future Directions

Innovations in robotic technology

Future innovations in robotic technology aim to further enhance the precision and versatility of RARP. Research and development efforts focus on integrating enhanced imaging modalities, and robotic-assisted navigation systems to optimize surgical planning and intraoperative decision-making.[61] A micro-transducer probe has been developed that is small enough to be used in narrow spaces and has proven useful in identifying hypoechoic lesions and in identifying and preserving the bladder neck.[62] These advancements hold promise for personalized treatment strategies and improved patient outcomes in prostate cancer surgery.

Integration of theranostics

Theranostics represents a transformative approach in prostate cancer management, combining diagnostic imaging with targeted therapeutic interventions tailored to individual patient profiles.[63] Recent studies explore the integration of molecular imaging techniques, such as PSMA PET/CT, to guide surgical planning and monitor treatment response in RARP patients.[42,64] This paradigm shift toward precision medicine aims to optimize oncological outcomes while minimizing treatment-related morbidity in prostate cancer care. Although still investigational, [177Lu]Lu-PSMA-617 is thought to be a treatment option for metastatic or micrometastatic disease.[65] Upfront [177Lu]Lu-PSMA-617 prior to prostatectomy has been shown to be safe with low complication rates and does not compromise the operative difficulty of RARP.[66]

Integration of artificial intelligence

Artificial intelligence (AI) refers to the simulation of human intelligence in machines designed to think, learn, and solve problems autonomously. AI could be used predict urinary continence, length of hospital stay, and risk for PSA recurrence.[67–69] The integration of AI into RARP could potentially improve surgical outcomes by providing real-time analytics and decision support during procedures.[70,71] For example, AI has been shown to be

able to recognize types of sutures and surgical tasks.[72,73] However, the integration of AI is still in its infancy and requires larger validating studies.[74]

Emerging trends

Emerging trends include the adoption of focal therapy techniques and salvage procedures using robotic platforms, aimed at preserving quality of life and functional outcomes in localized prostate cancer recurrence.[75,76] Multidisciplinary collaborations and ongoing clinical trials continue to drive innovation in RARP techniques and perioperative care strategies, reflecting the dynamic evolution of prostate cancer surgery.

Conclusion

Robotic-assisted radical prostatectomy has emerged as a cornerstone in the surgical management of prostate cancer, offering enhanced functional recovery and improved patient satisfaction compared to traditional approaches. While challenges persist, ongoing innovations in robotic technology and personalized treatment approaches underscore the transformative potential of RARP in advancing prostate cancer care. Future research endeavours and collaborative initiatives will continue to refine surgical techniques, optimize patient selection criteria, and expand the therapeutic landscape of RARP in urological oncology. In its current state, RARP remains a tool and an extension of the surgeon. The decision between open versus laparoscopic versus robotic prostatectomy should be dependent on the surgeon's experience and availability of equipment.

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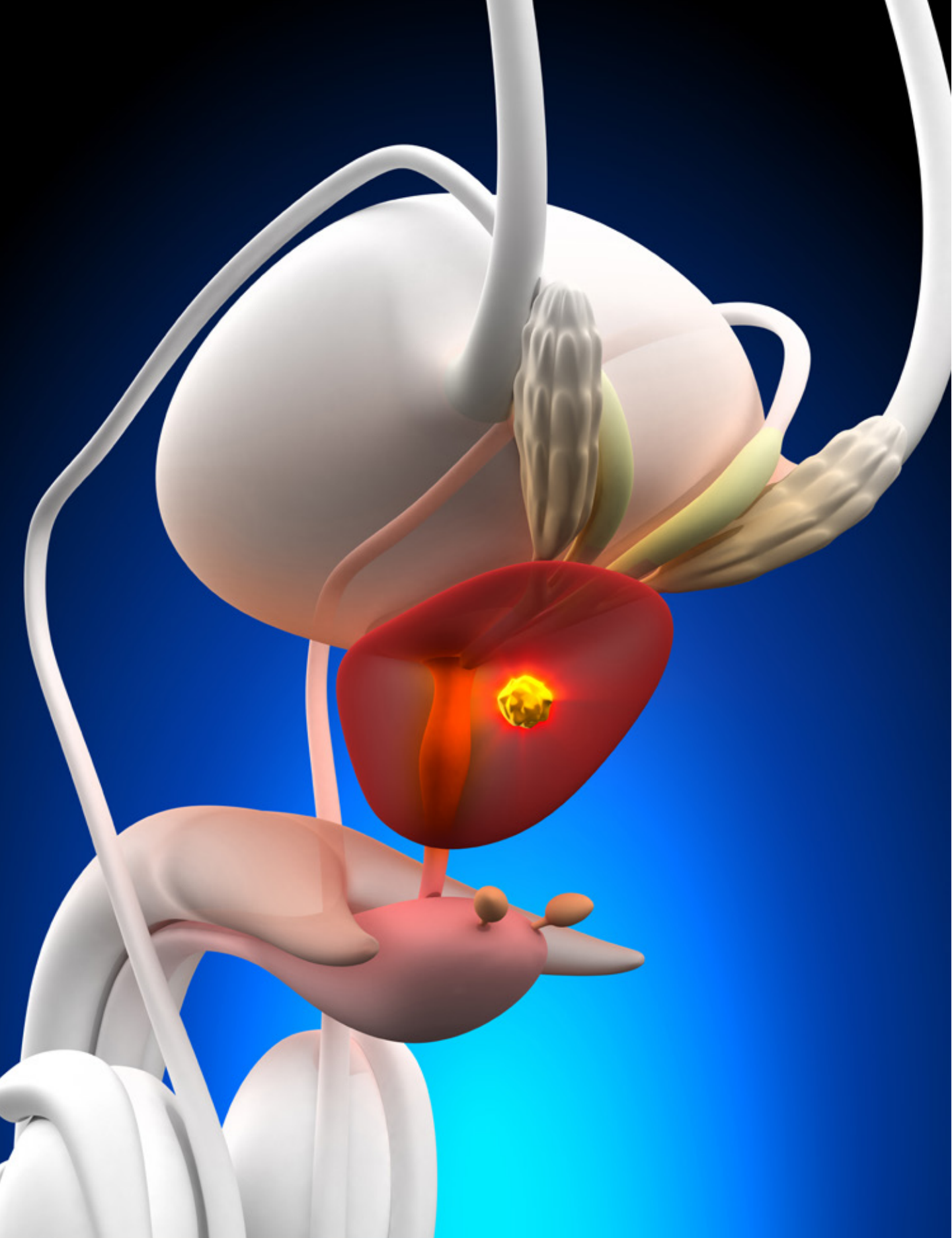
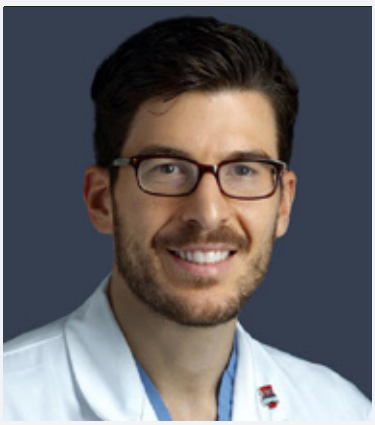


COMMITTEE 11

Advances in Robotic Prostatectomy Technique



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Introduction

The evolution of radical prostatectomy (RP) is a paragon of surgical innovation. Over the past century, advancements in technology, together with landmark anatomical studies, have transformed a rare, highly morbid operation into the gold-standard surgical treatment for localized prostate cancer.[2] Open techniques shifted to minimally invasive techniques for prostatectomy, yet all approaches advanced due to a more detailed understanding of prostate anatomy and its surrounding structures.

With the advent of robotic-assisted surgery, RP could be performed with reduced blood loss, pain, and length of hospital stay compared to all other approaches. As such, robotic-assisted radical prostatectomy (RARP) underwent rapid adoption and is today the preferred approach in many countries.[3,4]

Since its origin, several techniques for performing RARP have been proposed. Surgical innovation in the robotic era has focused on minimizing damage to the periprostatic structures and restoring anatomical and functional relationships in the pelvic floor following prostatectomy. Since pelvic anatomy remains complex and widely variable, the preferred technique to maximize oncologic and functional outcomes when performing RARP is yet to be determined.[5] This chapter focuses on the most recent advances in robotic prostatectomy techniques.

Anatomy

Regardless of the surgical approach, an in-depth understanding of prostate anatomy and its relationship to surrounding structures is fundamental.

Retropubic space

The retropubic space (also known as the prevesical space or space of Retzius) is a division of the extraperitoneal space located posterior to the pubic symphysis and anterior to the urinary bladder. It is bound superiorly by the parietal peritoneum, laterally by the arcus tendinous fascia and ischial spines, and inferiorly by the puboprostatic and pubovesical ligaments and the reflection of the superior fascia of the levator ani muscle.[6,7] Preserving structures within this space during radical prostatectomy has been associated with improved urinary continence outcomes.[3]

The detrusor apron and pubovesical/puboprostatic ligaments

The detrusor apron (DA) is an extension of the anterior bladder wall that is in direct continuity with the pubis and spreads around the prostate. Anterior to the prostate, the DA splits into an anterior, middle, and posterior layers. The anterior layer passes posteriorly to the pubococcygeal fibres and anchors onto the pubic bone. The middle layer is loose and joins with the fascial sheath of the dorsal venous complex (DVC). The posterior layer

fuses and extends into the prostate to form the anterior fibromuscular stroma (AFMS) of the prostate. Lastly, the DA condenses anteriorly and distally to form the puboprostatic and pubovesical ligaments.[8]

The puboprostatic and pubovesical ligaments are thought to stabilize and support the bladder and urethra via suspension from the pubic bone. Leaving them untouched during radical prostatectomy helps maintain the normal position of the bladder neck relative to the pubic symphysis. The bladder-to-symphysis ratio, which refers to the anatomical positioning of the bladder relative to the symphysis pubis, may play a significant role in male continence.[3] A low bladder-to-symphysis ratio, where the bladder neck and proximal urethra are positioned closer to the symphysis pubis, tends to provide better support and stability to these structures. This anatomical support is crucial for maintaining continence as it reduces the pressure on the urethra during activities that increase intra-abdominal pressure, such as coughing or lifting, thereby minimizing the risk of stress urinary incontinence. Conversely, a high bladder-to-symphysis ratio means the bladder is positioned more superiorly and posteriorly, which can decrease the mechanical support of the bladder neck and proximal urethra. This positioning can increase the strain on the sphincter muscles, potentially leading to sphincter dysfunction and a higher risk of incontinence, particularly during activities that elevate intra-abdominal pressure. Clinical studies have shown that preserving the supportive structures around the bladder neck, and urethra, especially in surgical contexts such as prostatectomy, is essential for optimizing postoperative continence outcomes. Similarly, preservation or restoration of these support structures using an anterior suspension suture has been promoted to improve early urinary continence outcomes.[9]

Vasculature: the dorsal vascular complex and accessory pudendal arteries

The arterial supply to the prostate has considerable inter- and intraindividual variability. Typically, there is a dual arterial supply composed cranially by the vesiculo-prostatic artery (anterior–lateral prostatic pedicle) and caudally by the prostatic artery (posterior–lateral prostatic pedicle). Accessory pudendal arteries (APAs) usually occur due to congenital anatomical variations but may also occur in internal pudendal atherosclerotic disease.[9] Current literature supports that penile blood supply can at least partly originate from APAs, and thus, attempts to preserve these vessels should be performed during radical prostatectomy.[5,10]

The dorsal venous complex, initially described by Santorini in 1724, is more accurately considered a dorsal vascular complex (DVC) given that it contains not only veins but also small arteries, nerve plexus, and external urethral sphincter fibres.[11] Standard ligation of the DVC during RP helps reduce intraoperative blood loss; however, it may risk injury to the urethral sphincter. Furthermore, during ligation of the DVC, small APAs can be encountered that provide additional blood supply to the sphincter and the corpora cavernosa. Selective ligation of open venous channels rather than *en bloc* ligation of the DVC may improve continence and erectile function postoperatively.[3]

Fascial support

Three separate fascial structures surround the prostate: Denonvilliers' fascia, the prostatic fascia, and the endopelvic fascia. A thorough understanding of these fascial layers and their intimate associations with the DVC, the neurovascular bundle (NVB), and the striated sphincter is imperative to optimize patient outcomes after RP.[3,12]

Denonvilliers' fascia lies between the prostate and the rectum, adherent to the prostate posteriorly. The prostatic fascia immediately surrounds the prostatic capsule anteriorly and laterally and forms the medial boundary of the NVB. Posteriorly, it fuses with and is indistinguishable from Denonvilliers' fascia.[12]

The endopelvic fascia covers the pelvic organs and can be divided into a parietal and a visceral layer. The parietal endopelvic fascia lines the walls and pelvic muscles and is continuous with the transversalis fascia. The visceral endopelvic fascia covers the bladder and anterior prostate, investing the pelvic organs and perineural and vascular sheaths. The parietal and the visceral components of the endopelvic fascia fuse along the pelvic sidewall, forming the fascial tendinous arch of the pelvis.[5]

History and Evolution of Radical Prostatectomy

Since the conception of RP, preserving pelvic anatomy to reduce treatment-related side effects has been central to the surgical technique. RP was first performed in 1904 by Dr. Hugh Young via a curved perineal incision. In 1939, the technique was modified by Dr. Elmer Belt, who described an approach to the prostate between the longitudinal fibres of the rectum and the circular fibres of the external anal sphincter that allowed for reduced blood loss. In 1945, Dr. Terrence Millin introduced a retropubic RP (RRP) via a low midline incision. Although the perineal approach was associated with decreased blood loss and postoperative pain, the retropubic approach quickly became the preferred open technique. This was due to increased surgeon familiarity with the anatomy, more accessible access to pelvic lymph nodes through the same incision, and reduced risk for rectal injury.

Still, the retropubic approach was not without risks. Severe blood loss incurred during transection of the DVC as well as impotence and urinary incontinence were commonplace. With the introduction of radiation therapy for prostate cancer in the 1950s, RRP failed to gain popularity owing to its excessive morbidity, and surgical management was not considered the gold standard of treatment.

In 1979, landmark anatomical studies by Dr. Walsh and colleagues provided a more detailed understanding of the prostate and its surrounding structures. They introduced technical refinements that drastically changed the way localized prostate cancer was treated. Walsh *et al.* identified that early ligation of the dorsal vein during RRP significantly reduced intraoperative blood loss. Moreover, their meticulous study of the autonomic nerves originating from the pelvic plexus eventually led to nerve-sparing techniques that improved sexual function. Given the significant decrease in surgical morbidity following these discoveries, RRP quickly became widely accepted for the treatment of prostate cancer.[3,13–15]

Towards the end of the 20th century, the increasingly popular concept of minimally invasive surgery and the advent of laparoscopy brought the next significant advance in radical prostatectomy. Laparoscopic RP (LRP) was first performed by Schuessler in 1991 and further refined and popularized by Guilloneau and Vallancien later that decade. The strengths of a minimally invasive approach included smaller incisions, decreased rates of blood loss, improved postoperative pain, and shorter hospital stays. However, LRP remained a technically challenging operation with a steep learning curve and poor ergonomics.[15,16]

Introducing robotic instrumentation with the daVinci Surgical System enabled surgeons to overcome the challenging technical learning curve to LRP. In 2000, the first robotic-assisted RP (RARP) was performed. Between 2003 and 2010, RARP went from 0.7% of all prostatectomies performed in the United States to 42%,[17] and most recent studies estimate that 80% to 90% of RPs performed worldwide are now done robotically.[13] In addition to the benefits of a minimally invasive approach, RARP offered vastly improved ergonomics, three-dimensional stereoscopic visualization, and finger-controlled movements with a range of motion surpassing that of the human hand.[16]

Traditional Robotic Prostatectomy Techniques

Transperitoneal multiport robotic prostatectomy

The anterior transperitoneal, or standard, approach to RARP involves releasing the bladder from its anterior abdominal wall attachments, including the bilateral medial umbilical ligaments and urachus, by incising the anterior parietal peritoneum, thus entering the retropubic space. The bladder neck is divided to posteriorly access the vas and seminal vesicles ampulla. Like RRP, this anterior approach necessitates the transection of the anterior detrusor apron, puboprostatic ligaments, and the DVC.[3] Another commonly performed transperitoneal RARP involves a posterior/anterior approach, according to the Montsouris technique, by starting the dissection posteriorly via a low peritoneal retrovesical incision to isolate the vas and the seminal vesicles before proceeding to the standard anterior approach.[18]

Extraperitoneal multiport

Extraperitoneal RARP involves accessing the retropubic space through an infraumbilical skin incision. A balloon dilator is introduced through the incision to create a preperitoneal space anterior to the bladder. Once this working space is established, the remaining robotic trocars are placed without entering the peritoneal cavity. The subsequent surgical steps can proceed similarly to an RRP or standard transperitoneal RARP. A key difference in this approach is the identification and dissection of the *vasa deferentia* and seminal vesicles, which are approached after dividing the posterior bladder neck. Unlike in open RRP, these structures are accessed neither transperitoneally nor retrogradely. It should be noted that this extraperitoneal approach is less commonly used compared to other methods.[19]

Reconstruction techniques

Despite improvements in perioperative outcomes associated with robotic surgery, there remains significant morbidity related to RARP, most notably urinary incontinence and erectile dysfunction. Hence, in the years since its origin, robotic surgical technique has continued to evolve. These modifications were adapted from Walsh's anatomical studies, which initially popularized open RRP and identified the surgical and anatomic principles underlying continence and nerve function preservation.[15]

Bladder neck preservation

Anatomically, the bladder neck serves as an internal sphincter with three distinct muscular layers: the inner longitudinal layer, the middle circular layer, and the outer longitudinal layer. The outer longitudinal layer contributes anterior fibres to the pubovesical muscle and may contribute to the opening of the bladder neck during micturition. Posteriorly, the outer longitudinal fibres interdigitate with deep trigonal fibers and may aid in bladder neck closure. Therefore, although the bladder neck may not contribute to voluntary continence, it is intuitive that bladder neck preservation (BNP) via meticulous dissection at the prostato-vesical junction during RARP may aid in the earlier return of urinary continence.[20]

Initial studies that examined BNP with open RRP and LRP raised concerns of increased risk for positive surgical margins and compromised cancer control.[21] However, more recent studies comparing standard RARP to RARP with BNP have shown improved early urinary continence with BNP compared with the standard technique. Freire *et al.* retrospectively compared 348 men undergoing BNP with 271 undergoing standard RARP and noted significantly improved urinary function with BNP at 4 and 24 months. Urinary continence was also considerably enhanced at 4 months (65.6 vs. 26.5%; $p<0.001$). Notably, there was no compromise in surgical margins when performing BNP, as suggested by older RRP and LRP series. Moreover, this series' update demonstrated earlier continence recovery throughout the 2-year follow-up interval and no differences in prostate-specific antigen (PSA) recurrence-free survival up to 5 years following RARP. Other groups have reported similar results as well.[22,23]

Some have attempted bladder neck reconstructive techniques in cases where the bladder neck structures cannot be preserved given unique patient characteristics (i.e., presence of median lobe, tumour invading bladder neck, benign prostatic hyperplasia). Lee *et al.* evaluated a novel bladder neck plication stitch technique during RARP to improve postprostatectomy continence. In a study involving 334 patients, 159 underwent the new technique and were compared with 175 in a control group. Key findings include a significantly shorter mean time to social continence (3.63 ± 3.01 weeks vs. 5.33 ± 4.89 weeks, $p=0.004$) and total continence (5.10 ± 3.80 weeks vs. 8.49 ± 6.32 weeks, $p=0.002$) in the plication group. The odds of achieving total continence improved significantly at 1 month (odds ratio [OR], 1.95 ± 0.72; $p<0.001$) and 12 months (OR, 2.07 ± 0.66; $p=0.005$) with the plication stitch. No bladder neck contractures or other urinary complications were observed.[24]

Urethral length preservation

Multiple studies have reported the importance of preserving membranous urethral length for optimal urinary continence. Hammerer and Huland used urodynamic testing to confirm that continent men had significantly longer urethral lengths than incontinent men following RRP.[20,25] Furthermore, von Bodman *et al.* examined preoperative imaging in 967 men undergoing RRP. They found that urethral length, urethral volume, and an anatomically close relationship between the levator muscle and membranous urethra were significantly associated with urinary continence recovery at 6 and 12 months.[26]

However, precisely identifying the junction between the prostatic apex and the proximal membranous urethra to maximize urethral length is challenging. The prostate shape at the apex may vary substantially, directly

influencing the form and length of the urethral sphincter after emerging from the apex.[27] Hence, Mizutani *et al.* studied the use of intraoperative transrectal ultrasound in 53 men undergoing LRP and found that longer membranous urethral length had significantly higher continence rates at 1, 3, and 6 months following LRP, with no difference in positive surgical margin rates.[20,28]

Periurethral reconstruction

Various surgical techniques have been studied to improve postoperative continence outcomes by reconstructing the anterior and posterior periurethral structures during RP. As described by Patel *et al.*, a simple technique involves a periurethral suspension stitch (PSS), performed by reversing the needle after ligation of the DVC and passing it through the perichondrium of the pubic symphysis. This maneuver can help control venous bleeding and mimic the function of puboprostatic ligaments, providing anterior urethral support. In their nonrandomized trial, Patel and colleagues showed earlier return of continence and higher continence rates at 3 months in men who underwent PSS, whereas similar urinary continence at 1, 6, and 12 months. Therefore, although PSS may help immediate urinary continence recovery, it does not appear to affect long-term urinary continence.[20,29]

Posterior reconstruction

A technique targeting posterior periurethral tissues was proposed by Rocco *et al.* during RRP and later adapted to RARP. This technique reconstructs the posterior musculofascial plate by suturing the median raphe of the urethra to the remnants of Denonvilliers' fascia posterior to the bladder before urethrovesical anastomosis. Theoretically, this stitch restores the anatomical length of the rhabdosphincter and provides posterior support by fixing the structure into its natural position.[20]

Continence outcomes following posterior reconstruction (PR) have been mixed in the era of RARP. Coelho *et al.* and Nguyen *et al.* showed early return of continence in patients undergoing PR during RARP at 4 and 6 weeks, respectively.[30,31] However, Nguyen *et al.* found no difference in continence rates at 3 and 6 months. Evidence from several randomized controlled trials failed to show the effectiveness of PR during RARP in improving postoperative continence rates.[15,20]

Combined anterior and posterior reconstruction

Surgeons performing RARP have tried combining the PSS and PR techniques for combined anterior and posterior reconstruction of periurethral structures with conflicting results. Some studies have shown no significant difference in early or late continence rates in men undergoing combined reconstruction. In contrast, others found significant short-term urinary continence improvement at 1 and 3 months following RARP. In a recent meta-analysis, Ficarra *et al.* found a small but significantly lower risk for urinary continence in men undergoing combined anterior and posterior reconstruction versus standard anastomosis (OR, 0.4; p=0.040). Similar to a posterior reconstruction, combined anterior and posterior reconstruction may have a small impact on urinary continence recovery; however, long-term outcomes are unknown, and randomized controlled trials have not shown universal benefit.[20,32]

Neurovascular bundle preservation

As described by Walsh in 1983, the NVB were reported to lie posterolaterally on either side of the prostate, enclosed in a fascial sheath, and accompanied by the prostatic vessels.[12] Recent studies have indicated the course of NVB is much more variable than previously suggested, and important supplementary nerve fibres can also travel on the anterolateral surface of the prostate.

Several techniques to preserve the NVB have been described based on the exact fascial plane of dissection (extrafascial, interfascial, and intrafascial). In extrafascial NS, dissection is performed over the endopelvic fascia and under the Denonvilliers' fascia. This approach results in the resection of the largest amount of tissue surrounding the prostate. It thus is the most oncologically safe dissection, but it carries with it probable complete erectile dysfunction if done bilaterally. Dissection within the plane between the prostatic and lateral pelvic fascia extends posteriorly in interfascial NS. This approach allows for a more significant safety margin around the prostate relative to the intrafascial dissection, presumably resulting in an oncologically safer approach.[27] In intrafascial NS, dissection occurs within the plane between the prostatic capsule and the prostatic fascia. NS grading systems like the one described by Montorsi *et al.* have divided NS into full, partial, and minimal as matching to intrafascial, interfascial, and partial extrafascial dissections, respectively.[33]

In a recent meta-analysis performed by Weng *et al.*, the intrafascial technique was superior to the interfascial technique in terms of functional outcomes, likely due to the preservation of nerve fibres on the anterolateral surface of the prostate. This study demonstrated better continence with the intrafascial approach at 6 and 36 months and better potency recovery at 6 and 12 months. Oncologic control was also better with the intrafascial technique. However, patients in the interfascial group presented higher-risk cancer than patients in the intrafascial group.[34]

The CEASAR study highlighted significant improvements in functional outcomes for patients undergoing bilateral nerve-sparing (NS) prostatectomies compared to unilateral NS. Specifically, at high-volume institutions, where surgical experience and procedural volume are greater, the study found superior potency and continence outcomes following bilateral NS. This was confirmed through multivariate analysis, which showed that bilateral NS was associated with better overall urinary function scores and continence at 12 months postoperatively ($p \leq 0.035$). These favourable outcomes underscore the benefits of performing such procedures at high-volume centres, where the expertise and experience can significantly enhance patient recovery and functional results.[35,36]

In addition to the varying approaches to nerve sparing, multiple modifications have been made to help preserve nerve function postoperatively. Studies have shown that both erectile function and urinary control are improved if the prostate pedicles and seminal vesicles are dissected athermally, since both are closely intertwined with the NVB. Athermal dissection generally entails the use of clips and sharp division.[37] Ahlering and colleagues have reported extensively on improvements in potency outcomes with their athermal technique of RARP, which uses bulldog clamps on hypogastric vessels. The potency rates at 3, 9, and 24 months in patients with and without thermal utilization (all underwent similar nerve sparing) were 8.3% and 14.7%, 63.2% and 38.1%, and 69.8% and 92%, respectively.[38]

Also crucial during this dissection is limiting the amount of traction or displacement of the NVB, as this has been shown to affect potency significantly. Kowalczyk *et al.* proposed a counter traction-free dissection by placing traction on the prostate (i.e., the medial motion of the instruments while performing blunt dissection rather than lateral) and dissecting it away from the neurovascular bundle. They examined 610 patients undergoing RARP by a single surgeon; 342 patients who underwent a counter traction-free dissection of the neurovascular bundle demonstrated earlier potency recovery (45% vs. 28% potent at 5 months). Overall potency rates at 1 year were similar between the groups.[36]

Traditional RARP outcomes

Most studies have suggested comparable cancer control and survival outcomes between surgical approaches (open RRP vs. LRP vs. RARP), with a clear advantage for RARP regarding perioperative outcomes such as blood loss, pain, and hospital length of stay.[15,33] Hence, the focus of innovation has increasingly been on the preservation of urinary and sexual health–related quality of life. Data on these functional outcomes after RARP have been inconsistent. Much of the variability in reported outcomes is related to disparate surgeon experience, outcome assessment tools, and patient populations. Additionally, the preponderance of data are comparative retrospective rather than randomized.

In a prospective, multicentre comparison of open RRP and RARP (PROST-QA/RP2 Consortium), a robotic approach had no significant change in patient-reported, long-term urinary and sexual health-–related quality of life.[37] LAPPRO, a Swedish nonrandomized trial of RARP versus open RRP, showed a small benefit of RARP over RRP with regard to erectile dysfunction but not with regard to urinary continence or oncologic outcomes.[39] A large cohort study by Wu *et al.* that studied 1,407 patients who underwent open radical prostatectomy (ORP), LRP, and RARP also showed that men who underwent RARP had several notable benefits. They experienced significantly shorter hospital stays, averaging 1.64 days less than ORP patients and 0.57 days less than LRP patients. RARP patients also had lower odds of requiring blood transfusions, with an adjusted odds ratio of 0.25 compared to ORP and 0.58 compared to LRP. For postoperative pain, RARP was associated with a decrease in moderate-to-severe pain for up to 12 weeks post-surgery, with an adjusted odds ratio of 0.40 at 12 weeks compared to LRP. In terms of long-term outcomes, 3 years after surgery, RARP patients had lower odds of erectile dysfunction, with an adjusted odds ratio of 0.74 compared to ORP and 0.60 compared to LRP. They also had lower odds of urinary incontinence, with an adjusted odds ratio of 0.93 compared to ORP and 0.60 compared to LRP. Additionally, the incidence of hernia was lower in the RARP group, with adjusted odds ratios of 0.51 compared to ORP and 0.82 compared to LRP.[40] These findings highlight the advantages of RARP in both short-term recovery and long-term functional outcomes. These outcomes are consistent with other studies, such as those by Ficarra *et al.* and Kowalczyk *et al.*, which reported incontinence rates ranging from 4% to 31% and erectile dysfunction rates between 10% and 46% 1 year after RARP.[32,41]

Studies comparing extraperitoneal to standard transperitoneal RARP are mostly limited to single-surgeon or single-centre experiences. Chung *et al.* found the extraperitoneal approach was associated with significantly shorter console time, lower postoperative pain scores, and decreased incidence of ileus and hernia compared to transperitoneal RARP. Functional and oncologic outcomes were similar between groups.[42] Given the lack of

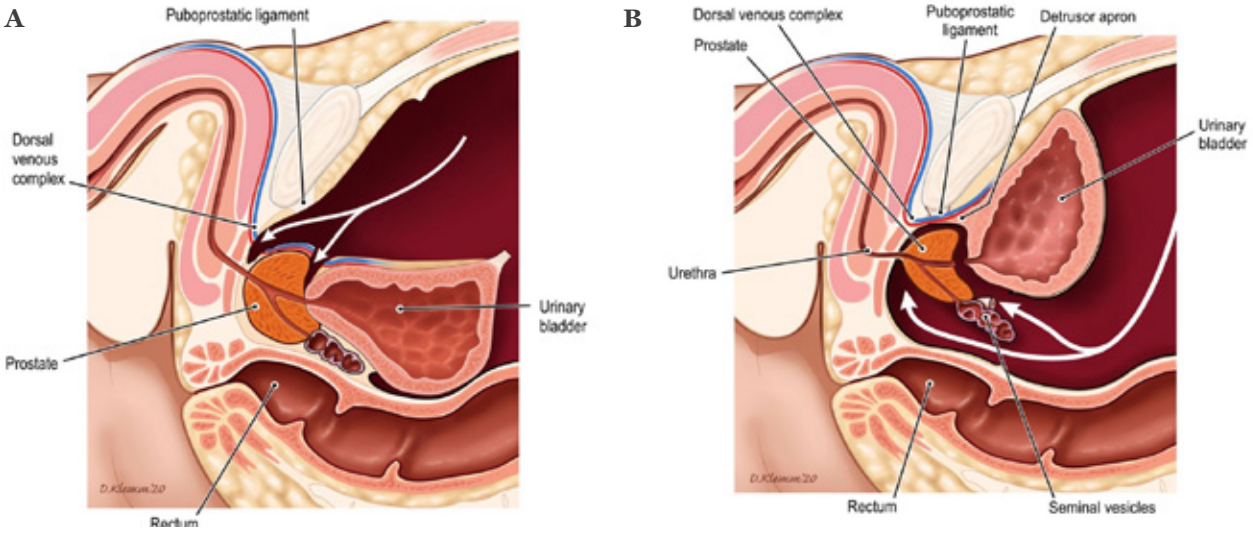
high-level evidence showing the superiority of one robotic approach over the other, either technique is acceptable, and surgeons should continue with the approach they are most familiar with.

Novel Robotic Prostatectomy Techniques

Pelvic-fascia sparing prostatectomy: Bocciardi technique

In 2010, Aldo Bocciardi and colleagues at the Niguarda Hospital of Milan, Italy, first described the pelvic fascia sparing, or Retzius-sparing, robot-assisted radical prostatectomy (PFS-RARP).[43] The Bocciardi technique approaches the prostate in an antegrade fashion from the rectovesical pouch, first dissecting the seminal vesicles and subsequently progressing caudally behind the gland. This allows for maximal preservation of the normal pelvic anatomy. This is in contrast to the traditional approach anterior to the bladder (**FIGURES 1A and 1B**).

FIGURE 1A and 1B Overview of the difference between S-RARP and posterior PFS-RARP approaches.



Abbreviations: PFS-RARP, pelvic fascia sparing, or Retzius-sparing, robotic-assisted radical prostatectomy; S-RARP, standard robotic radical prostatectomy.
Sourceline: *Images courtesy of Keith J. Kowalczyk, MD.*

Specifically, the technique aims to preserve all the anterior structures that may play a role in the mechanisms of continence and erection. In particular, the puboprostatic ligaments are theorized to stabilize the prostate, the urethra, and the bladder to the pubic bone. Preserving these ligaments is thought to increase the likelihood of early urinary continence recovery.[44] As the bladder is not dropped from its standard anatomical location, there is no bladder neck descent, and the angle between the bladder neck and urethral sphincter does not change,[45,46]

the surgical trauma is minimized, and the normal pelvic anatomy is maximally preserved, reasonably leading to an enhanced urinary continence recovery. Essentially, PFS-RARP provides the same advantages as the open perineal approach but without disrupting the perineal floor musculature.

The endopelvic fascia may also be involved in continence preservation, as its parietal component covers the medial aspects of the levator ani muscle, while its visceral component covers and supports the pelvic organs, including the prostate, bladder, and rectum. The thickening of the visceral endopelvic fascia originates from the aforementioned puboprostatic ligaments that insert on the posterior surface of the pubic bone, anterior to the urethral sphincter.[27]

The detrusor apron consists of muscle fibres originating from the outer layer of the detrusor and extending ventrally over the prostate. The detrusor apron anteriorly covers the dorsal vascular complex, which drains blood from the penile, urethral, and lateral pelvic veins.[47] It is not uncommon to find small arteries during the DVC dissection. While the role of these vessels is still a matter of debate, a possible role of the accessory blood supply of the striated sphincter and the corpora cavernosa cannot be excluded; therefore, the preservation of the apron and the DVC has been hypothesized to yield better functional results, in addition to decreasing surgical blood loss.[43]

The neurovascular bundle is a network of vascular and nervous fibres surrounding the proximal prostate, the seminal vesicles, and the lateral aspect of the bladder neck, in a cage-like fashion, responsible for continence and sexual functions.[27] It receives sympathetic fibres from the hypogastric nerve (ganglia of T11–L2) and is responsible for ejaculation.[48] It also receives parasympathetic fibres (including *nervi erigentes*) that primarily derive from the pelvic and sacral splanchnic nerves (ventral *rami* of S2–4) and are responsible for vasodilation in the *corpora cavernosa* during erection.[49] Since roughly one-third of these nerves lie on the anterolateral surface of the prostate with a spray-like distribution, the posterior approach allows their maximal preservation. [50,51]

The prostatic artery terminates in two major pedicles. The posterior pedicle surrounds the seminal vesicle and *vas deferens* and reaches the prostatic base. The anterior pedicle reaches the prostatic apex as an anterior capsular branch. Preserving the latter might enhance postoperative erectile function recovery as it contributes to the ancillary penile blood flow.[52,53]

PFS-RARP: surgical technique

Currently, RS-RARP has been standardized using different surgical platforms, namely da Vinci Xi® and Single Port (SP) systems (Intuitive Surgical; Sunnyvale, CA, USA), HUGO robot-assisted surgery (RAS) system (Medtronic; Minneapolis, MN, USA) and Versius system (CMR Surgical; Cambridge, UK). This section will focus on utilizing the da Vinci Surgical System since it is currently the most commonly used.

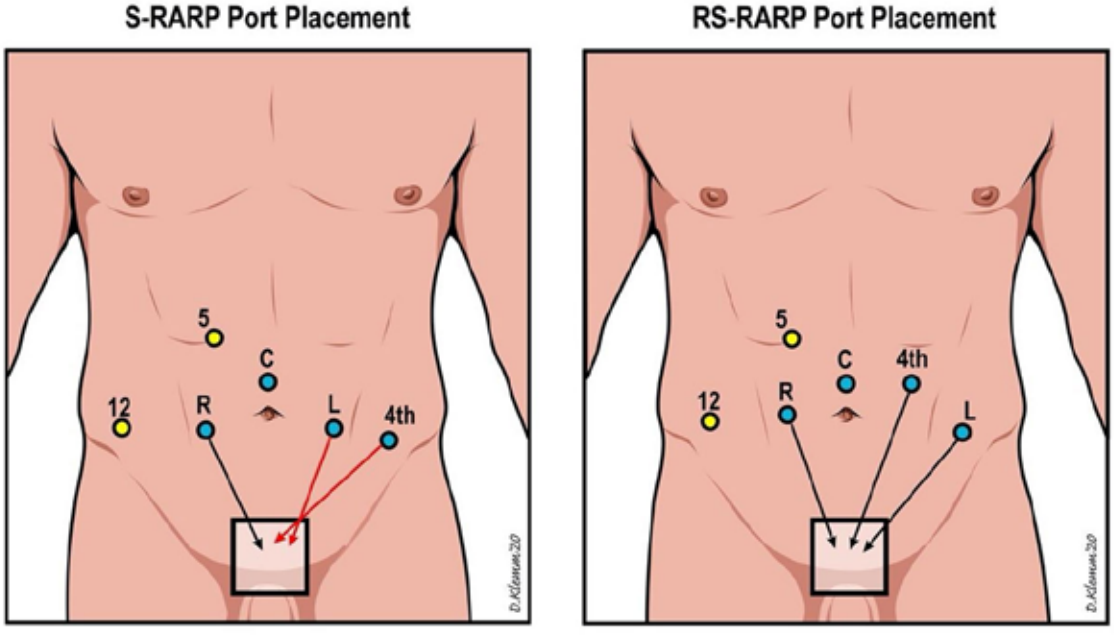
1. Patient positioning and port placement

The 30° lens camera is accommodated through the supra-umbilical 8-mm trocar, downwards oriented during the first phase of the procedure and upwards after the dissection of the seminal vesicles. The primary operative

arms are placed in 8-mm trocars on a transversal line crossing the umbilicus, at least 8 cm of distance from one another. A 12-mm and a 5-mm port are positioned for the assistant on the right, with the lateral 12-mm port connected to the Airseal insufflation system when available, as this assists with maintaining visualization with the small retrovesical space.

Instrument placement may mimic that of standard RARP. However, some authors have preferred placing the ProGrasp retractor (fourth arm) medially while moving the left working arm laterally to allow better exposure and less clashing of instruments. Additionally, some authors have omitted the 5-mm right upper quadrant assistant port to utilize a five-port technique and replaced the 12-mm Airseal trocar with an 8-mm trocar to reduce the risk for hernia (**FIGURE 2**).

FIGURE 2 Port placement for S-RARP and PFS-RARP (also known as RS-RARP).



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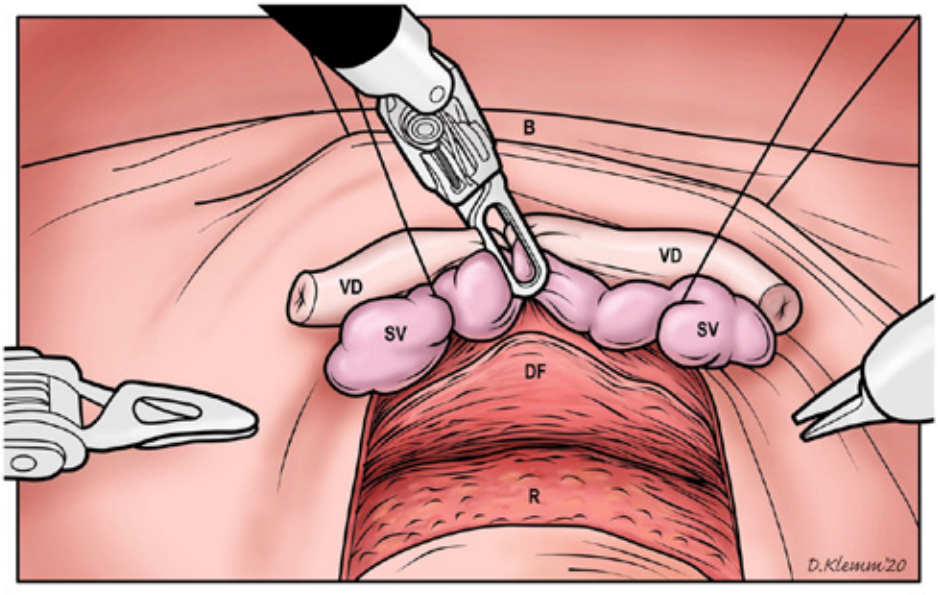
2. Seminal vesicles dissection

A horizontal semicircular incision is made at the level of the *vasa deferentia*, bilaterally identified as an arch anterior to the rectum, about 1 cm over the reflection of the Douglas space (**FIGURE 3**). *Vasa deferentia* and

seminal vesicles are isolated and incised, preferably minimizing cautery. Once the seminal vesicles are entirely dissected down to the prostatic base, two transabdominal suprapubic stitches (Ethilon 2-0, straight needle) can be passed to lift the bladder and retract the seminal vesicles, with a significant widening of the surgical space.

FIGURE 3 Exposure following seminal vesical dissection.



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3. Posterior plane, pedicles, and nerve sparing

The nerve-sparing plane is chosen depending on the clinical risk assessment of the cancer grade and location, as well as the preoperative conditions of the patients. Hence, the dissection of the prostate's posterior aspect begins with the Denonvilliers' fascia incision from the midline, where the slightly less dense vascularization offers a clear plane. The dissection proceeds towards the prostatic capsule, reaching an extra-, inter-, or intrafascial plane. Approaching the apex along the midline and proceeding laterally to the bundles yields a harmless isolation of the prostatic pedicles (**FIGURE 4**). Thus, the lateral prostatic pedicles are sectioned, and the neurovascular bundles are spared or sacrificed according to the planned surgical strategy.

Recently, some of the authors (KJK, JCU) have progressed to "clipless" nerve sparing, using only light bipolar cautery (**FIGURE 5**). Another option is cold cutting and spot fulguration. Clips can be imprecisely placed by the assistant, and even with the robotic clip applier, leading to an undesirable dissection plane too far into the nerve bundle or the prostate. Additionally, crush ischemia from surgical clips is likely at least as bad, if not worse,

than the damage caused by the minimal thermal spread when using precise bipolar. Clipless nerve sparing can also save operative time and has been shown to have the same oncologic and functional outcomes compared to routine RARP with clips in a prospective single-surgeon series.[54]

FIGURE 4A and 4B Isolation of the lateral pedicles and progressing the dissection posterior to anterior leading to the nerve-sparing plane, endopelvic fascia, and eventually detrusor apron.

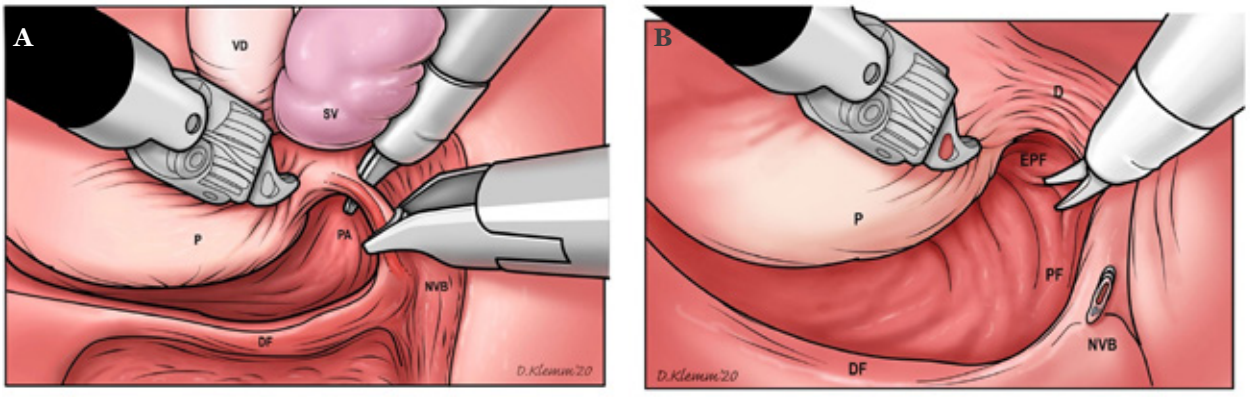

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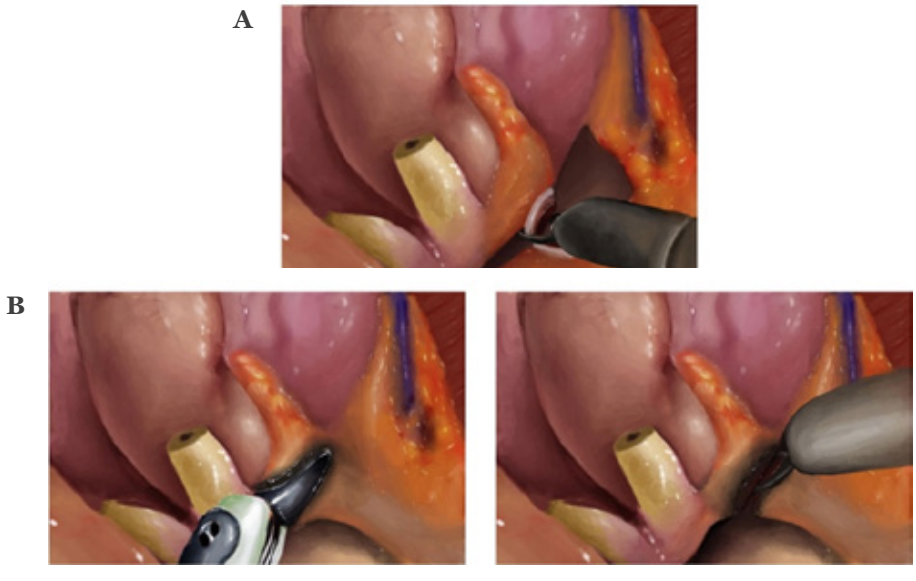
FIGURE 5A and 5B Illustration of the prostatic pedicle dissection with the (A) clips and (B) bipolar approach.

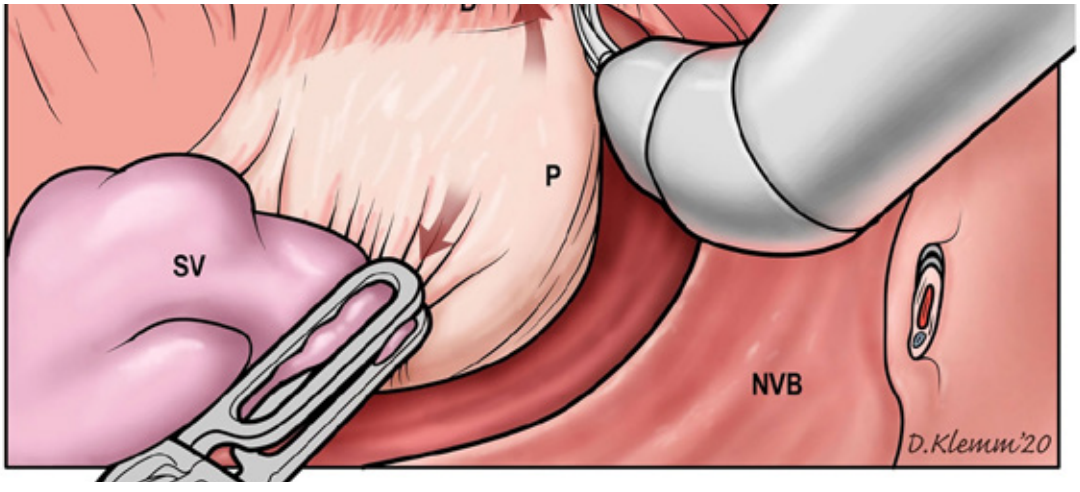


Sourceline: *Images courtesy of Jim C. Hu, MD.*

4. Bladder neck dissection

After securing the pedicles and establishing the desired nerve-sparing plane, the lateral and anterolateral prostate is separated from the endopelvic fascia on the side and the detrusor apron in the middle with blunt dissection. The fourth-arm retraction is adjusted to pull the prostate down and medially so the plane between the detrusor fibres and the anterior and apical prostate is more easily identified. Separating the anterior and apical as far to the side as possible helps to identify the bladder neck (**FIGURE 6**).

FIGURE 6 Anterior retraction by the bipolar forceps on the detrusor apron combined with posteromedial traction at the base of the prostate by the Prograsp forceps aids in identifying crossing detrusor fibres inserting into the anterior prostate. Staying in this dissection plane allows for easy bladder neck identification and avoids iatrogenic entry into the prostate capsule.



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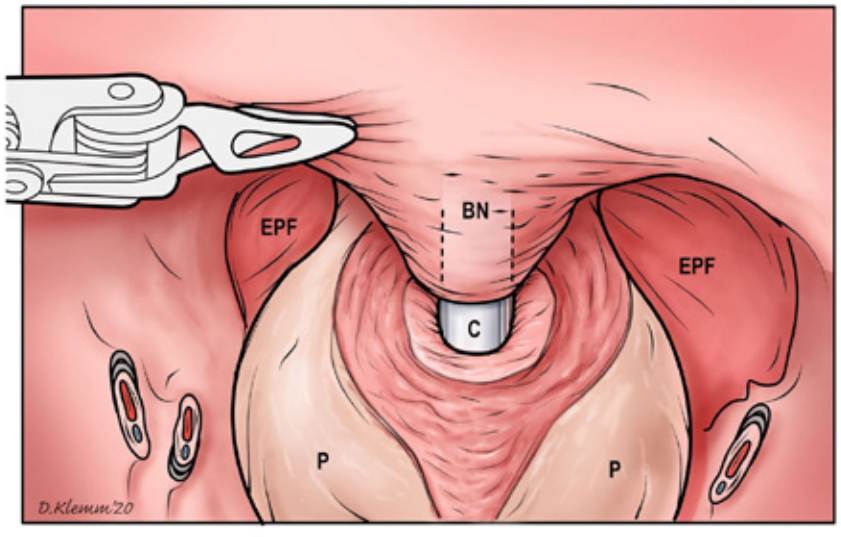
The bladder neck is approached posteriorly, where the vesicoprostatic muscle covers the ring-shaped muscle fibres of the bladder. These fibres can be moved away from the prostate on both sides as much as possible with blunt dissection before opening the bladder neck (**FIGURE 7**). Then, two absorbable stay stitches at 6 and 12 o'clock to the bladder neck can be placed to help expose the mucosa and improve bladder neck preservation when beginning the anastomosis.

FIGURE 7 Dissection and preservation of bladder neck after dissection of the anterior prostate posteriorly off the detrusor apron.



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5. Dorsal vascular complex (Santorini plexus) control and prostatectomy

The isolation bluntly advances on the anterior surface of the prostate, carefully avoiding opening the dorsal vascular complex (DVC, the Santorini plexus) whenever it is oncologically safe. Since more than one-third of the striated urethral sphincter's surface area is located ventrally to the DVC, sparing the DVC reduces the damage to the urethral sphincter and may allow for an earlier continence recovery.[55,56] In the case of locally advanced anterior prostate cancer, an extrafascial dissection usually implies a partial or complete resection of the Santorini plexus.[57] The apex is isolated, and the urethra is sectioned (**FIGURE 8**).

6. Urethrovesical anastomosis

The urethrovesical anastomosis begins at 12 o'clock to the bladder neck and urethra using two separate 3-0 barbed stitches, securing the anterior anastomosis, in contrast to 6 o'clock during standard robotic radical prostatectomy (S-RARP), which can be disorienting early in the learning curve (**FIGURES 9 and 10**). The suture starts from the 12 o'clock position up to the 9 o'clock position on the left, while the other suture is taken from the 12 to 3 o'clock positions. The urethral catheter may be placed at this time to assist in the alignment and visualization of the bladder neck and posterior urethra. The right- and left-sided sutures are then carried out up to 6 o'clock positions. The anastomosis is checked for a leak with irrigation of saline into the bladder. Some of the authors

will then place a suprapubic catheter under direct laparoscopic visualization and, if there is no leak, remove the urethral catheter before extubating.[58,59]

FIGURE 8A and 8B After transecting the bladder neck, the plane is developed under the dorsal venous complex (A), and the apex and urethra are eventually identified and dissected (B).

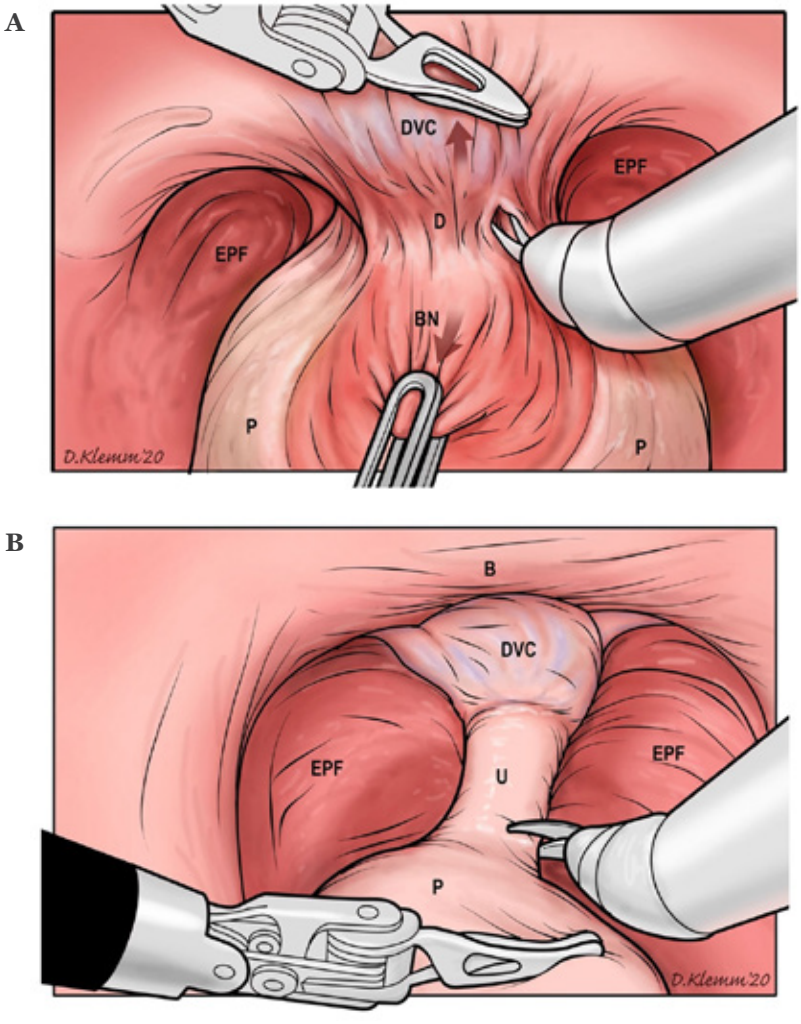

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FIGURE 9 Urethovesical anastomosis starts from the 12 o'clock position with two separate barbed sutures continuing to 6 o'clock, counterclockwise on the left side and clockwise.

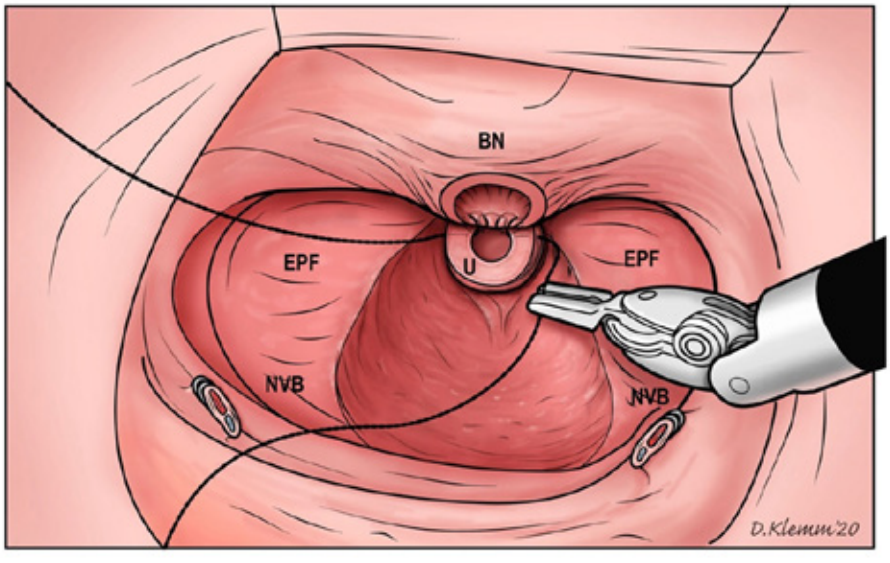

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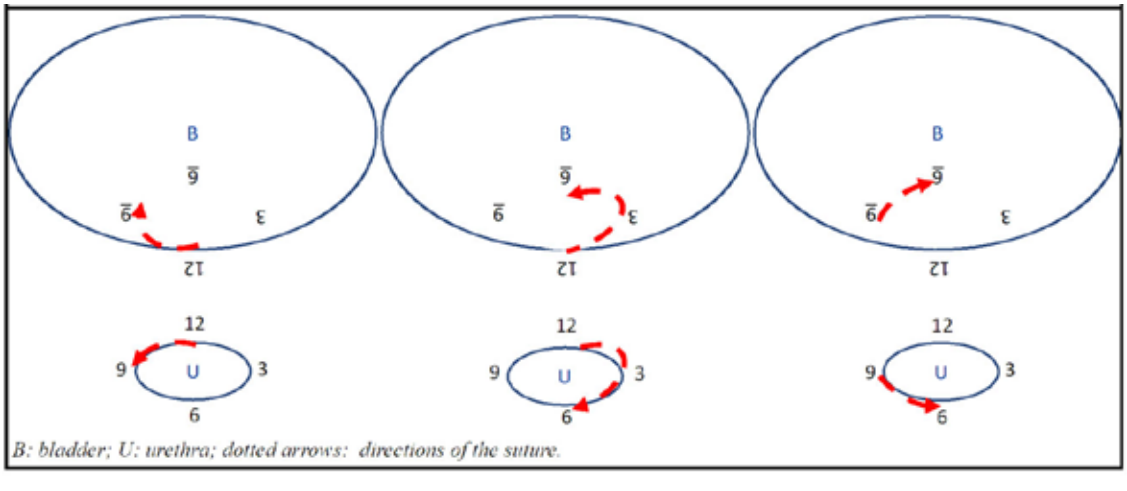
FIGURE 10 Scheme of the urethrovesical anastomosis



Sourceline: *Image courtesy of Antonio Galfano, MD.*

PFS-RARP outcomes

An increasing body of literature comparing S-RARP with PFS-RARP regarding surgical, oncologic, and functional outcomes has become available. Since 2019, such evidence has primarily been retrospective reports from prospective single-surgeon databases, with only one valid randomized trial by Dalela *et al.*[60] Outcomes have also been summarized within 10 meta-analyses.

Robust recent pooled data from more than 1,100 patients did not show significant differences between PFS-RARP and S-RARP regarding blood loss, operative time, complications, and hospital length of stay.[61] During the learning curve, the duration of the procedure and the complication rate consistently decreased from the 20th PFS-RARP, while a *plateau* seems to have been reached around the 40th PFS-RARP for experienced surgeons.[62]

Positive surgical margins (PSMs) represent an independent predictor of biochemical recurrence. Consequently, PSMs are an undesired surgical outcome whose real impact on long-term survival is still debatable.[63,64] O'Connor-Cordova *et al.* published the latest meta-analysis comparing PFS-RARP vs. S-RARP and PSMs.[65] Respectively, eight studies were included in the analyses on overall PSMs (n=1,276 patients), 11 studies in the analyses regarding PSMs in the pT2 stage (n=951 patients), and finally, 11 studies in the analyses regarding PSMs in the pT3 stage (n=648 patients). In all these scenarios, PFS-RARP did not reach the independent predictor status for increased PSMs, albeit a trend toward significance must be acknowledged. However, biases could be operational within such analyses. First, in 6 of 17 included studies, the rate of pT3-stage patients was consistently higher in the PFS-RARP group.[60,66–70] One may argue this could invariably undermine any conclusions on oncologic efficacy given the imbalance of cancer stages. Additionally, significant heterogeneity in surgical experience (i.e., high experience in S-RARP vs. initial or no expertise in PFS-RARP) characterized the majority of the studies,[71–74] including those performed in a prospective randomized fashion.[60,66,75] The learning curve is crucial when addressing PSMs in radical prostatectomy.[76] Previously, for both pT2 and pT3 stages, a significant decrease in PSMs was recorded after 100 procedures performed with the posterior approach.[77] Consequently, results concerning PSMs are controversial, and ambiguities exist. This means more robust conclusions will only be achieved once well-designed randomized clinical trials regarding PFS-RARP versus S-RARP are performed, such as the PARTIAL trial.[78]

The minimal surgical trauma and the enhanced preservation of all the anterior structures strongly related to the continence mechanism represent the technical pivot of the posterior approach. Preserving these structures may translate into better urinary continence at catheter removal and 3 and 12 months after surgery. Nonetheless, Rosenberg and colleagues, who produced a rigorous Cochrane Review in 2020,[79] defined the certainty of such evidence as low/moderate due to the shortage of prospective randomized data. Current literature reports rates of immediate continence recovery up to 70% and 1-year continence recovery up to 95%[60,67,73,75,80] following PFS-RARP.

Recently, several publications emphasized less favourable continence recovery after PFS-RARP in unique clinical settings. Specifically, in patients with D'Amico high-risk prostate cancer, immediate and 1-year continence recovery rates decreased to 53–66% and 84–89%, respectively.[81,82] Even worse outcomes were recorded in patients with a personal history of previous surgery for benign prostate obstruction[83] and very large glandular volumes.[84] Nevertheless, outcomes in men undergoing S-RARP in these scenarios remained worse even in expert hands.[85] Finally, according to the currently available evidence, adjuvant radiotherapy was not independently related to unfavourable continence recovery.[86]

Currently, scarce evidence exists regarding sexual function recovery after PFS-RARP. Only four studies included erectile function after radical prostatectomy among the outcomes of interest [67,71,74,80]. Despite heterogeneity in scoring systems (e.g., SHIM, IIEF-5, EPIC score), all concluded the absence of substantial difference in potency recovery after PFS-RARP versus standard anterior RARP. Recently, Egan and colleagues recorded 66% of patients achieving satisfactory intercourses after PFS-RARP. When analyzing the subset of men with high-risk prostate cancer, rates of potency recovery after PFS-RARP were 43 and 50% at, respectively, 1 and 2 years from surgery.[80,82] It is important to note that current anatomical data does not support the benefit of erectile function recovery from the preservation of meaningful nerves located laterally or anterior to the prostate, suggesting that the observed clinical outcomes may not be directly attributable to nerve preservation techniques used in PFS-RARP.

Intraoperative complications represent one of the most underreported outcomes in surgical literature. Albeit relatively infrequent, intraoperative complications may significantly impact the patient's postoperative course and the patient's and surgeon's psychological well-being.[87,88] At the Niguarda Hospital of Milan (Italy), of the nearly 2,000 procedures performed during the past decade, 40 (2.2%) were burdened by intraoperative adverse events. Such events have been graded according to the European Association of Urology recommended system (EAUiaiC),[89] and in agreement with the quality criteria for accurate and comprehensive reporting of intraoperative adverse events purposed by the Intraoperative Complications Assessment and Reporting with Universal Standards (ICARUS) Global Surgical Collaboration Project.[90] Detailed description and classification of the intraoperative adverse events are reported in **TABLE 1**.

TABLE 1 Intraoperative PFS-RARP Complications at ASST Grande Ospedale Metropolitano Niguarda of Milan, Italy

Event	Description	Grade	n (%)
Anesthetic	Desaturation during pneumoperitoneum induction requiring open conversion	Grade 2	1 (2.5)
	Hemodynamic instability during ePLND (only one side performed)	Grade 4b	1 (2.5)
Access and trocar placement-related	Epigastric artery injury	Grade 1	5 (12.5)
Injury of intra-abdominal organs	Bladder Injury	Grade 1	5 (12.5)
	Sigmoid injury managed with immediate repair	Grade 1	4 (10)
	Small bowel injury managed with running suture	Grade 1	5 (12.5)
	Small bowel injury requiring resection and anastomosis	Grade 2	1 (2.5)
Vascular injury	Minor internal iliac artery injury	Grade 1	3 (7.5)
	Internal iliac artery injury	Grade 3	2 (5)
	Gluteal vein injury	Grade 1	2 (5)
	Iliac vein injuries	Grade 1	2 (5)
Nerve injury	Obturator nerve injury	Grade 2	3 (7.5)
Ureteric injury	Ureteral injury managed with running suture and ureteral stenting	Grade 2	2 (5)
	Ureteral injury with anastomosis/reimplantation	Grade 4a	2 (5)
Others	Needle loss	Grade 1	1 (2.5)
	Robot malfunction	Grade 4b	1 (2.5)

Abbreviation: ePLND, extended pelvic lymph node dissection.

Anterior pelvic fascia sparing: Hood technique

Despite better PFS-RARP immediate urinary continence outcomes after catheter removal, many surgeons continue to prefer robotic prostatectomy using the standard anterior technique. This preference may be due to a perception that the standard anterior approach is more versatile, as it allows more working space and a familiar vantage point of the bladder, including the ureteral orifices and median lobe, enables detailed apical dissection and simultaneous lymph node dissection, and permits better access to the periprostatic space for incremental nerve sparing without entering the rectovesical pouch.[91] Learning from the anatomical lessons of PFS-RARP, several surgeons have developed new surgical strategies to spare the puboprostatic ligaments, endopelvic fascia, and other anterior structures during anterior RARP.[92–94] The anterior approach is similar to S-RARP and was first described by Tewari *et al.* as the "Hood Technique," or anterior pelvic fascia sparing (APFS) robotic prostatectomy. In this approach, the detrusor apron, arcus tendinous, puboprostatic ligament, anterior vessels, and some detrusor muscle fibres are preserved after prostate removal.[93]

APFS was also specifically developed to improve the return of urinary continence after radical prostatectomy, which depends both on bladder function and the urethral sphincter complex.[95] Retrospective studies associated factors such as the length of the membranous urethra, the bladder neck angle, the support and vascularity of the vesicourethral junction, overall bladder compliance, the coordinated contraction of the sphincter complex, and the preservation of the periprostatic nerves with the return of urinary continence.[96,97] The puboprostatic ligamentous complex includes the puboprostatic ligaments, arcus tendinous, and puboperinealis muscle. The detrusor apron consists of three layers of smooth muscle that circumferentially cover the bladder. The detrusor apron's longitudinal layer on the prostate's anterior surface joins the puboprostatic ligaments, creating a sling continence mechanism.[47] Thus, like PFS-RARP, APRFS technically maintains major structures critical to the support and innervation of the sphincter complex needed for continence while taking a more familiar anterior approach to the prostate.

Although the exact anatomy of the periprostatic nerves has not been defined, an innervation system has been proposed, consisting of the proximal neurovascular plate or pelvic plexus in the rectovesical pouch, the predominant neurovascular bundle, and the accessory neural pathways. The pelvic plexus includes the sympathetic fibres of the hypogastric nerve, parasympathetic fibres of the pelvic splanchnic nerve, and somatic fibres from the S2-S4 sacral spinal cord, all of which play vital roles in the autonomic and somatic innervation of the urethral sphincter. Similar to the RS-RARP technique, the APFS technique allows the preservation of the majority of these nerves that run posterolaterally; it additionally allows preservation of the detrusor apron and puboprostatic ligamentous complex, which cover the prostate anterolaterally.[91]

APFS surgical technique

1. Patient positioning and port placement

The patient is placed in steep Trendelenberg position. Pneumoperitoneum is induced, and five laparoscopic trocars are placed as described in our standard approach.[98] A da Vinci SP® system may also be utilized, wherein we use an extraperitoneal approach to perform APFS. This approach will be discussed later in the chapter.

2. Development of the retropubic space

The anterior approach also enables an extraperitoneal approach, which is impossible with posterior PFS-RARP. The peritoneum is opened with an inverted U-shaped incision cephalad to the bladder, the same as during the traditional transperitoneal approach. Overlying fat tissues are removed with sharp and blunt dissection to expose the bladder and anterior prostate without exposing the puboprostatic ligaments.

3. Bladder neck dissection

The bladder neck is spared by early identification of the longitudinal fibres of the bladder neck as it coalesces to form the prostatic urethra. Fourth arm anterior tension on the posterior base of the prostate/median lobe, if present, facilitates completion of the posterior bladder neck incision to the fat that overlies the vas deferens and seminal vesicles.[22]

4. Vas deferens and seminal vesicle dissection

The vasa are individually identified and divided at a level at or below the midportion of the seminal vesicles. A Prograsp in the fourth arm is gently lifted to lift the seminal vesicle, and each seminal vesicle is dissected to the tip of the seminal vesicle. Arterial blood supply flows inferiorly and laterally, and these arteries are ligated with bipolar cautery and sharply divided. Dissection continues to the base of the prostate. The seminal vesicles are then lifted anteriorly with the vas deferens, and a posterior plane is developed by incising Denovilliers' fascia and continuing dissection toward the apex. The posterior plane is lateralized until the veins of the neurovascular bundles are encountered.[99]

5. Lateral pedicles

Using bipolar cautery and sharp dissection, the lateral pedicles are slowly divided stepwise. The dissection is continued until the capsule of the prostate is encountered on the base of the prostate. This defines the nerve-sparing dissection plan, which is then performed in an antegrade fashion.[98]

6. Anterior pelvic fascia sparing

The detrusor apron is incised just proximal to the anterior base of the prostate, where bladder neck dissection was performed. The contour of the prostate laterally is used to gauge the depth of this incision. Once the curved, convex contour of the prostate is identified anteriorly, this plan is dissected distally, undermining the arterial component of the dorsal vascular complex. Often, venous sinuses comprising the dorsal vascular complex are entered, and the posterior component of the sinuses may be left on the anterior curve of the prostate as a landmark. If the venous bleeding is profuse, we suture ligate these sinuses with 3-0 vicryl in a mattress fashion.

7. Circumferential apical dissection

The prostate is retracted to one side, and anterolateral dissection is performed with preservation of the urethral sphincter; this is then repeated on the contralateral side. Care is taken to release the neurovascular bundle at the prostate apex prior to this dissection.

8. Dorsal venous complex control

Once the posterior urethra and apical dissections are complete, the prostate and lymph nodes are placed in the specimen bag, and mattress sutures are placed to achieve hemostasis of the dorsal vascular complex components.

9. Urethrovesical anastomosis

The authors prefer to place a 3-0 vicryl suture on the inside of the bladder neck to bring the bladder to the urethra stump. Next, a double-armed 3-0 quill suture is used to complete the anastomosis in a posterior to anterior direction. After tying the two ends together, the bladder is filled to 180 mL to ensure a water-tight anastomosis. The working catheter is then exchanged for the final catheter.

APFS outcomes

Tewari *et al*. described the outcomes of this technique in 330 consecutive patients. Patients with anterior prostate lesions on biopsy or magnetic resonance imaging (MRI) were excluded from the Hood technique, as well as those with prior prostate cancer therapy. Patients were followed for 2 years with continence defined as entirely pad-free. In the 300 patients who underwent the APFS technique, continence was 21%, 36%, 83%, 88%, 91%, and 94% at 1, 2, 4, 6, 12, and 24 weeks following catheter removal, respectively.[93] The 30 patients who underwent RARP without APFS had respective continence rates of 12%, 22%, 76%, 85%, 86%, and 88%, highlighting the earlier return of urinary continence with this technique.[100] The positive surgical margin rate was 6% and 14% in the APFS versus standard groups, though the authors neither characterized the margin locations, specifically anterior margins, nor conducted a multivariate statistical analysis comparing approaches. Additional research and analysis are needed to better characterize the early return of urinary function and ensure adequate cancer control with the Hood/APFS technique. Additionally, there has been no direct comparison of APFS with PFS-RARP as of publication.

Single-Port Robotic Assisted Radical Prostatectomy (SP-RARP)

The standard robotic radical prostatectomy (S-RARP) is considered the gold standard for the management of clinically localized prostate cancer. With the procedure traditionally performed using a multiport (MP) system, the recent introduction of the novel purpose-built Single-Port (SP) robotic platform (Intuitive Surgical; Sunnyvale, California) has opened a new frontier in the minimally invasive surgical landscape of prostate cancer. Of note, the SP platform offered several unique features, including the narrow profile of the single robotic arm with four instrument drives that can simultaneously accommodate one double-jointed endoscopic camera and three robotic instruments with seven degrees of freedom, which allows for 360-degree anatomic access from a single pivot point. The movements of the endoscopic camera and the robotic instruments resemble the human elbow and wrist movements, which aid intracorporeal triangulation and reduce the risk of instrument clashing.[101–104]

The SP platform's maneuverability and ergonomics have been proven helpful, especially when performing surgeries in shallow and more confined surgical working spaces. Hence, in addition to its utility for conventional RARP techniques, such as transperitoneal, extraperitoneal, and Retzius-sparing approaches, the SP platform has provided the unique opportunity for surgeons to develop more regionalized surgical approaches, with examples including transperineal and transvesical SP-RARP. [105–108]

Several benefits of the transvesical approach have been recently demonstrated, including improved patient comfort, increasing rates of opioid-sparing same-day discharges, earlier Foley catheter removal, and earlier return of urinary continence.[109,110] Furthermore, with a direct percutaneous entry into the bladder, the procedure has been an alternative in patients with previous abdominal surgeries. The supine patient positioning has also allowed transvesical SP-RARP to be completed with patients awake under regional anesthesia.[111] This section

highlights the clinical experience and several notable RARP approaches that can be safely and effectively performed using the SP robotic platform.

Preclinical and early clinical experience

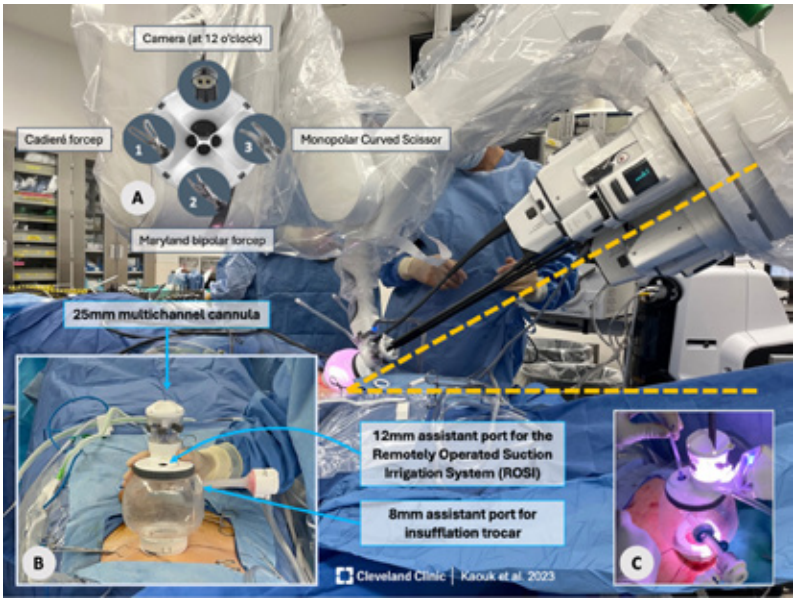
The first human clinical trial of the SP platform was performed by Kaouk *et al.* in 2010 using the da Vinci SP 999 (Intuitive Surgical; Sunnyvale, CA, USA) with successful completions of 19 cases, including eleven radical prostatectomies that were performed transperitoneally via a transumbilical incision.[102] Following the United States Food and Drug Administration (FDA) approval in 2018, the first clinical experience of SP-RARP was introduced by Kaouk *et al.*, which included two cases of extraperitoneal SP-RARP with bilateral pelvic lymph node dissection (BPLND). Both cases were completed successfully without any intraoperative complication through a single 25-mm periumbilical incision through which the GelPOINT Mini Advanced Access Platform was secured (Applied Medical, Rancho Santa Margarita, CA, USA).[103]

Following the initial experience, the surgical toolbox for the SP platform has been expanded. In place of the GelPOINT® Mini Advanced Access Platform, a purpose-built SP Access Kit (Intuitive Surgical, Sunnyvale, California) is routinely used. The SP Access Kit consists of an inner wound retractor that is connected to the bubble chamber, which houses the 25-mm multichannel cannula for the SP instruments along with two additional working ports—one 12-mm assistant port adjacent to the multichannel cannula that is commonly used for the Remotely Operated Suction Irrigation (ROSI) system (Vascular Technology Inc., Nashua, New Hampshire) and another through the side of the bubble chamber for insufflation (**FIGURES 11 and 12**). The two assistant ports can accommodate various laparoscopic instruments as clinically indicated, including a stapler and tenaculum. Of note, the bubble chamber design of the SP Access Kit facilitates the floating docking technique, which provides a creative solution to address the required 10-cm working distance for the SP instruments as well as improving the flexibility and range by up to 360 degrees, especially in a narrow and shallow surgical working space **(FIGURE 12)**.[112]

FIGURE 11 OR setup for single-port robotic assisted radical prostatectomy.

Sourceline: *Photo courtesy of Jihad Kaouk, MD.*

FIGURE 12 SP robot configuration at docking.



Abbreviation: SP, single port.
Sourceline: *Photo courtesy of Jihad Kaouk, MD.*.

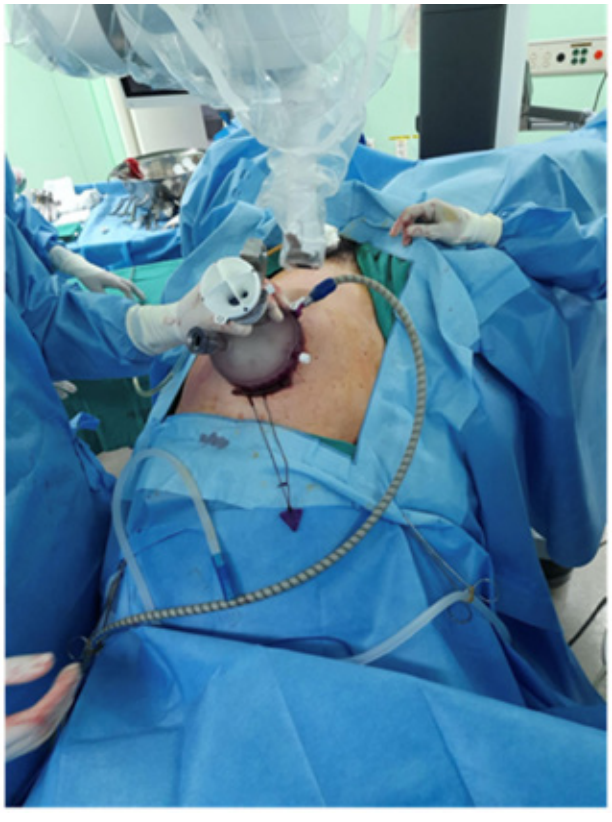
Extraperitoneal SP-RARP technique

Extraperitoneal SP-RARP is routinely performed with the patients positioned supine and with the SP Access Kit inserted via a 3-4-cm midline infraumbilical position at approximately 2 cm below the umbilicus. A retroperitoneal expanding balloon can be used to open the extraperitoneal space prior to the placement of the SP Access Kit. An additional assistant port is usually not required but can be placed depending on surgeon preference or clinical circumstances. Once the instruments are inserted, the radical prostatectomy can be completed by first mobilizing the bladder from the anterior abdominal wall, followed by exposure of the endopelvic fascia, ligation of the dorsal venous complex, and dissection of the anterior bladder neck. The base of the prostate can then be carefully dissected from the posterior bladder neck until the vas deferens and seminal vesicles are exposed and dissected. Afterward, the prostatic pedicles can be transected, the urethra can be divided just distal to the prostatic apex, and the prostate can be freed from its remaining attachments. Vesicourethral anastomosis is subsequently completed using two unidirectional V-loc sutures. If lymphadenectomy is required, the SP platform can be used to perform all the dissection steps through the same incision without repositioning or redocking.[92,113] To reduce the risk for postoperative lymphocele, a small peritonotomy can be made at the end of the procedure prior to fascial closure.[114] The outcomes of extraperitoneal SP-RARP have been previously demonstrated. When compared to the MP approach, extraperitoneal SP-RARP contributes to a significantly reduced length of stay (median, SP 4.3 hours vs. MP 26.1 hours; $p<0.001$) and opioid utilization on discharge (SP 35% vs. MP 87%; $p<0.001$), all while maintaining comparable oncological and functional outcomes.[113]

Transperitoneal single-port PFS-RARP

A 3-cm incision is made 15 cm cephalad to the pubic symphysis at the level of the periumbilicus. Transperitoneal access is made using the Hasson open technique, and the incision is fitted with an Alexis O Wound Protector-Retractor (Applied Medical; Rancho Santa Margarita, CA, USA). The da Vinci SP cannula with a 2.5-cm inner diameter is fitted into the GelPOINT Mini Advanced Access Platform at the 6 o'clock position and a 1.2-cm cannula in the 10 o'clock position, as in **FIGURE 13**. After securing the trocar, the patient is placed in the usual Trendelenburg position, with arms tucked at the sides and pressure points padded. The da Vinci SP cannula can be rotated to position the camera at each of the four quadrants (with the boom rotating and docking to match the camera position); the authors prefer the camera down position, which places the camera at 6 o'clock position anatomically, and as the inferior-most arm in the intraoperative view. For a right-handed surgeon, all three SP robotic arms are inserted through the SP cannula as follows: monopolar curved scissors on the right, Maryland bipolar forceps on the left, and Cadiere forceps superiorly with bedside assistance at the patient's left side.

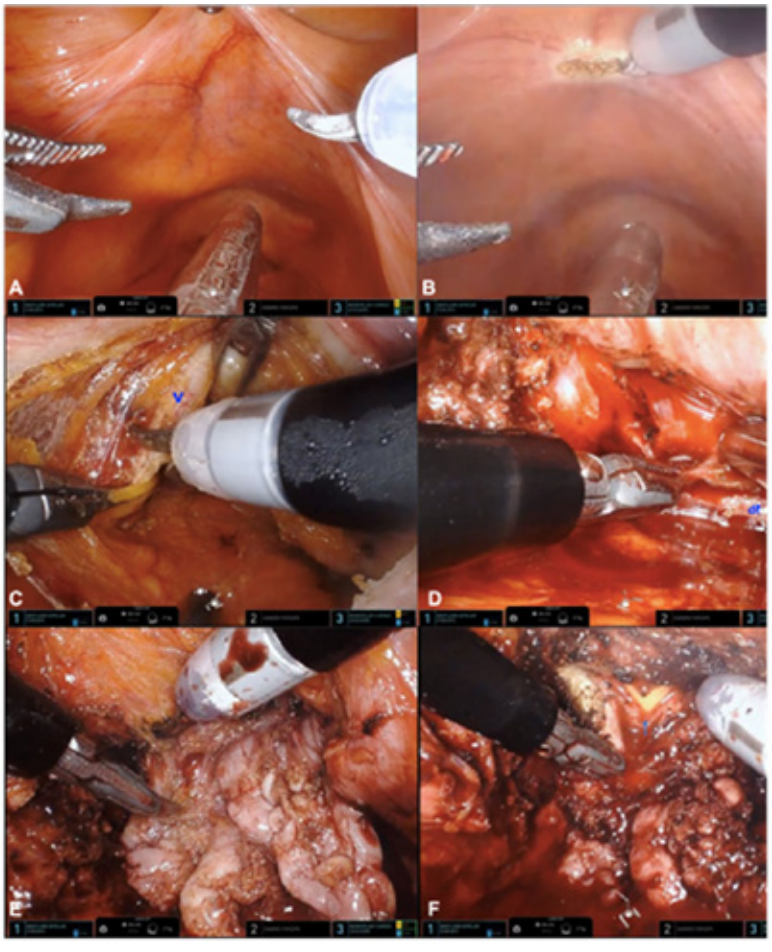
FIGURE 13 The da Vinci SP cannula with a 2.5-cm inner diameter is fitted into the GelPOINT Access Platform at the 6 o'clock position and a 1.2-cm cannula in the 10 o'clock position.



Sourceline: *Photo courtesy of Koon Rha, MD.*

Only minor changes are needed to the original multiport approach once the robot is docked. The technique for PFS-RARP is highly standardized and described stepwise below and in **FIGURES 14 and 15**.

FIGURE 14 Steps of single-port PFS-RARP through seminal vesicle and vas dissection.

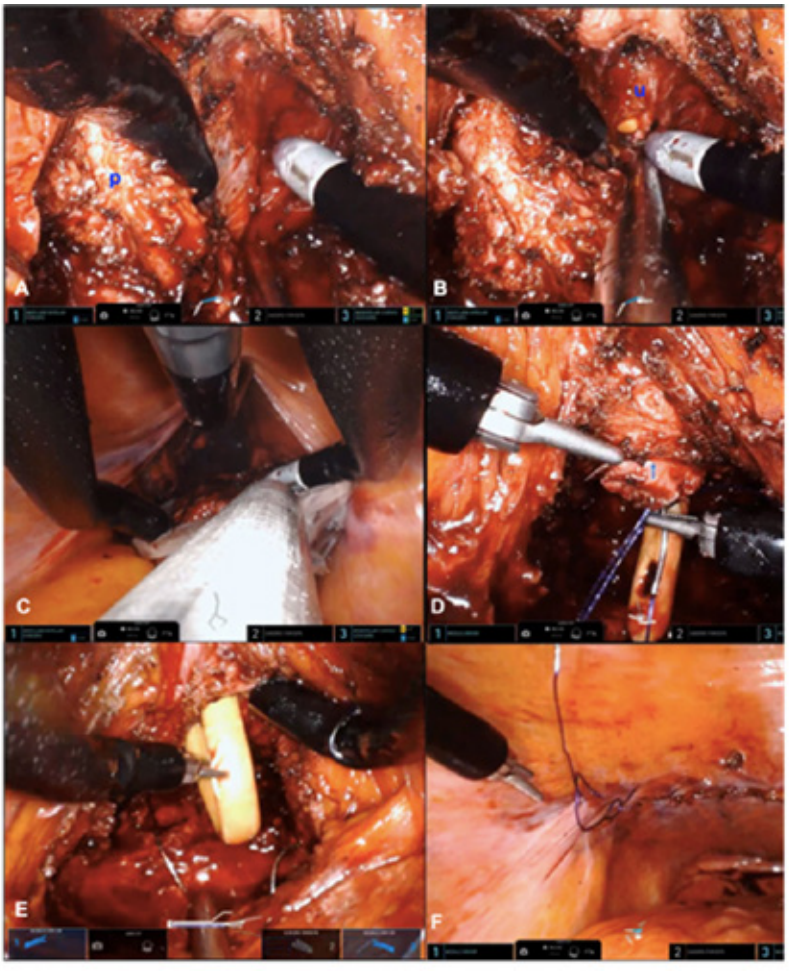


Abbreviation: PFS-RARP, pelvic fascia sparing, or Retzius-sparing, robotic-assisted radical prostatectomy.
Sourceline: *Photos courtesy of Koon Rha, MD.*

The grasper lifts the peritoneum covering the bladder (**FIGURE 14A**). The peritoneum is incised 4 cm above the reflection of the Douglas space (**FIGURE 14B**), higher than traditionally described. The authors have discovered that this creates more room behind the prostate and stops the back wall of the bladder from folding and blocking the view. Dissection is continued, leaving a thin peritoneal fold that overly overlies the vas and seminal vesicles. The vasa are coagulated and ligated at their take-off laterally (**FIGURE 14C**). Upon freeing each vas, the grasper exerts traction in an upward and contralateral direction; the seminal vesicles are freed off

the surrounding tissue using a combination of titanium clips, minimal diathermy, and sharp dissection. The Denonvilliers' fascia is peeled off from the posterolateral surface of the prostate (**FIGURE 14D**), and dissection proceeds in an antegrade fashion. Diathermy is avoided as posterior dissection proceeds toward the apex of the prostate. After meticulous posterior dissection, the vesicoprostatic junction is identified. The starting point of this dissection is the anterior surface and base of the seminal vesicles (**FIGURE 14E**). The bladder is entered, and the Foley catheter is identified (**FIGURE 14F**), ensuring adequate surgical margins.

FIGURE 15 Steps of SP PFS-RARP—nerve sparing through anastomosis and peritoneal closure.



Abbreviation: SP PFS-RARP, single-port pelvic fascia sparing, or Retzius-sparing, robotic-assisted radical prostatectomy.
Sourceline: *Photos courtesy of Koon Rha, MD.*

Attention is brought to the lateral prostate (**FIGURE 15A**), where bilateral nerve-sparing was done for all patients in this series, maintaining athermic dissection in the interfascial plane until the apex of the prostate and, subsequently, the urethra is reached. The urethra is cut, and the Foley catheter is found and pulled back (**FIGURE 15B**). Urethral transection is completed using sharp dissection. The prostate is now expected to be mobile with few remaining attachments, most commonly to the posterior Denonvilliers' fascia. The prostate is rolled off the prostatic fossa, which combines effective traction with sharp dissection. The specimen bag is inserted, and the prostate is secured within (**FIGURE 15C**). Diligent hemostasis of the prostatic fossa is accomplished prior to suturing. The authors use a polydioxanone barbed 2-0 suture with a triangular stopper for a knotless first bite, Monofix®-PDO (Polydioxanone) (Samyang Biopharmaceuticals Corp, Seoul, South Korea) for the urethrovesical anastomosis. The anastomosis is done anteriorly in a single-layer running fashion with two threads (one running clockwise to the right and one counterclockwise to the left), first securing the anterior bladder (**FIGURE 15D**) to the anterior urethra. After the anterior sutures are in place, the catheter is inserted up to the bladder to serve as a guide in keeping the lumen open for the posterior stitches. (**FIGURE 15E**), after which the posterior sutures are completed. The posterior urethrovesical sutures are placed inside-to-outside to avoid inadvertent injury to the catheter. The anastomosis is secured with a Lapra-Ty clip on each suture or by knotting both ends together.

The peritoneal incision is closed in a running fashion (**FIGURE 15F**). The surgeon guides a drain into the assistant port into the pelvis. The instruments are removed, and the robot is undocked. The access platform is removed; the drain is exteriorized at a separate point beside the incision. The fascia is repaired in an interrupted fashion, and the wound is closed with subcuticular absorbable sutures.

Transperineal SP-RARP

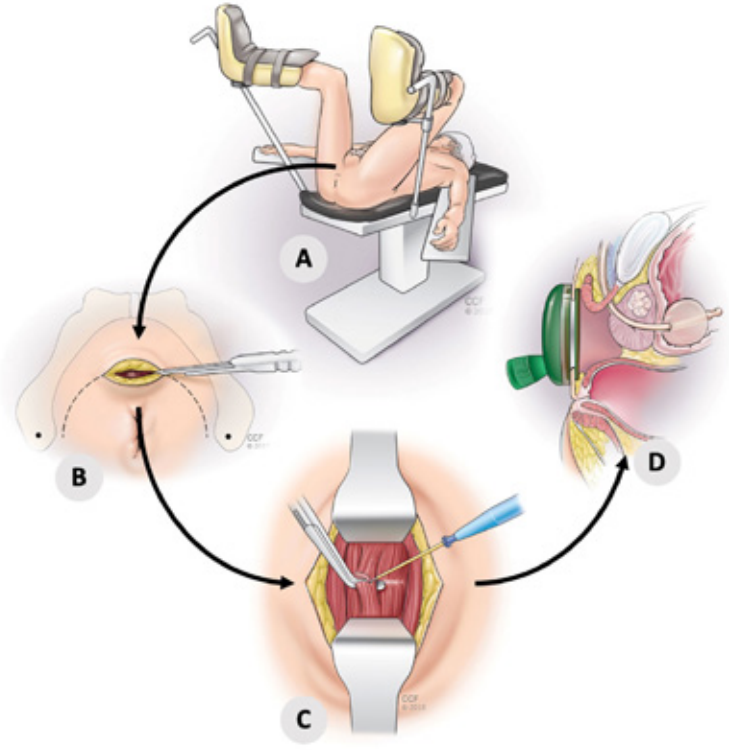
The surgical steps for Transperineal SP-RARP were first described by Lenfant *et al.* With the patient positioned in a dorsal lithotomy position with 10° Trendelenburg, a semilunar incision was made between the ischial tuberosity, followed by the dissection of the subcutaneous tissue and rectourethralis muscle (**FIGURE 16**). Following the docking of the SP robot, dissections were commenced posteriorly. Contrary to other radical prostatectomy approaches, the prostatic apex and urethra were dissected first, while bladder neck dissection was completed last. Although Transperineal SP-RARP provides some advantages as alternative surgical access in patients with previous abdominal surgeries or previous bladder injuries, the relatively steep learning curve of the surgery remains the most significant deterrent toward broader adoption of the technique.[106]

Transvesical SP-RARP (TV-RARP)

Further regionalization of RARP was demonstrated by Kaouk *et al.* with the introduction of the transvesical single-port robot-assisted robotic-assisted radical prostatectomy (TV-RARP) in 2020. Like the extraperitoneal technique, patients are positioned supine. Percutaneous bladder access was obtained through a suprapubic incision. A confirmatory needle aspirate for urine was done prior to performing the cystotomy. With TV SP-RARP, insufflation is regionalized to involve only the bladder. Insufflation should be kept below 12 mmHg to minimize the risk for air embolism. Dissection steps were commenced by first circumferentially marking the vesicoprostatic junction, followed by posterior dissection, dissections of the seminal vesicle and vas deferens,

lateral dissection including for the neurovascular bundle preservation, anterior dissection, apical dissection, and urethral transection (**FIGURE 17**). The specimen is removed from the bladder and placed within the bubble chamber of the SP Access Kit. The vesicourethral anastomosis can then be completed using two unidirectional barbed sutures in a continuous, semicircular manner. The first suture is used for left-sided anastomosis in a clockwise fashion from the 5 o'clock position, while the second suture runs counter-clockwise for right-sided anastomosis.[114] All surgical steps can be completed under direct vision from within the bladder without disrupting the supporting structures of the bladder and the extraperitoneal space.[105,109] The cystotomy and the surgical incision site are subsequently closed in layers.

FIGURE 16 During transperineal SP-RARP, the patient is positioned in a dorsal lithotomy position with 10° Trendelenburg, a semilunar incision was made between the ischial tuberosity, followed by the dissection of the subcutaneous tissue and rectourethralis muscle.

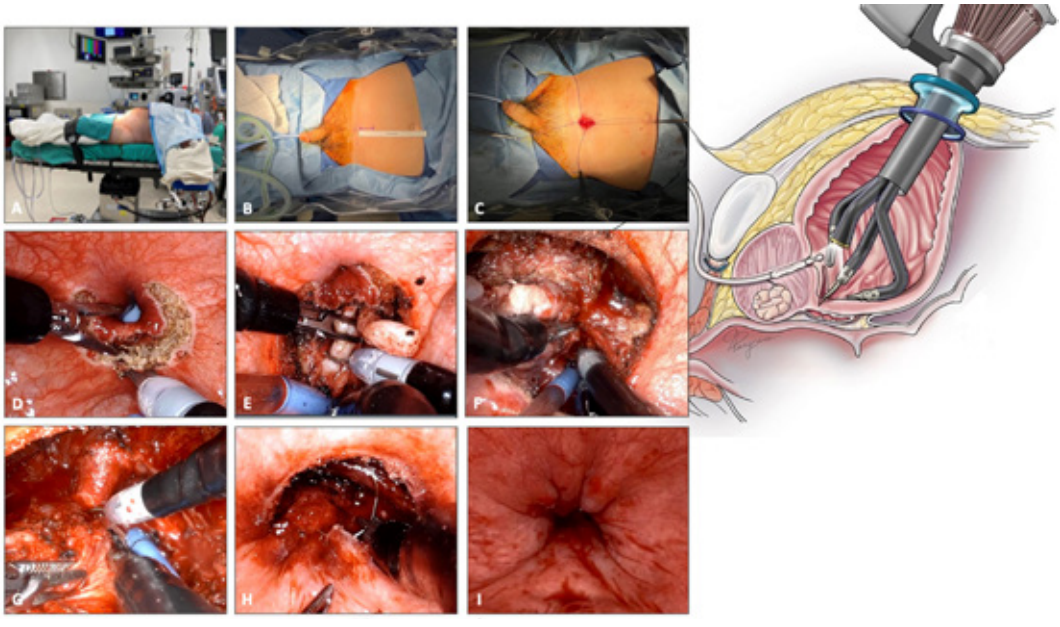


Abbreviation: SP-RARP, single-port robotic radical prostatectomy.
Sourceline: *Photo courtesy of Jihad Kaouk, MD.*

Like the extraperitoneal approach, TV-RARP offers significant perioperative benefits with a reported median length of stay of 5 hours and a 91% rate of opioid-sparing discharges. In addition, by ensuring the quality of the anastomosis with direct visualization from within the bladder, the postoperative urethral catheter may also be safely removed within 3–4 days in most cases.[109,110] One of the most important benefits of the TV-RARP was

earlier return of urinary continence, with 47% achieving urinary continence within 3 days of Foley catheter removal. The percentage of continent patients subsequently increases to 66%, 77%, 93%, and 96% in 6 weeks, 3 months, 6 months, and 1 year, respectively (**FIGURE 18**).

FIGURE 17 Illustrated surgical steps of TV-RARP

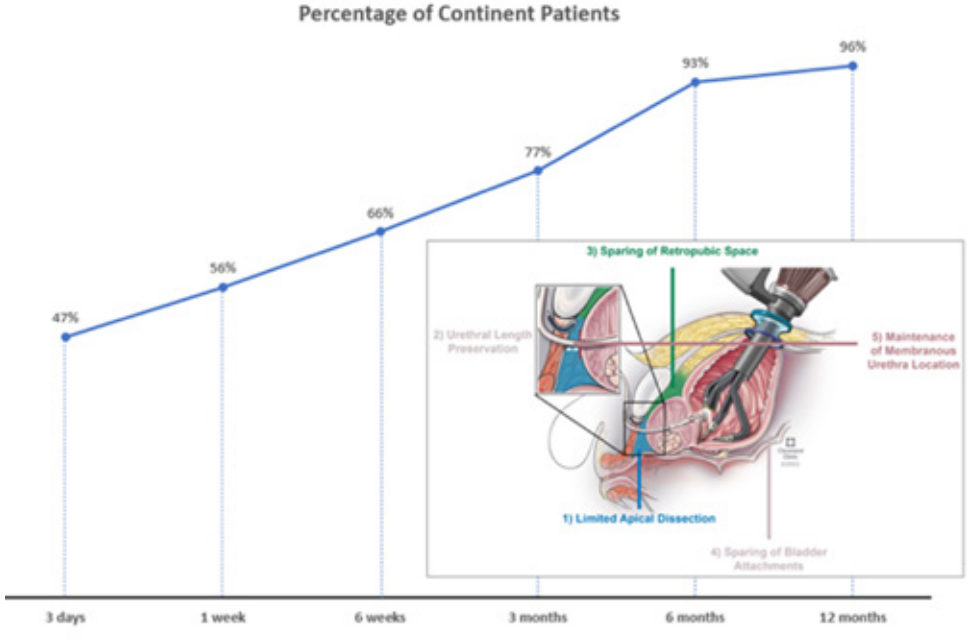


Abbreviation: TV-RARP, transvesical single-port robot-assisted robotic-assisted radical prostatectomy.
Sourceline: *Photo courtesy of Jihad Kaouk, MD.*

The significantly improved continence outcomes, especially compared to multiport RARP, may be due to several anatomical factors. Of note, TV-RARP spares the retropubic space, also allowing for maximal preservation of urethral length in addition to the anterior bladder attachments that hold the bladder and membranous urethra in their anatomical positions within the pelvis.[100,115]

As part of the initial experience, the selection criteria for TV-RARP included patients with low- to intermediate-risk prostate cancer and with prostate volumes of ≤ 80 mL.[109] With the expansion of the SP toolbox and technical refinements, TV-RARP has since been performed on larger prostate glands of up to 150 cc. The oncological outcomes of the group were favourable, with positive surgical margins being identified in 11% and 12-month biochemical recurrence noted in 3 patients. When clinically indicated, lymph node dissection can also be performed during TV-RARP following the removal of prostate specimens by turning the SP instruments laterally on the prostatic fossa and continuing the dissection toward the obturator lymph nodes. Alternatively, the inner ring of the SP Access Kit can be withdrawn from the bladder and kept beneath the rectus muscle to complete the BPLND via an extraperitoneal approach.

FIGURE 18 TV-RARP continence outcomes over time



Abbreviation: TV-RARP, transvesical single-port robot-assisted robotic-assisted radical prostatectomy.
Sourceline: *Photo courtesy of Jihad Kaouk, MD.*

The introduction of the TV-RARP extends beyond alternative surgical access for RARP. Instead, it alters the landscape of the contemporary surgical management of prostate cancer, especially in terms of our patient selection. Of note, the regionalized, direct percutaneous intravesical entry allows for radical prostatectomy to be pursued in patients where conventional techniques may either be challenging or contraindicated, such as in patients with multiple previous abdominal surgeries or a frozen pelvis. Recently, Ferguson *et al.* reported the outcomes of 33 patients who underwent TV-RARP.[116] Inclusion criteria included multiple abdominal surgeries performed through an open laparotomy, including ileoanal anastomosis (J-Pouch), history of ileostomy or colostomy, and open bowel resections. All procedures were completed successfully without complications. Immediate urinary continence was achieved in 30%, and 82% and 92% reported urinary continence in 6 and 12 months, respectively. Regarding oncological outcomes, data is limited, with PSM in 39% and biochemical recurrence in 11% with only 6 months of median follow-up.

With regards to perioperative morbidity, a recent publication from the Single-Port Advanced Research Consortium (SPARC) has highlighted the relatively low risk for perioperative complications and 90-day risk for hospital readmission associated with three main SP-RARP approaches that were comparable to previous reports on various MP techniques. When compared with the transperitoneal and extraperitoneal approaches, TV-RARP was found to have a significantly lower rate of significant complications of Clavien-Dindo grades ≥ 3a

(transperitoneal 3.7% vs. extraperitoneal 4.1% vs. transvesical 2%; $p<0.05$). Furthermore, the more regionalized, peritoneal-sparing approach has also been associated with a reduced risk for non-urological complications (transperitoneal 8.2% vs. extraperitoneal 6.3% vs. transvesical 3.4%, $p<0.05$), including hernia. Hence, surgeons have been able to limit patient postoperative activity restrictions to only 2 weeks and thus allow for earlier return to their respective level of functioning.[114]

Single port: future directions

In a further attempt to customize surgical technique, especially in the era of focal therapy for prostate cancer, the TV-RARP can also be utilized to perform partial prostatectomy in patients with low-volume, clinically localized prostate cancer. The more targeted approach was conceptualized to provide additional benefits for maximum preservation of the neurovascular bundle, seminal vesicle, and ejaculatory ducts to improve outcomes further. The technique was first introduced by Kaouk *et al.*, which involves the patients positioned in a supine lithotomy position and with the assistance of an intraoperative transrectal ultrasound that was fused with preoperative MRI to identify the index lesion in real-time (Koelis Inc., Princeton, New Jersey, USA). Following the dissections, margin status can be assessed by performing an intraoperative frozen section prior to the completion of vesicourethral anastomosis.[117] Although early clinical experience demonstrates the procedure's feasibility, safety, and efficacy, further research remains necessary to evaluate the appropriate candidates and confirm the long-term oncological outcomes.

The growing armamentarium of RARP approaches necessitates further research to understand perioperative outcomes better, refine techniques, and improve the patient selection process. The Single-Port Advanced Research Consortium (SPARC) was established in 2018 to support the evolving field. The multi-institutional collaborative group now possessed the largest, prospectively maintained database with more than 2500 urological procedures completed with the SP platform. The continuing contribution from the group will be instrumental in validating the perioperative outcomes reported in the initial series and provide valuable insights into the long-term functional and oncological outcomes following various approaches of SP-RARP.

Robotic Prostatectomy in Unique Patient Populations

Renal transplant patients

Among the options for renal replacement therapy, kidney transplantation has long been the standard for the management of end-stage renal disease. The 10-year overall graft survival has improved with advances in transplantation techniques and post-transplantation care. In addition, 41% of recipients are 50–64 years old,[118] matching the age group for whom prostate cancer screening is most adopted. Given the chronic immunosuppression and associated comorbidities in this cohort, there is an increased potential for complications. Early detection of prostate cancer allows for timely intervention, which can prevent the progression of the disease and reduce the

need for more aggressive treatments that might exacerbate the patient's overall health condition. This proactive approach helps balance the need for regular screening and management of prostate cancer in kidney transplant recipients, potentially improving their overall outcomes and quality of life.

Various modalities of treatment of localized prostate cancer in renal transplant recipients (RTRs) have been studied and each modality comes with a consistent set of adverse events. Previous pelvic operation and possible past peritoneal dialysis make intraperitoneal pelvic surgery, both minimally invasive and open, higher risk. Various series have reported the feasibility of robot-assisted laparoscopic radical prostatectomy in RTR. The previous historical standard of perineal prostatectomy has been supplanted by newer, less invasive modalities that afford the same benefit of minimal manipulation to the graft or transplant ureter.

Salvage robotic prostatectomy

Salvage RP is an option for highly selected patients with local prostate cancer recurrence after external beam radiation therapy, brachytherapy, or cryotherapy in the absence of metastases.[119] Historically, salvage RP is an infrequently performed operation due to its notable surgical complexity and high complication rates, including rectal injury, incontinence, anastomotic stricture, high positive surgical margins, and biochemical recurrence rates. Recent data suggest that lower complication rates may be possible with robotic surgical techniques compared to historical data, making this a more viable option.[120,121]Despite reduced perioperative morbidity with the robotic approach, rates of urinary incontinence after salvage RARP remain as high as 30-40%.[120,122]

Using PFS-RARP in salvage cases has improved continence outcomes, especially in early return to continence.[74,80,99] Several groups have examined PFS-RARP in the salvage setting and found promising results. Kowalczyk *et al.* carried out a multicentre, retrospective study of patients who underwent salvage RARP with either standard or PFS approach and found that salvage PFS-RARP significantly reduced postoperative incontinence compared to salvage S-RARP, with 78.4% vs. 43.8% of men reporting 0-1 pad use per day, respectively. They also found that men undergoing salvage PFS-RARP had earlier return to continence (median 47 vs 180 days).[69] A similar study by Madi et al. showed that patients undergoing salvage PFS-RARP had significantly better immediate and long-term continence rates than salvage S-RARP patients. The rates of biochemical recurrence and positive surgical margins in both studies were not significantly different between the two groups.[123]

Given the current evidence, PFS-RARP is a safe option in the salvage setting for experienced robotic surgeons and may improve continence outcomes for these patients. However, more high-level evidence is needed to confirm the long-term oncologic outcomes and establish the superiority of one surgical technique over others.

Development of Alternative Robotic Platforms

The exponential increase in awareness and accessibility of robotic surgery is owed, in part, to the rise of novel robotic systems that aim to challenge the da Vinci monopoly. The expiry of certain critical patents held by Intuitive Surgical (Sunnyvale, California, USA) in 2019 was critical to the entry of market competition. These novel robotic systems and their many applications in various fields of specialty are discussed exhaustively elsewhere, and those approved for medical use and commercial sale are summarized in **TABLE 2**, along with referenced resources.[124,125] The systems with robotic prostatectomy applications and brief techniques used by each pioneering team are discussed below. It is important to note that most teams who worked on transitioning from da Vinci to the novel system were already experienced surgeons, having performed hundreds of robotic cases. In addition, extensive dry and wet laboratory training dedicated to the new systems was used before clinical use.

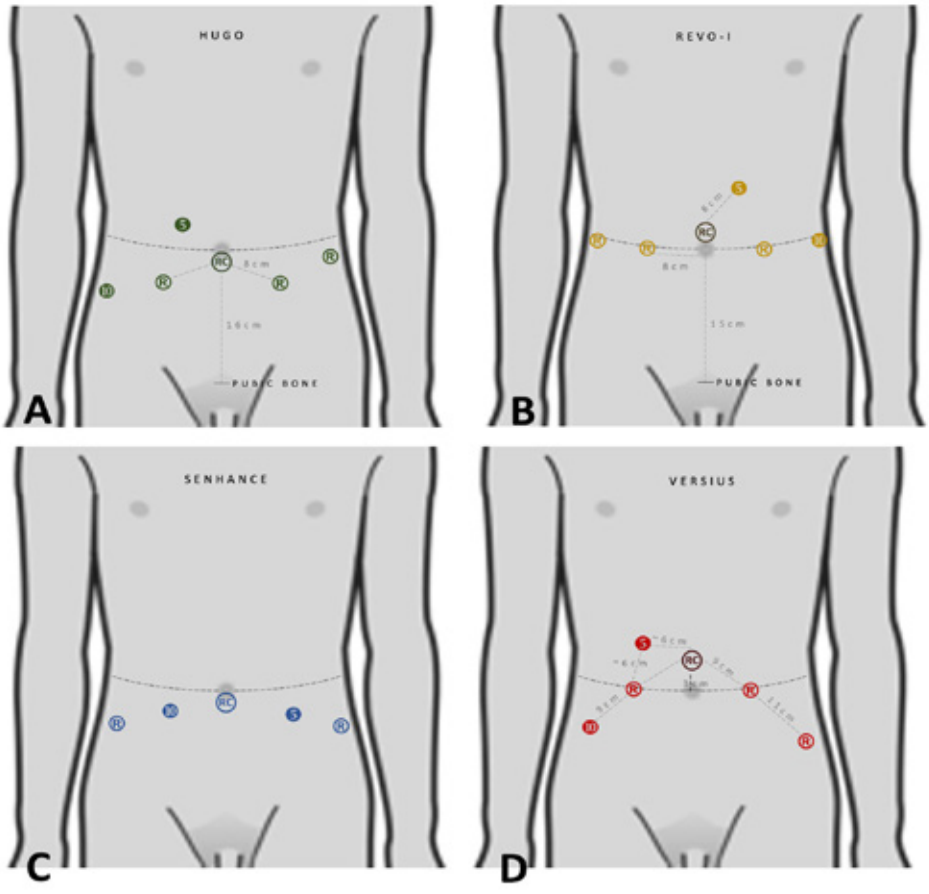
TABLE 2 Summary of Alternate Robotic Systems in Development

Robotic system	Console type	Hand grip type	Arm and instrument details	First regulatory approval and year granted
avatera® (avateramedical GmbH; Jena, Germany)	Closed system	Pincer / precision grip	Four arms, Single use 5-mm instruments with seven degrees of freedom[12]	CE Mark (Conformité Européenne) in 2019
hinotori™ (Medicaroid Corporation; Kobe, Japan)	Closed system	Pincer / precision grip	Four arms in a single boom	Japanese Ministry of Health, Labor, and Welfare in August 2020; Regulatory approval from Health Sciences Authority (HSA) in Singapore in September 2023
Hugo™ (Medtronic, Minneapolis, MN USA)	Open system	Pistol grip	Four arms, wristed instruments with seven degrees of freedom	
Revo-i (MeereCompany Inc; Seongnam, Republic of Korea)	Closed system	Pincer / precision grip	Four arms, wristed instruments with seven degrees of freedom	Korean Ministry of Food and Drug Safety in 2018
Senhance® (previously Telelap Alf-X; Asensus Surgical, formerly TransEnterix Surgical Inc; Morrisville, NC, USA)	Open Console	Pistol grip (controlling laparoscopic instruments)	Multiple modular arms, instrument reusability, no wristed degrees of freedom	Gastroenterology / Urology Use granted by the Food and Drug Administration in the USA in 2017
Versius® (CMR Surgical; Cambridge, UK)	Open console	Game controller grip, controlled entirely by the handheld unit with no foot pedal controls	Three modular arms, wristed 5-mm instruments with seven degrees of freedom	CE Mark in March 2019

Hugo™ robot-assisted surgery system (Medtronic; Minneapolis, MN, USA)

The Hugo RAS by Medtronic is a competitor to the traditional da Vinci system. However, Hugo significantly differs in using independent modular arms instead of the boom system used on the patient cart of the DaVinci. It comprises one system tower with a Valleylab™ (Medtronic; Minneapolis, MN, USA) electrosurgical generator, independent and modular arm carts, and an open surgeon console. The feature that sets it apart is a "pistol-like" hand controller, with the thumb and index finger moving the instruments and the trigger representing a clutch function. Each arm is docked independently 45–60 cm from the operative bed, keeping in mind the optimal docking angle for each arm to avoid collisions.[126] Most studies performed the RARP through a transperitoneal anterior approach with four robotic arms, one camera arm, and two assist ports (**FIGURE 19A**).

FIGURE 19 RARP port placement schemes for various alternative robotic platforms.



Abbreviation: RARP, robotic-assisted radical prostatectomy
Sourceline: *Photo courtesy of Koon Rha, MD.*

The earliest work on Hugo prostatectomy is from Belgium and Italy, with the most recent study done on 112 RARPs with ePLND by expert robotic surgeons. These patients included a cohort with extraprostatic extension, comprising one-third of the total study population; prostate volumes ranged from 32 through 55 grams with a PSA range of 5.8 through 10.7 ng/mL. At 3 months, 81% of patients were continent; early oncologic control was excellent, with PSA of < 0.1 ng/mL in 88% of patients. Comparative data on 542 patients has also come from the same team, with the Hugo RAS not performing differently from the da Vinci concerning operative time, estimated blood loss, PSM, complication rate, and continence recovery.[127]

Revo-i (Meerecompany, Seongnam, Republic of Korea)

The authors have experience with the Revo-i, participating in post-marketing studies at the Yonsei University Medical Center in Seoul, South Korea. The robot resembles the da Vinci Si, with the traditional four arms on a boom system and a closed surgeon console. Instruments are wristed with seven degrees of freedom. Numerous urologic procedures have been performed on the Revo-i. The first comparison study of a new robotic system to perform 66 PFS-RARP utilizing 33 on Revo-i vs. 33 on da Vinci showed no difference in blood loss, complication rate, PSM, and biochemical recurrence rate (BCR) at 6 months between a cohort of 33 Revo-i RARPs and 33 da Vinci–matched controls, although the study was underpowered to observe meaningful differences.[128] No significant statistical differences were noted in console time, suture time, and total operative time. Of note, this data is from an experienced surgeon and dedicated surgical team who performed approximately 3,000 RARPs with the da Vinci Si and Xi consoles before trialing the Revo-i.

Senhance® (Asensus Surgical, Morrisville, NC, USA)

With the seamless integration angle of "digital laparoscopy," the Senhance robotic system entered the market under TransEnterix, which has since been renamed Asensus Surgical. The platform has an open console design, with 4K 3D vision eye-tracking and reusable instruments with haptic feedback.[129] Arms are modular; each arm has a separate base, boom, and cords and is positioned independently of the other.

In 2017, the TransEnterix European Patient Registry for Robotic Assisted Laparoscopic Procedures in Urology, Abdominal Surgery, Thoracic, and Gynecologic Surgery (TRUST) was launched as an open observational registry trial in participating European centres.[130] The study released an interim analysis in 2019.[131] This report included data from 871 patients undergoing robotic surgery with the Senhance platform; 168 underwent prostatectomies. The most recent study out of the University Hospital Centre Zagreb, Croatia, includes 350 RARPs done by two surgeons, one of the largest databases of a new system. Prostate sizes ranged from 15 to 100 cc, with all patients with Gleason 6 through 9, stage cT2c and below. Console time was 130 minutes on average. There were six converted to laparoscopic prostatectomy and two open conversions. The team performed RARP using three robotic arms, one camera arm, and two instrument arms, and two laparoscopic assist ports were also utilized. The ports were positioned as a semicircle infraumbilically (**FIGURE 19B**). Another significant study, done by Yuan *et al.* in the same year, was a prospective cohort of 65 Senhance RARP cases compared with historical da Vinci Si and Xi controls. The RARP was performed using the standard transperitoneal approach with similar port placement. A posterior dissection was done for those with previous transurethral resection of the prostate.

Otherwise, an anterior approach was performed.[132] A learning curve of 30 cases was ascertained after regression analysis in this study. A cost comparison was also done, with a median cost of $4,169 for each procedure with the Senhance and $7,750 for the da Vinci.

Versius® robot surgical system (CMR Surgical, Cambridge, UK)

The Versius robotic surgical system comprises a console and up to four modular visualization bedside units (BSU) operating a 30-degree or 0-degree camera and instruments. Each instrument is wristed with seven degrees of freedom and 720 degrees of rotation, anchored in a 5-mm port. Each Versius arm is set up independently to focus instrument motion on the target area. A case report from Italy by Rocco *et al.* is the first description of the RARP clinical setup using this system. Docking by a dedicated robotic team took 30 minutes for their first case after cadaveric laboratory training and two full cadaver procedures.[133] The team highlighted unique features of the system, including exclusive handgrip control, including handgrip energy controls, and a longer instrument length of 30 cm. A case series of 18 patients described the setup in detail; port placement is similar to a standard RARP but slightly higher in the abdomen, anchoring the optical port 1 cm supra-umbilically.[134] (**FIGURE 19D**) Inclusion criteria were Gleason Score 8 or below, cT1c through T2c, PSA 30 ng/mL or below, and a reasonable life expectancy. There were no conversions to laparoscopic or open surgery in this series. Setup time was shorter than previously reported, ranging from 7 to 10 minutes; median console time was 201 minutes. PSM was, however, remarkably high at 83%, which the authors attributed to pT3 disease on final histopathologic examination and the small sample size. Continence was comparable to most published data, at 55% 0–1 pad at 1 month and 72% at 2 months. The authors underscored the potential advantages of modularity and lightweight (100 kg per BSU and 180 kg for the surgeon console), which obviated the need for a dedicated (or retrofitted) operating theatre. They postulated that these advantages may lead to decreased waiting time for robotic surgery.

Artificial Intelligence and Robotic Prostatectomy

Artificial Intelligence (AI) is one of the most revolutionary technologies of the 21st century and will transform many aspects of society, including healthcare. AI is defined as using computers and large datasets to enable problem-solving. In surgery, AI has a broad application spectrum, including skills training, simulation, intraoperative decision-making, or prediction of outcomes.[135] Currently, RARP is one of the most investigated surgical operations using AI.[136] These studies have significant limitations due to small datasets, a lack of external validation, and heterogeneous methodologies that are difficult for non-specialists to understand. Nonetheless, AI has the potential to lead to a new class of medical devices that could significantly improve the safety and efficiency of robotic-assisted surgery.

Enhanced surgical planning and outcomes prediction

Some studies have focused on using AI to analyze surgeon and patient characteristics to predict postoperative complications, including risk for urinary continence, length of stay, or biochemical recurrence. Kwong *et al.* demonstrated that an AI-based Side-specific Extra-Prostatic Extension Risk Assessment tool (SEPERA) could correctly predict extraprostatic extension better than other contemporary nomograms. This AI-based tool could inform surgical planning and patient counselling for patients with localized prostate cancer.[137] Chu *et al.* noted several AI algorithms that have been developed utilizing MRI to predict the pathologic stage of prostate cancer with high sensitivity and specificity.[138] This significant achievement underscores the potential for AI to individualize surgical strategies based on detailed imaging, enhancing the surgeon's ability to plan the extent of resection and nerve sparing with greater precision. This level of accuracy in preoperative prediction models allows for unprecedented surgical approach tailoring based on each patient's case, potentially reducing the incidence of positive surgical margins and improving functional outcomes.

AI in surgical education

Incorporating AI and machine learning into movement analysis can significantly enhance the learning experience for trainees. By providing feedback based on the precise and efficient movements of experienced surgeons, AI enables trainees to develop their skills in a targeted and efficient manner. This approach accelerates the learning curve and ensures that the trainees adopt best practices early in their training, setting a foundation for excellence in surgical performance.

Chen *et al.* used machine learning to predict surgeon experience by analyzing detailed and granular sub-stitch data during RARP.[139] Laca *et al.* investigated the impact of real-time feedback on surgical performance, mainly focusing on robotic tissue dissection tasks. The research demonstrates that such feedback can considerably improve the efficiency and precision of surgeons, suggesting a vital role for immediate feedback mechanisms in refining surgical techniques, especially for trainees.[140]

Ma *et al.* explored how surgical gestures could quantify surgical performance and predict patient outcomes. Highlighting the utility of AI in analyzing surgical gestures provides a novel method of assessing surgical skills and offers insights into potential patient outcomes, thereby laying the groundwork for gesture analysis in surgical training and real-time assistance.[141] Lastly, Hung *et al.* focused on using AI to automate the assessment of suturing skills from videos. This approach leverages AI to evaluate surgical proficiency objectively and scalably, potentially revolutionizing how surgical skills are assessed and learned.[142]

Navigating ethical, legal, and regulatory challenges

Integrating AI into robotic prostatectomy raises ethical, legal, and regulatory considerations. Ensuring the privacy and security of patient data, maintaining transparency in AI's decision-making processes, and developing clear guidelines for the clinical use of AI are paramount. These measures are essential for maintaining patient trust and ensuring that AI enhances surgical care responsibly and ethically.

Integrating specific data from seminal studies into this discussion highlights the profound transformative potential of AI in robotics, from enhancing surgical planning and intraoperative support to postoperative care and surgical education. As AI continues to evolve, its application in robotic prostatectomy promises to advance the field, improving patient outcomes and shaping the future of surgical practice.

Conclusion

The evolution of radical prostatectomy, especially with the advent of robotic-assisted techniques, represents a significant leap forward in the surgical treatment of localized prostate cancer. The meticulous understanding of prostate anatomy and its surrounding structures has been pivotal in transforming prostatectomy from a highly morbid operation to a procedure with fewer complications and increasingly shorter hospital stays, including same-day discharge.[143]

Innovations in robotic prostatectomy techniques continue to evolve, with a focus on minimizing morbidity related to urinary incontinence and erectile dysfunction. Techniques like bladder neck preservation, urethral length preservation, and various reconstruction approaches have been adapted to improve early urinary continence outcomes and sexual function postoperatively. However, most importantly, an increased understanding of pelvic anatomy has allowed for a proliferation of robotic prostatectomy techniques that spare the retropubic space, detrusor apron, pubovesical/puboprostatic ligaments, vasculature, and fascial support structures. These anatomical insights are crucial for preserving structures associated with improved urinary continence outcomes and minimizing damage to periprostatic structures, aiming for optimal oncologic and functional outcomes.

Additionally, the emergence of new robotic platforms and approaches, such as single-port and transvesical prostatectomy, offer the potential to refine surgical techniques further, enhancing recovery and functional outcomes. Integrating novel robotic systems signifies a promising future direction, aiming at precision medicine in urology to optimize patient outcomes while minimizing surgical morbidity.

The journey from the origins of prostate surgery to contemporary robotic-assisted techniques underscores a profound shift toward precision, minimally invasive care. Advances in anatomical understanding, coupled with technological innovations, herald an exciting era in the treatment of prostate cancer, emphasizing the importance of balancing oncologic control with quality-of-life considerations.

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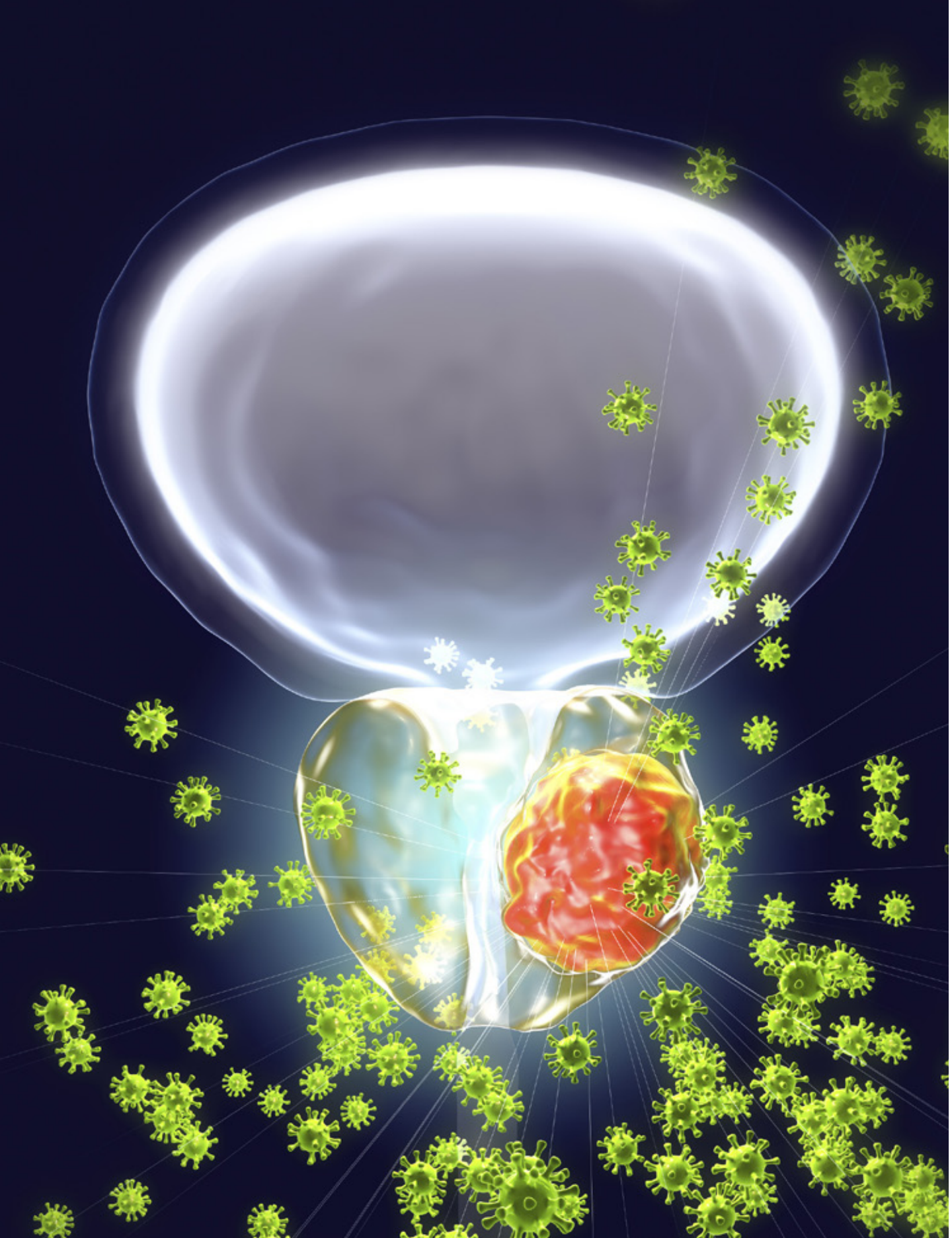

COMMITTEE 12

Emerging Radiotherapeutic Modalities in the Management of Clinically Localized Prostate Cancer

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Introduction

In the realm of prostate cancer treatment, the historical development over the past 120 years has been markedly different for surgical therapy and radiotherapy. Series from the early 1900s involving the removal of the prostate more frequently addressed the indication as "senile enlargement" rather than prostate cancer, and the procedure was associated with mortality rates of approximately 15% for both perineal and suprapubic prostatectomies.[1,2] In 1947, Millin lauded the merits of the retropubic approach for treating prostate cancer in a limited number of cases, and 32 years later, Reiner and Walsh took this approach to another level by more carefully describing anatomic details heralding the era of radical retropubic prostatectomy (RRP).[3,4] With the advent of robot-assisted prostatectomy, the transition to our modern era reached a plateau of technological refinement.[5] In contrast, the transition from the earliest forms of radiotherapy to the present techniques and the prospects for the future evolution of curative radiotherapy are more technology dependent and the advancements more dramatic.

Radiotherapy (RT) is the single most active agent in the treatment of cancer and has been used to treat prostate cancer for more than 100 years.[6] Numerous examples of the curative potential while preserving organ function have been well documented, including cancers of the head and neck, lung, anus, bladder, cervix, skin, and beyond. In addition to being older than RRP, there are more large, prospective, phase 3 randomized trials with longer-term studies, including cohorts of patients with localized prostate cancer using RT rather than surgery. Based on trials completed to date, survival rates appear to be comparable at 10 years, but quality of life (based on preservation of sexual function and continence) is better with RT than RP. In addition, there are fewer contraindications related to age and comorbidity and less dependency on provider skills. Furthermore, patients with locally advanced high-risk disease are at high risk of requiring postoperative RT without compelling evidence that RP followed by RT adds an increased survival rate compared to dose-escalated RT combined with androgen deprivation therapy (ADT). Finally, and most relevant to this chapter, the technology involved in managing prostate cancer with RT has evolved incrementally as imaging, computers, and the understanding of normal tissue tolerances and a greater understanding of the radiobiology of prostate cancer have progressed.

We can now use transrectal ultrasound (TRUS), computed tomography (CT), magnetic resonance imaging (MRI), and prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging and, with an improved understanding of the most likely extension of microscopic disease, better define the most appropriate RT treatment volumes. We also now leverage implanted intraprostatic markers with electronic portal imaging (EPID), cone beam CT (CBCT), or MRI imaging to perform near–real-time adjustments for target motion and setup errors. We must credit our urologic colleagues for providing important pathologic staging information nomograms that have allowed us to understand better the extension of the disease and the limitations of imaging. The availability of imaging technology combined with a better understanding of "truth" and the associated target volumes, the doses of radiation required, as well as the tolerances of normal tissues helped redefine what was safe and possible. In addition, the availability of drugs to enhance the effectiveness of radiation, multimodal artificial intelligence, and predictive biomarkers have translated into improved effectiveness, less toxicity, and a better quality of life (QoL).[7–9]

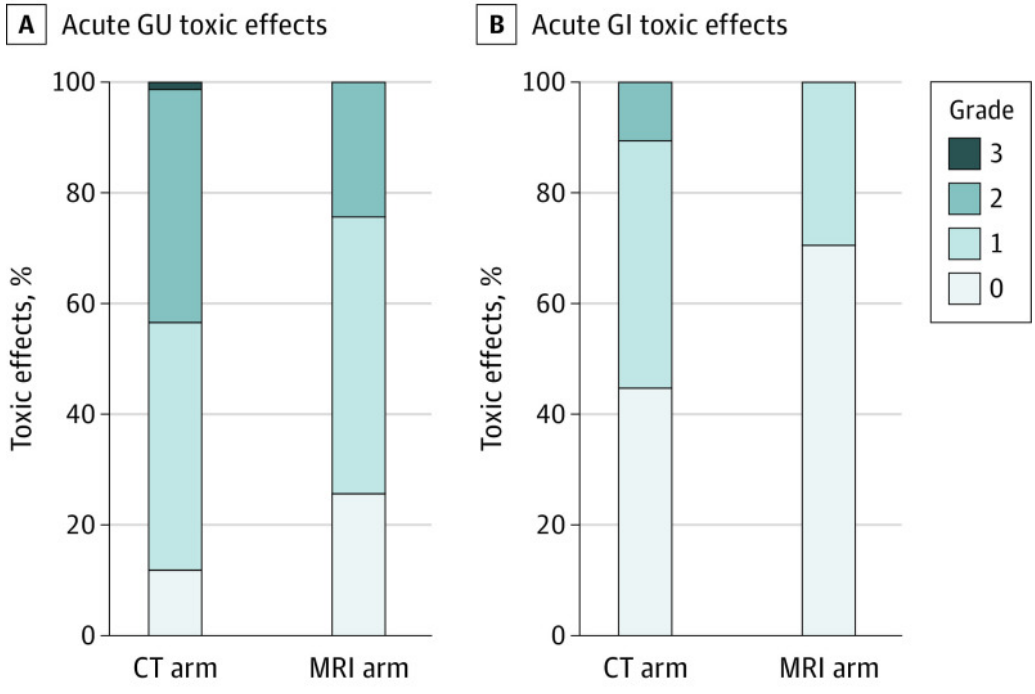
This chapter provides a critical review of some of the active areas of ongoing research that are being pursued by investigators involved in improving and advancing the use of therapeutic radiation for prostate cancer. In the interest of space, we will *not* cover the incorporation of the prognostic and/or predictive tissue-based advances such as multimodal artificial intelligence (MMAI), genomic classifiers, or other tissue-based tools that can be applied to improving outcomes.[7,8,10] Instead, we will describe the status of present and future radiotherapeutic approaches that extend beyond photon (X-ray)-based therapeutic external beam radiation (EBRT) and include charged particles such as proton beam RT (PBRT), carbon ion radiotherapy (CIRT), as well as spatially fractionated and FLASH RT. First, however, we will have a critical look at the recently published MRI-guided radiotherapy (MRIgRT), phase 3, randomized trial (MIRAGE) that purports to demonstrate the benefits of this technology over conventional linear accelerator (linac)-based stereotactic body radiotherapy (SBRT) for clinically localized prostate cancer with traditional CT marker-based image guidance. In addition to critically discussing the MIRAGE MRIgRT trial, comparing photon SBRT with proton and heavy ion short hypofractionation, and presenting spatially fractionated RT techniques, we discuss some of the evidence that the delivery of RT at ultra-high dose rates can profoundly modify normal tissue tolerances and has the potential to usher us into a new era of radiotherapy for prostate cancer, revolutionizing treatment protocols and outcomes.

MRI Linac-Guided Radiotherapy for Prostate Cancer

MIRAGE was a randomized trial aimed at demonstrating that margin reduction using an MRI linac (linear accelerator) combined with image guidance would reduce the toxicity of prostate SBRT compared to SBRT with a conventional linac.[11] This single-institution study was closed early with a minimum follow-up of 3 months with the authors concluding ". . . MRI-guided SBRT significantly reduced both moderate acute physician-scored toxic effects . . . " (**FIGURE 1**).

To explain why we are *not convinced* this technology has been proven to transform the treatment of prostate cancer, we encourage the readers to perform the following "thought experiment." Imagine there was a randomized trial comparing two different brands of MRI imaging devices, machine S and machine B (technically identical), evaluating toxicity after SBRT for prostate cancer. Further, assume that, with little justification, we decided to use larger margins on machine B (bigger) than machine S (smaller). Adopting the results from MIRAGE (Supplement 2), assume this choice of margins resulted in a median volume irradiated of 102.1cc for B (CT) versus 70.5 cc for S (MRI), $p<0.001$. As might be expected, the side effects were reported to be significantly lower on the S arm. Would it be logical to conclude that this randomized trial proved that treatment with machine S was preferred over machine B? Based on the design of our thought experiment, the answer would be "no." The thought trial does not isolate the effect of the machine from the effect of the treatment margin. The tighter margins could have led to worse tumour control. How is this different than what was done in the MIRAGE trial? The investigators did not provide a strong rationale for using 2-mm margins for the MRI arm. An alternative strategy could have been to use non-uniform margins based on individual patients' anatomy, accounting for the location of the cancer while maintaining dose constraints to reduce the risk for toxicity.[12]

FIGURE 1 Rates of acute genitourinary (GU) and gastrointestinal (GI) toxic effects.



All toxic effects were scored based on the Common Terminology Criteria for Adverse Events, version 4.03 scale.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.
Source: *Reproduced from Kishan AU, Ma TM, Lamb JM,* et al. *Magnetic resonance imaging-guided vs computed tomography-guided stereotactic body radiotherapy for prostate cancer: the MIRAGE randomized clinical trial.* JAMA Oncol. *2023;9(3):365–373. doi:10.1001/jamaoncol.2022.6558.*[11]

Since identical MRI planning was used for target delineation for the conventional linac-based treatment (control arm) and for the MRIgRT, the MIRAGE study implies that the possibility of target motion adjustments for MRIgRT justified the small margins and was the key to the apparent benefits. This assertion rests on two major assumptions: (1) that interobserver variability is as good or better among the therapists using MRI guidance compared to CT guidance with fiducials in place; (2) there is a significant advantage because of the amount of target motion that could be adjusted for using MRIgRT. We previously disproved a similar assumption about ultrasound-based image guidance. Despite its widespread adoption at major centres around the United States, we showed that it was associated with substantial interobserver variability (and this approach subsequently "died").[13] Exactly how much better a 0.35 T MRI image is than the transabdominal ultrasound approach for localizing the prostate remains unknown. They did report, however, that automatic beam hold adjustments were *only* initiated "If greater than 10% of the prostate volume moved outside a 3-mm gating boundary . . . ."

They did not tell us how often this occurred, but we do know that the median post-imaging delivery times were nearly 5 times longer for the MRIgRT group compared to the CT-guided group (1,133 vs. 232 secs). Thus, the MRIgRT group was substantially *more likely* to require motion management than the CT-guided group (larger margins and shorter delivery times). The CT-based margins could potentially result in better tumour coverage and cancer control rates, but there is no data on treatment efficacy.

Risk of placebo effects and observer bias

Placebo effects in clinical trials have been well documented. For example, a University of Cincinnati study tested the effect of blue and pink stimulants and sedatives, respectively, on medical students; unbeknownst to the students, the stimulants and sedatives were all placebos.[14] The blue placebo sedatives were 66% effective (sedative effects), compared with 26% for the pink ones (stimulating effects). Clearly, a stronger argument might be made to patients about how using MRI guidance and smaller margins might be associated with fewer side effects, creating a ripe opportunity for a brisk placebo effect. It is well established that unblinded studies (including both the observers and participants) with subjective endpoints are notoriously unreliable.[15] The physicians managing the patients were at high risk of being unconsciously biased observers. Of note, patients usually report greater toxicity than physicians do.[16] However, in the MIRAGE study, this pattern appeared reversed at 3 months, which might be seen as evidence of the possibility of physician bias. For example, as shown in Supplement 2 (Table 4 in their publication), by physician-reported outcomes, there were statistically significant differences in multivariate analysis for acute grade ≥2 genitourinary toxicities (p=0.02).[11] In contrast, based on patient-reported outcomes, there were no statistically significant differences in the longitudinal changes in urinary irritative/obstructive and total urinary Expanded Prostate Cancer Index Composite-26 (EPIC-26) scores, the proportions of patients with clinically relevant declines in the EPIC-26 scores urinary subdomains, or longitudinal changes in total International Prostate Symptom Score (IPSS) and IPSS Quality-of-Life scores (Figures 1, 2, and 3 in their publication).[11]

Higher than typical doses and potential imbalances in treatment arms

The doses of SBRT used in the MIRAGE trial exceeded the doses used in nearly 90% of patients reported in a systematic review and meta-analysis of > 6,000 patients.[17] It is also important to note that they allowed the investigators to use even higher doses, at their "discretion," delivering ". . . a simultaneous integrated boost to the dominate intraprostatic lesion (42 Gy 5 fractions) and a . . . boost to a pelvic node deemed to be involved . . . . " Given there were more high-risk patients on the CT arm, and a higher absolute number of risk factors likely to impact gastrointestinal (GI) toxicity, this could easily create bias favouring the MRI arm. As shown in **TABLE 1** below, 93 adverse factors were present among the 77 patients in the CT-guided group versus 74 among 79 patients in the MRIgRT group. Since patients in the CT-guided group had more high-risk features, we can infer that they were more likely to have received higher doses.

TABLE 1 Potential Imbalances in Factors Reported in the MIRAGE Trial That Might Impact Toxicity

Characteristic*	CT % (n=77)	MRI (n=79)	Comment
High or very high risk	39% (30)	25% (20)	Might favour MRIgRT group due to smaller target volumes drawn
No rectal spacer use	58% (45)	53% (42)	Might favour MRIgRT group due to more spacer use
Baseline GI comorbidity	23% (18)	15% (12)	Might favour MRIgRT group due to lower baseline GI comorbidity rates
Total number of potentially adverse factors reported*	93	74	Combination of factors could cause biased results

Abbreviations: CT, computed tomography; GI, gastrointenstinal; MRI, magnetic resonance imaging; MRIgRT, MRI-guided radiotherapy.
*Some patients may have had > 1 factor.
Source: *Modified from Supplement 2 [Table 4] in publication: Kishan AU, Ma TM, Lamb JM,* et al. *Magnetic resonance imaging-guided vs computed tomography-guided stereotactic body radiotherapy for prostate cancer: the MIRAGE randomized clinical trial.* JAMA Oncol. *2023;9(3):365–373. doi:10.1001/jamaoncol.2022.6558.*[11]

While the investigators can be applauded for launching a randomized trial, in our opinion, the apparent superiority of SBRT-delivered MRI guidance in this trial is likely to be "just a Mirage." In conclusion, while MRIgRT may hold great promise for treating some deep-seated solid tumours, the available data to date does not support an advantage for treating clinically localized prostate cancer.

Charged Particle Beam Radiotherapy and Stereotactic Body Radiotherapy

Most EBRT for prostate cancer is performed with high energy photons (X-rays); however, in the past decade, charged particle beam RT (usually using proton radiation [PBRT] and, less commonly, carbon ions [CIRT]) has rapidly increased.[18–20] The major theoretical advantage of carbon lies in its higher relative biological effectiveness (RBE). Despite the increased use in this setting, very few trials have been completed evaluating charged particle beam RT for prostate cancer.[21] We have proposed a phase 2 randomized trial comparing SBRT using either heavy ions (carbon), protons, or photons ("SHIPP") for men with unfavourable intermediate risk (UIR) prostate cancer as defined by the National Comprehensive Cancer Network (NCCN); unfortunately, this trial has not been funded to date. The rationale for such a trial is that UIR prostate cancer is one of the most common subsets and is associated with a 20% to 25% recurrence rate within 5 years (**TABLE 2**), despite aggressive local photon-based SBRT. If carbon or proton SBRT could reduce the risk for local and distant recurrences by 10%, many thousands of men with prostate cancer could potentially benefit in terms of cancer control and a reduced risk for distant metastases. In addition, it is possible that these particles might reduce local regional morbidity and possibly the risk for second cancers.[22]

TABLE 2 Selected Series Reporting Outcomes of Unfavourable Intermediate Risk Prostate Cancer with SBRT

1st Author (yr)	No. of pts	5-yr BNED	Comments
Katz (2016)[67]	515	80%	9.1% UIR (*n*=47), authors concluded, "Patients with UIR . . . have significantly worse outcomes after SBRT, and should be considered for clinical trials . . ."
Kishan (2019)[68]	2,142	~80%	12.4% UIR (*n*=265) 7-yr cumulative incidence of late ≥ grade 3 GU toxicity ~2.4%; late ≥ grade 3 GI toxicity 0.4%.
Franzese (2020)[69]	178	75%	Authors concluded, ". . . Linac-based SBRT continues to be a valid option . . . control remains high at 5 years, albeit with some concerns regarding the optimal schedule for UIR PC."
Fuller (2022)[70]	259	75%	10% UIR (*n*=46), authors concluded, "SBRT . . . prescribing 38 Gy/4 fractions . . . high long-term disease control rates without ADT ***except*** . . . UIR patients."

Abbreviations: ADT, androgen deprivation therapy; BNED, biochemical no evidence of disease; GI, gastrointestinal; GU, genitourinary; PC, prostate cancer; SBRT, stereotactic body radiotherapy; UIR, unfavourable intermediate risk.

Prostate cancer might be an ideal cancer site for particle SBRT because (1) it is the most common cancer treated definitively with photon-based EBRT and the most common cancer treated with CIRT;[23–26] (2) increasingly, SBRT is being used as a very cost-effective way to treat intermediate-risk prostate cancer in 4 or 5 fractions;[17,27,28] (3) there are reasons to believe that CIRT (due to the tighter penumbra) should allow physical dose escalation or increased sparing of neurovascular structures and the penile bulb, resulting in improved erectile function and favourably impacting QoL;[29–32] (4) the higher RBE of CIRT should improve local and, possibly, distal control compared to photon or proton-based SBRT;[33–35] (5) hypoxia and other mechanisms of radiation resistance may be overcome with CIRT;[33,36] (6) CIRT may be associated with a lower risk for second cancers compared to photon therapy, which is relevant to patients with prostate cancer who are expected to have normal longevity;[22] and (7) intermediate endpoints such as PSA nadir (the lowest PSA after treatment) could be used to efficiently assess the relative merit of each of these modalities.[37–39]

SBRT photons vs. protons vs. CIRT

The major push for charged particle beam RT comes from the unique biology associated with ions, which involves the dramatic reduction of exit doses common with photons. In addition to the physical dose distribution advantage, carbon beams are associated with increased effectiveness against radioresistant and hypoxic (poorly oxygenated) tumour cells and increased effectiveness in *some* prostate cancer models.[40,41] When compared among three different prostate cancer sublines, carbon ions showed a much smaller variation of the radiation response, with the authors concluding their results ". . . support the use of hypofractionated carbon ion treatments in radioresistant tumors."[40,41] In addition to promising animal studies, studies assessing the impact of CIRT in men with prostate cancer suggest a more favourable impact on QoL compared to photon-based RT and very high cancer control rates.[24,42,43] Of note, in a head-to-head dosimetric comparison of SBRT using a CyberKnife™ (CK)

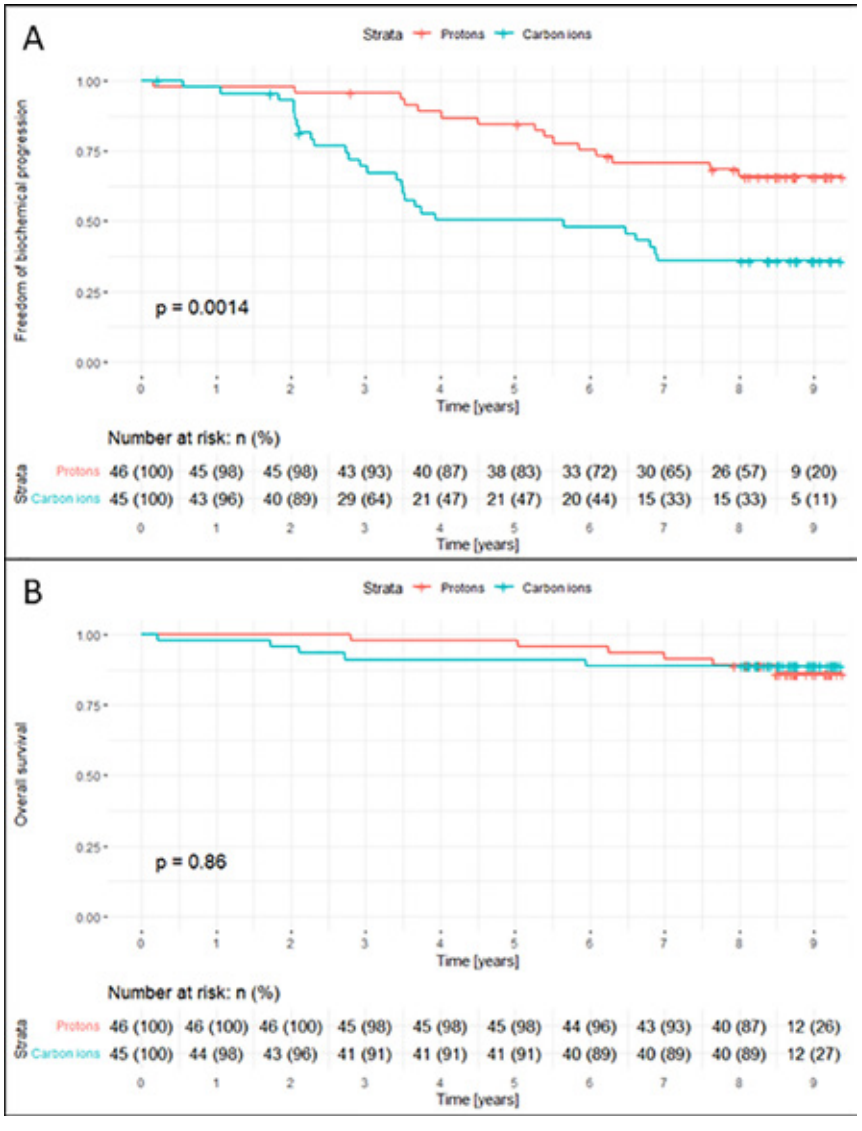
device versus CIRT, Huang *et al.* reported that ". . . when CIRT was used for treating localized prostate cancer, the dose distribution in target volume was more homogeneous and the coverage rate was higher; the average dose of [organs at risk (OARs)] was lower."[44] However, they also noted that CK-based SBRT resulted in ". . . better CI (conformity index) and higher dose in target volume; the dose hotspot was lower in OARs." Thus, it remained unclear which was, in fact, better dosimetrically.

Complicating our ability to answer these important questions is the reality that, to date, the technical challenges, such as range uncertainty (uncertainty as to exactly where charged particle beams stop), have not adequately been addressed. It is well known that PBRT and CIRT can spare adjacent normal structures because of the Bragg peak and lower doses of radiation scattered to surrounding normal tissues, but photon-based intensity-modulated radiotherapy (IMRT) can also achieve very conformal dose distributions. However, the use of photon-based IMRT and SBRT results in substantially larger volumes of normal tissue exposure to intermediate and low doses of radiation, which might be associated with the weakening of the immune system and an increased risk for second cancers.[45]

The use of photon-based SBRT for prostate cancer has risen sharply over the past 10 years due to reduced cost, patient convenience, and underlying biological principles supported by excellent clinical outcomes, which appear to be comparable to conventionally fractionated and hypofractionated IMRT or high-dose-rate (HDR) brachytherapy.[17,27,46–51] The outcomes associated with ultra-fractionated PBRT to 38 Gy (RBE) in 4 or 5 fractions have been compared to conventionally fractionated protons to 79.2 Gy (RBE) in 44 fractions and found to be comparable.[52,53] CIRT for localized prostate cancer has routinely been administered in a hypofractionated schedule (12–16 fractions) for more than 20 years and is believed to be associated with outstanding clinical outcomes (i.e., cancer control and low toxicity).[20,23,24] Despite the numerous theoretical reasons that protons and CIRT might offer better cancer control and less morbidity than photon-based SBRT, there is very limited data available comparing these options "head-to-head."[26,54,55] There are three trials that we are aware of testing PBRT for prostate cancer. The first two (COMPPARE (U Florida) [*NCT03561220*] and Protons for High Risk (Emory) [*NCT04725903]*) are *non-randomized,* and the third (PARTIQoL (Mass Gen H) [*NCT01617161*]) comparing protons versus IMRT is currently not recruiting. However, none of these trials includes SBRT or compares protons to CIRT.

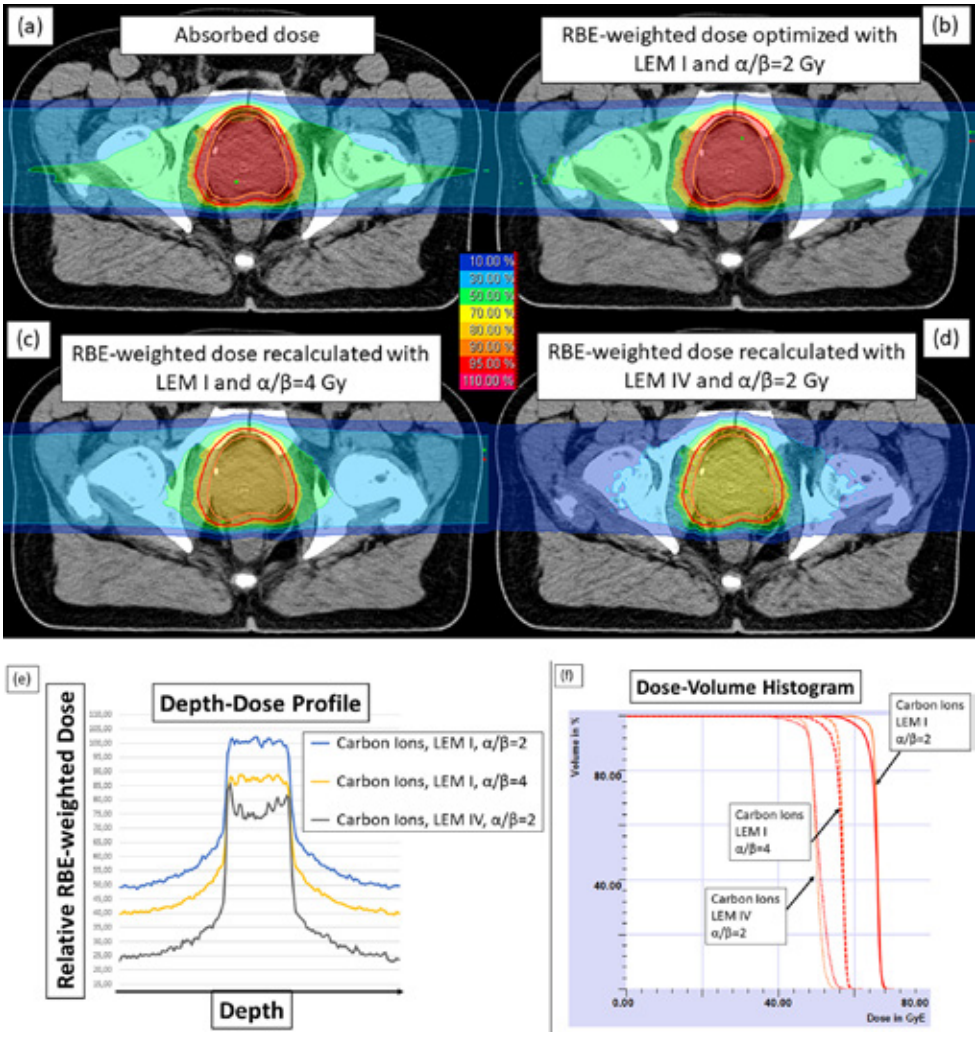
Relevant to the proposed SHIPP trial is the recently reported phase 2 randomized trial conducted by Heidelberg Ion Treatment (HIT) in Germany.[54] The investigators completed a phase 2 trial and reported their experience with lessons learned thus far. Initially, they reported acceptable toxicity with either type of charged particle therapy.[54] This trial also confirmed that it is feasible to complete randomized trials comparing protons to carbon for localized prostate cancer using conventional fractionation. Surprisingly, however, with long follow-up, they reported a ". . . *significant lower effectiveness* of the calculated RBE-weighted dose in the carbon ion as compared to the proton arm" (**FIGURE 2**).[55] They also concluded that using the RBE model called "LEM I and $\alpha/\beta = 2$ Gy overestimates the RBE for carbon ions . . . ." "They further concluded that ". . . Adjusting the biological dose calculation by using LEM I with $\alpha/\beta = 4$ Gy could be a pragmatic way to safely escalate dose in carbon ion radiotherapy in prostate cancer . . ."[55]

FIGURE 2 Freedom from biochemical progression (A) and overall survival (B) compared between proton and carbon ion groups.



Source: *Reprinted from Eichkorn T, Karger CP, Brons S,* et al. *Results of a prospective randomized trial on long-term effectiveness of protons and carbon ions in prostate cancer: LEM I and alpha/beta = 2 Gy overestimates the RBE.* Radiother Oncol. *2022;173:223–230. doi:10.1016/j.radonc.2022.06.006,*[55] *with permission from Elsevier.*

FIGURE 3 Example of the delivered absorbed (a) and RBE-weighted (b) carbon ion dose distribution optimized with LEM I and alpha/beta = 2 Gy as well as the recalculated RBE-weighted dose distributions for LEM I with alpha/beta = 4 Gy (c) and LEM IV with alpha/beta = 4 Gy (d). CTV and PTV are represented by the orange and red contours, respectively. Note: 100% dose refers to 21.97 Gy in 20 fractions for the absorbed dose (a) and 66 Gy (RBE) in 20 fractions for the RBE-weighted dose (b-d). Examples of the delivered corresponding (to a-d) RBE-weighted depth-dose profiles, starting at the right and ending at the left femoral head, as well as the dose histograms (f), are displayed.



Abbreviations: CTV, clinical target volume; PTV, planning target volume; RBE, relative biological effectiveness.
Source: *Reprinted from Eichkorn T, Karger CP, Brons S,* et al. *Results of a prospective randomized trial on long-term effectiveness of protons and carbon ions in prostate cancer: LEM I and alpha/beta = 2 Gy overestimates the RBE.* Radiother Oncol. *2022;173:223–230. doi:10.1016/j.radonc.2022.06.006,*[55] *with permission from Elsevier.*

These results demonstrated just how critically dependent the PSA control rate is on assumptions about what the α/β ratio is *and* the RBE resulting from this assumption with the RBE model in use. As shown in **FIGURE 3**, using LEM I and an α/β ratio = 2 Gy resulted in overestimating the actual carbon dose delivered, compared to LEM I with an α/β ratio = 4 Gy or LEM IV and an α/β ratio = 2 Gy. The HIT investigators believe this overestimation of the biological dose is responsible for the unexpected biochemical results. The depth-dose profiles and dose-volume histograms (DVHs) corresponding to these scenarios are shown in **FIGURES 3e** and **3f**. These sobering data highlight the need for randomized trials involving low- and high-LET radiation modalities (photon and proton vs. heavy ion SBRT) and raise questions about the utility of animal models in predicting outcomes in humans.

There are no CIRT facilities operating in North America despite evidence that as many as 25% of cancer patients might benefit from CIRT.[56,57] However, in 2022, Mayo Clinic Jacksonville announced plans (*Jax Daily Record*, August 5, 2022) to build an Oncology Center including carbon ions. As of May 2024, the Mayo Clinic Integrated Oncology Building in Jacksonville is still under construction. The building, including PBRT and CIRT, is expected to be completed in early 2025. Japanese investigators have recently completed accrual to a prospective clinical trial, a phase 1 dose-escalation trial using CIRT with 4 fractions for prostate cancer patients categorized as low/intermediate-risk disease (UMIN000032340) (QST in Japan).[23] It is expected that data from this trial will provide confidence that a 4 or 5-fraction CIRT regimen is safe. Of note, however, a post-hoc analysis of their earlier studies suggests that the RBE of carbon decreases with increasing fraction sizes, so CIRT may not be ideal for SBRT-type ultra-hypofractionation.[58] Thus, despite the *hype* and considering the high upfront expense, the role of particle therapy for the definitive management of clinically localized prostate cancer remains to be defined.[21]

Spatially Fractionated and FLASH Radiation: Truly Transformative Approaches to EBRT?

On August 20–21, 2018, the NCI/NIH, in collaboration with the Radiosurgery Society, held a workshop entitled "Understanding High-Dose, Ultra-High Dose Rate, and Spatially Fractionated Radiation Therapy." The workshop participants, experts in their respective fields, discussed the potential biological mechanisms of emerging radiation techniques, including GRID/LATTICE and microbeam (spatially fractionated) and FLASH (ultra-high dose rate) RT. Spatially fractionated RT (GRID/Lattice and microbeam radiation) involves the creation of non-homogeneous regions of radiation, which are delivered as 2D (GRID) or 3D (LATTICE) patterns of very high and low doses with high dose gradients between them (as opposed to the usual uniform dose). Apparently, this approach can result in the increased repair of normal tissues exposed to radiation. For example, Dilmanian *et al.* demonstrated a significant increase in central nervous system (CNS) tolerance when rat brain was irradiated with 0.68-mm microbeams spaced 1.32 mm apart. The peak dose of the microbeams was 170 Gy, which was well tolerated. The authors compared this to the ED_{50}, i.e., the dose of radiation that caused brain necrosis in 50% of cases, of 22 Gy from non-spatially fractionated radiation in rats in historical experiments, a greater than 7-fold higher tolerance factor.[59] This suggests that microbeams could offer a more effective and safer approach to treating brain conditions.

TABLE 3 Pros, Cons, and Current State of Knowledge for Spatial Fractionation and Ultra-High Dose Rates

	GRID/LATTICE	Microbeam	FLASH
Pros			
Reduction in treatment Evidence level / translational potential	Yes / medium	Yes/?	Yes / high
Normal tissue sparing Evidence level / translational potential	Yes / multiple clinical studies	Yes / numerous preclinical reports, large animal studies	Yes / several preclinical reports (multiple models), case report
Increased clinical response Evidence level / translational potential	Yes / multiple clinical reports	? / little clinical data	Medium / case report
Mechanism of action understood Evidence level / translational potential	Partial / medium	Partial / limited	Partial / high
Proimmune function Evidence level / translational potential	Suggested preclinical	? / preclinical	Medium / ?
Cons			
Limited use / applications Evidence level / translational potential	TBD / dedicated clinical studies needed	Likely tougher to implement clinically	TBD / data on larger treatment volumes needed
Difficult to obtain technology Evidence level / translational potential	No	Yes / synchrotron based	Maybe / higher beam energies and field sizes needed
Cost Evidence level / translational potential	Low	High	Medium / high
Sites access (deep / superficial) Evidence level / translational potential	Options growing	Yes / numerous brain studies	Not known / superficial confirmed

Abbreviation: TBD, to be determined.

Source: *Adapted from Griffin RJ, Ahmed MM, Amendola B,* et al. *Understanding high-dose, ultra-high dose rate, and spatially fractionated radiation therapy*. Int J Radiat Oncol Biol Phys. *2020;107(4):766–778. doi:10.1016/j.ijrobp.2020.03.028,*[61] *with permission from Elsevier.*

Most of the clinical work using the three types of spatially fractionated RT has been carried out in the setting of large tumours (especially those treated in a palliative setting), but we are aware of at least one prospective trial involving prostate cancer.[60] This phase 1 trial tested the feasibility and toxicity of a LATTICE ablative dose technique. With a median follow-up of 66 months there were no grade 3 acute/subacute genitourinary or gastrointestinal adverse events. The authors concluded that ". . . spatially fractionated, stereotactic high dose . . . boost is feasible and was not associated with any unexpected events." The technique is now part of a follow-up phase 2 randomized trial (NCT02307058). The subsequent publication of the NCI-sponsored workshop featured the pros, cons, biological considerations, and challenges of spatially fractionated RT using the different modalities used (**TABLE 3**).[61] The details of the spatially fractionated RT modalities are beyond the scope of this review, but the potential for FLASH radiation will be considered in more detail next.

In 2014, Favaudon *et al.* demonstrated in a mouse study that a single dose of ultra-high dose-rate (> 40 Gy/sec) electron radiation was equally effective at controlling cancer but less toxic to normal lung, compared to radiation given at a conventional rate (< 0.03 Gy/sec).[62] This "FLASH effect" of ultra-high dose-rate irradiation was noted histologically as sparing of smooth muscle and epithelial cells from acute radiation-induced apoptosis. The authors speculated that FLASH RT might be used to completely eradicate lung tumours and reduce the risk for early and late normal tissue complications. In subsequent years FLASH RT has been touted as perhaps the most promising advance in EBRT directed at curing cancer. Although the exact mechanism of the FLASH effect remains unknown, the potential promise of this technology is striking.

The "FLASH effect" is defined as the demonstration of radiation protection of normal tissue observed after irradiation of > 10 Gy at ultra-high dose rates (> 40 Gy/sec) under conditions of physiological oxygen without changing the tumour response. This dose rate contrasts with conventionally delivered radiation, typically given in 1–4 Gy/minute. It appears that by delivering radiation more than 600 times faster than conventional radiation, there is a differential biological response linked to the molecular radiochemistry of oxygen metabolism that allows protection of normal but not tumour tissues. However, it is not decided whether the time structure of the delivered dose is critical to the effect, with most recent experimental evidence indicating that the average dose rate is more important than the radiation's micro- or nano-second time structure. Most of this potentially transformative novel form of radiation delivery has been buttressed by animal models that demonstrate the ability of FLASH to reduce damage to brain, lung, skin, and other normal structures while retaining anticancer activity in tumour tissue. However, clinical demonstration, other than in a few cases, is still lacking.

Specifically important to prostate cancer RT is the fact that the mechanisms of radiation-induced erectile dysfunction involve injury to small blood vessels and nerves.[63] If these critical structures could be spared by the neuroprotective and vascular effects of FLASH RT shown in animal models, erectile dysfunction and radiation cystitis and avoiding immunosuppression associated with FLASH RT might reduce much of the pelvic toxicity of EBRT.[64,65] Not only might FLASH dose rates reduce normal tissue toxicity and retain antitumour activity in the treatment of deep-seated solid tumours in humans, but there are other theoretical potential advantages to the use of FLASH to treat cancers in mobile sites such as the prostate. First, very fast treatments combined with shorter courses of therapy (i.e., a single dose) could result in high patient throughput, substantially reducing cost and

improving patient convenience. Furthermore, issues related to target motion could be eliminated because of the absence of significant motion during the ultrashort delivery times.

There are two major barriers to the development of FLASH, including (1) the limited availability of commercial technology to perform animal studies and clinical trials with deep-seated tumours, and (2) most importantly, a lack of understanding of the mechanism of FLASH RT action, to properly guide these trials. Opportunities and barriers involve issues related to developing technologies for optimizing radiation type (photons, protons, or carbon) and delivery, and understanding the biology and clinical implementation. Animal studies have shown that adding microbeams to FLASH radiation can further enhance the safety profile compared to FLASH alone.[66]

Elucidating the underlying mechanisms of action of biological effects associated with delivering ultra-high dose rates of FLASH RT has the highest priority. Pilot studies in (small) animals have demonstrated the FLASH effect (significant sparing of normal tissues at equal tumour effectiveness). This could have a profound impact on definitive EBRT for prostate cancer. Applying FLASH RT technology could substantially reduce the side effects of radiation for cancer therapy, reduce cost, and improve tumour targeting, tumour cure rates, and quality of life. This will require an internationally integrated multidisciplinary approach and more FLASH-ready facilities.

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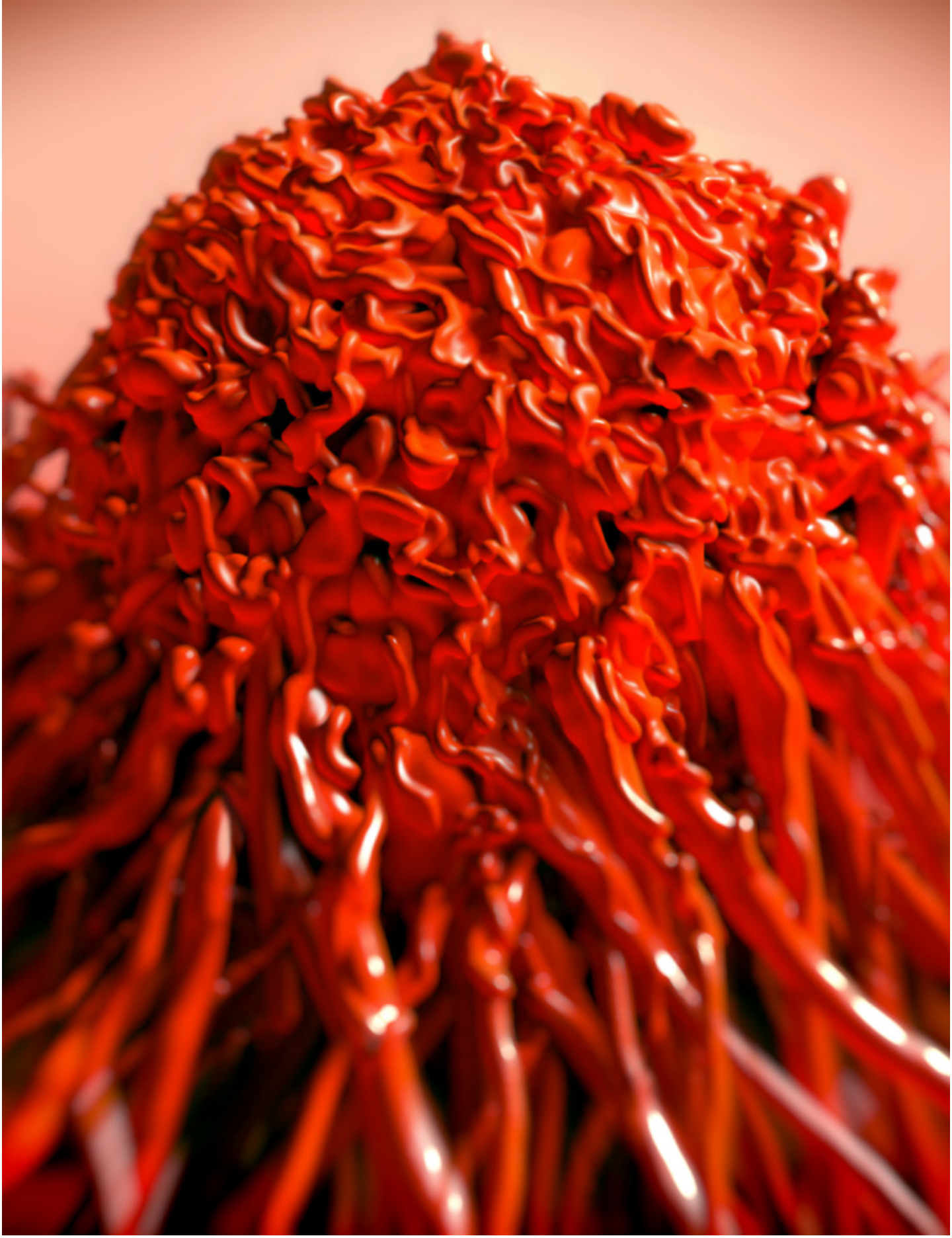

COMMITTEE 13

Focal Therapy—Principles and Outcomes

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Table of Contents

Introduction

Definition of focal therapy for prostate cancer

Focal therapy (FT) for prostate cancer (PCa) refers to a targeted approach for localized disease treatment. The side-effect profile of radical treatments is well recognized and associated with a significant risk for urinary incontinence, erectile dysfunction, and bowel function alteration.[1] FT's challenge is to be as oncologically efficient as whole-gland treatments while preserving surrounding healthy tissue and thus minimizing morbidity and side effects.[2,3]

Various energies have been developed to destroy cancerous tissue. High-intensity focused ultrasound (HIFU), cryoablation, irreversible electroporation (IRE), focal laser ablation (FLA), and photodynamic therapy (PDT) are among the more common. Tumour destruction is achieved by utilizing different tissue-damaging techniques, including temperature extremes (HIFU, cryoablation, FLA) or other specific cytotoxic processes (IRE, PDT).

Evolution of treatment approaches for prostate cancer

The historical standard of care in the 20th century for localized PCa treatment remains radical treatment, namely radical prostatectomy (RP) or radiotherapy (RT). However, minimally invasive treatments are spreading. FT approaches have gained attention and have been explored for their effectiveness and potential to reduce side effects.

In the mid-1990s, cryoablation began to emerge as a salvage option for patients who had failed RT, and by the end of the 20th century, HIFU was also emerging.[4] Subsequently, technological improvement has allowed treatment planning and monitoring for both primary whole-gland and focal ablation. Time also brought an evolution in treatment indications, providing FT as an emerging primary treatment alternative for low- to intermediate-risk candidates.[5]

Rationale for focal therapy in prostate cancer care

Patient selection is the cornerstone of FT and has improved in recent years with the emergence of imaging as an integral part of the workup of elevated prostate-specific antigen (PSA). Multiparametric magnetic resonance imaging (mpMRI) has enhanced the ability to detect and precisely localize clinically significant PCA (csPCa) tumour foci.[6] Multiparametric MRI provides target lesions for biopsy and FT planning, while also assisting in lesion monitoring over time.[7,8]

PCa is a multifocal cancer. There is increasing evidence that the largest tumour focus within the prostate would be the most aggressive lesion and would drive the natural history of the tumour.[9] FT relies on identifying this largest tumour focus, or the "index tumour".[10,11] It is therefore essential to define and target the index tumour to obtain effective FT.

Patient Selection for Focal Therapy

Risk stratification and patient eligibility

Proper patient selection is critical for successful FT. However, firm guidelines have not yet been established, with each study and institution utilizing heterogeneous selection criteria.[12]

According to a recent International Delphi Consensus, FT is recommended in patients with magnetic resonance (MRI)-visible intermediate-risk cancer, defined as Gleason score (GS) 3+4 or 4+3 PCa with cancer foci smaller than 10–15 mL on mpMRI. No specific PSA cutoff value was agreed upon for treatment eligibility, and more than half of the participants did not consider PSA an eligibility criterion for treatment. Patients with low-risk cancer, GS 3+3, were deemed not to be eligible for FT by the majority of panelists, who believed that active surveillance (AS) is the best option in this setting.

Today, guidelines recommend FT in intermediate-risk disease within clinical trials or prospective registries in light of the lack of high-quality data comparing ablation outcomes to RT, RP, and AS.[13,14] The only properly powered randomized controlled trial (RCT) reporting on FT in low-risk PCa showed that focal PDT could lower the likelihood of cancer progression and rates of surgery/radiation compared to AS, despite an increased likelihood of mild urinary or erectile dysfunction.[15] Therefore, due to its excellent long-term outcomes, AS remains the preferred approach in this setting.[13,14]

Imaging techniques for localizing prostate cancer lesions

Accurate localization of the index lesion(s) within the prostate is primary to successful FT.

Historically, transrectal ultrasound (TRUS) has been the standard for identifying PCa for many years. PCa is hypoechoic due to replacing normal loose glandular prostate tissue with densely packed tumour cells with fewer reflecting interfaces on B-mode imaging.[16] Occasionally, it can appear hyperechoic due to a desmoplastic reaction within the tumour.[17] While hypoechoic areas are seen in approximately half the cases on conventional TRUS, the positive predictive value (PPV) of a hypoechoic area on TRUS is reported at 18% to 42%.[16,18] Conversely, more than 30% of cancers are isoechoic and not visible on conventional TRUS, making them impossible to diagnose without systematic biopsy.[19] An older study of almost 4,000 patients published in 2004 revealed that hypoechoic lesions were not associated with increased cancer prevalence compared with biopsy cores from isoechoic areas, showing a comparable tumour detection rate.[20] In another study, TRUS biopsy has also been shown to be inaccurate in classifying grade or laterality in 30% to 50% of cases.[21] However, due to the high-quality images and the inexpensive and simple procedure, it is still the most optimal technique for guiding prostate biopsies, but as a standalone diagnostic approach, it fails to accurately assess the true disease burden.

Today, the gold standard for the identification of PCa lesions within the prostate is mpMRI. The PROMIS trial was one of the first studies revealing the high sensitivity of mpMRI for csPCa compared to TRUS biopsy (93%,

95% CI, 88%–96% vs. 48%, 95% CI, 42%–55%; $p<0.0001$) using transperineal template prostate mapping as the reference standard.[7] The following studies showed that mpMRI can localize the index lesion in approximately 80% to 95% of cases, with higher accuracy as Gleason grade and lesion size increase.[22] For this reason, patient selection for FT now always requires pretreatment evaluation with mpMRI.

Multiparametric ultrasound (US) and prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) have been investigated as an alternative option to mpMRI to improve the accuracy of PCa detection. They are discussed in the section "Prostate Cancer Lesion Identification and Localization" in this chapter.

Pretreatment assessment and evaluation

Several international multidisciplinary consensuses focused on patient evaluation that should precede FT.[8,23,24]

Complete medical history assessment and physical examination are standard requirements for any surgical procedure, including FT. A recent PSA measurement is essential to confirm the surgical indication and monitor post-ablation follow-up. PSA density is another useful tool for patient selection and follow-up.[25] Other PSA derivatives, such as PSA velocity and PSA doubling time, are not recommended, as their role is controversial.[23] The execution of a urine culture to guide the intra- and postoperative antibiotic choice is a common practice in FT programs.

Multiparametric MRI is a key element within the context of FT. It is essential to guide first the diagnostic biopsy and subsequently the focal ablation.[8,24] Before the surgery, mpMRI should be reviewed with a radiologist to check for factors potentially impacting prostate ablation, such as technical considerations (motion degradation, signal-to-noise ratio), calcifications, or the close proximity of the index lesion to the urethra, urethral sphincter, or rectum. This may guide the choice of the type of energy or device used.

Patients' functional status at baseline is equally important. Validated questionnaires should be used to assess preoperative urinary symptoms, sexual function, and bowel status (see section titled "Focal Therapy Outcomes and Follow-Up" in this chapter). Quality of life (QoL) should also be evaluated.[23] The execution of uroflowmetry is not essential but may provide additional data on outlet obstruction and postvoid residual, which can (temporarily) worsen following FT.[23]

All these assessments are essential to monitor the oncological, functional, and QoL outcomes in the post-ablation follow-up.

Prostate Cancer Lesion Identification and Localization

Multiparametric MRI

A complete mpMRI consists of a combination of anatomic (T1- and T2-weighted [T1W and T2W]) and functional images (diffusion-weighted imaging [DWI] and dynamic contrast-enhanced imaging [DCE]). These four sequences work together to detect the presence of areas suspicious for PCa within the prostate. DCE provides a baseline assessment of the tumour's characteristics and a comparator to assess success or failure post-FT and plan for possible repeat or salvage FT.

T1W images are essential to rule out the presence of biopsy-related residual hemorrhage that can hinder accurate visualization of tumours within the prostate. T2W images offer high-resolution anatomical detail, enabling the visualization of abnormalities within the prostate gland. Areas of low signal intensity on T2W sequences correlate with cancerous lesions. DWI is valuable in assessing tissue cellularity. Malignant lesions typically exhibit restricted diffusion due to increased cell density, leading to elevated signal intensity in these images. From this sequence, the apparent diffusion coefficient (ADC) mapping is derived, which provides quantitative information about the diffusion of water molecules in prostate tissue. Areas with lower ADC values are suspected areas of cancer. Finally, DCE images provide functional information regarding tissue vascularity and perfusion dynamics. Due to its tumour-induced neoangiogenesis, cancer generally shows early and high peak enhancement and early washout.[26]

By combining these mpMRI sequences, suspicious areas are classified according to a standardized scoring system, the Prostate Imaging–Reporting and Data System (PI-RADS), currently at its 2.1 version. This classification system establishes a common language for radiologists and clinicians to communicate findings, reducing ambiguity and variability in the interpretation of imaging results in the primary diagnostic pathway.[27]

Multiparametric MRI provides a nuanced view of the prostate gland, allowing for the detection, localization, and characterization of PCa. According to a Cochrane systematic review, mpMRI has a good performance in detecting csPCa, with a sensitivity of 91% (95% CI, 83%–95%).[28] Its PPV for csPCa varies according to the PI-RADS score, being low (16%; 95% CI, 7%–27%) for PI-RADS 3 and improving for PI-RADS 4 (59%; 95% CI, 39%–78%) and 5 (0.85; 95% CI, 73%–94%).[29] The negative predictive value (NPV) is also high (88%; interquartile range [IQR], 85%–92%) despite a non-negligible variability among studies, depending on PCa prevalence, quality of images, and experience of the readers.[30]

MRI-targeted fusion TRUS-guided biopsy

Prostate biopsy is performed using two different strategies. The systematic or mapping biopsy aims to homogeneously sample all the portions of the prostate to rule out the presence of PCa within the whole prostate.

The MRI-targeted biopsy aims to sample MRI-visible areas, as these are more likely to harbour csPCa.[7,31]

Systematic and template mapping biopsies

In the setting of FT, systematic biopsy is key, as it provides precise information about the local distribution of the tumour within the prostate gland. This is necessary to accurately select the most suitable candidate for FT. As FT can also be offered to patients with small foci of GS 6 PCa outside of the planned treatment of the index lesion, systematic or mapping biopsy is fundamental for identifying and monitoring these cancers over time.

Several systematic or mapping templates using different core numbers and core distributions have been adopted over time.

Originally conceived as a sextant template, the systematic biopsy evolved into an extended-sextant template including the sampling of the base, mid, and apex of each prostatic lobe, generally for a total number of 12 cores.[32–34] This approach showed a higher cancer detection rate compared with only a slightly increased detection of non-csPCa and did not negatively impact patients' morbidity.[35–37]

To maximize PCa detection, especially in case of persistent tumour suspicion despite prior negative biopsies, the concept of saturation biopsy or template mapping biopsy was introduced. This approach employed a greater number of cores, more than 20 and sometimes up to 40 or more, with the aim of accurately sampling other gland regions generally not biopsied. The usual approach for saturation biopsy is transperineal, and it is generally guided by specific template grids. Despite the potential for increasing PCa detection, this approach has a higher morbidity, with higher rates of urinary retention and infection.[38–40] Therefore, the clinical utility of saturation biopsy in the setting of repeat biopsy remains uncertain, especially in the current MRI-driven diagnostic pathway.[41]

Today, international guidelines recommend the use of at least 12 cores for systematic biopsy.[14] Although many examples of 12-core systematic biopsy templates are described in the literature, no systematic template has proven substantially superior to the others.

Fusion imaging and targeted biopsy

MRI-targeted prostate biopsy consists of the precise sampling of the lesion visible on mpMRI. Several trials compared MRI-targeted biopsy with systematic biopsy, revealing that the first can increase the detection of csPCa up to 20%–40% while reducing the rate of non-csPCa. This decreases the rate of rebiopsy, overtreatment, costs, and patient discomfort.[6,7,28,42–45]

The MRI-targeted prostate biopsy can be performed through three different modalities: cognitive, MRI/US software–based fusion, and, less frequently, in-bore guidance.

With the in-bore approach, mpMRI is performed at the same time as the prostate biopsy. Its images are fused with real-time TRUS to confirm the correct sampling of suspicious MRI-visible lesions. With the cognitive approach, the location of targets on TRUS is estimated mentally using preprocedural mpMRI as a reference. With the MRI/

US software–based fusion approach, specialized platforms are used to overlap preprocedural mpMRI onto real-time TRUS, allowing for the precise identification of MRI-visible lesions on TRUS images. Needle trajectories can be tracked and saved for postoperative review and can act as a reference at subsequent biopsies and/or treatments. This function is extremely useful for systematic biopsies, whose exact location may not otherwise be known. Some platforms also enable post-procedural 3D pictures that can assist in organizing multiple past positive biopsy targets, for instance, for AS.

Although high-quality comparative trials are lacking, cognitive fusion seems less accurate than the other two modalities. Indeed, despite being a significant addition to the "blind" systematic sampling, the accuracy of MRI/US software–based fusion may be skewed by the operator's ability to read mpMRI and TRUS imaging, especially in the case of small lesions and large prostates.[46,47] Despite being extremely accurate, the in-bore approach is expensive and time-consuming, making it uncommon in everyday clinical practice. Conversely, the software-based fusion approach is affordable, reproducible, precise, and, therefore, widely used.

Multiparametric ultrasound

Multiparametric US (mpUS) combines specific US techniques, including conventional B-mode TRUS, colour-doppler, contrast-enhanced US, and US elastography. All these modalities together allow for the characterization of different features of the gland, including not only its volume and vascularization but also its composition and architecture, with stiffness and enhancement properties, representing a promising tool to increase the detection and localization of PCa.[48]

Compared to each single US modality alone, mpUS has shown a higher sensitivity (74%) and a comparable specificity (59%).[49] Existing comparisons with mpMRI have provided controversial and immature evidence, with some reporting equivalence in detection rate and diagnostic accuracy, and other inferiority.[50–52] Nevertheless, the combination of mpUS with mpMRI may increase the overall detection rate. However, it is important to acknowledge that the utilization of mpUS is influenced by inter-individual variability and entails the need for training and additional time compared to individual techniques.[53] Hence, by now, the role of mpUS can be justified only when combined with mpMRI within the setting of a mpMRI-mpUS fusion biopsy or FT.

Molecular imaging techniques

In recent years, new molecular imaging techniques have been extensively investigated in the PCa setting. Among these, PSMA PET/CT scan is the most studied, being an important tool not only for PCa staging and recurrence but also for PCa initial diagnosis or staging and assessment for the risk of recurrence.

In a head-to-head comparison between PSMA PET/CT and mpMRI using RP as the reference standard, the cancer detection rate was high and similar for both imaging modalities (85% for PSMA PET/CT and 83% for mpMRI; p=0.093).[54] Interestingly, the combination of the two modalities outperformed the individual modality alone (detection rate of 87%; p=0.001).[54] Similar results were observed in a prospective multicentre trial reporting that the combination of the two methods led to an increase in NPV for csPCa compared with MRI alone (91% vs. 72%;

$p<0.001$), missing only 3% of csPCa cases when both PSMA PET/CT and mpMRI were negative.[45] Nevertheless, mpMRI was more accurate in detecting extraprostatic extension and seminal vesicle invasion. Thus, despite its promising utility, PSMA PET/CT is still less informative than mpMRI in the primary diagnostic setting, especially for T-staging.

PSMA PET/CT has also been considered to guide prostate biopsy. In a single-arm prospective trial, this imaging modality achieved accurate detection of csPCa (sensitivity 100%; specificity 68.4%; accuracy 80.6%; PPV for molecular imaging PSMA [miPSMA] 2–3, 66.7%; NPV for miPSMA 0–1, 100%). However, the detection rate of PET/TRUS-guided biopsy was not significantly higher than that of systematic sampling (38.7% vs. 32.3%; $p=0.25$).[55]

The main drawback of PET/CT scan is the limited intrinsic spatial resolution (around 3–5 mm), which is potentially insufficient for smaller PCa lesions. PSMA PET/MRI can overcome this limit, but unfortunately, its high costs and logistic shortcomings hamper its widespread adoption.

While today, PSMA PET/CT or /MRI still presents limitations, it has the potential to improve tumour extent delineation when combined with MRI or coregistration/fusion of PSMA PET/CT and mpMRI images during prostate biopsy.

Focal Therapy Techniques

Historically, the first energies used to treat PCa were cryotherapy and HIFU. With the increased enthusiasm for this treatment option due to its promising oncological control and optimal safety profile, new technologies using different energies have been developed during the past two decades, including FLA, PDT, IRE, and others under study.

Overview of focal therapy modalities

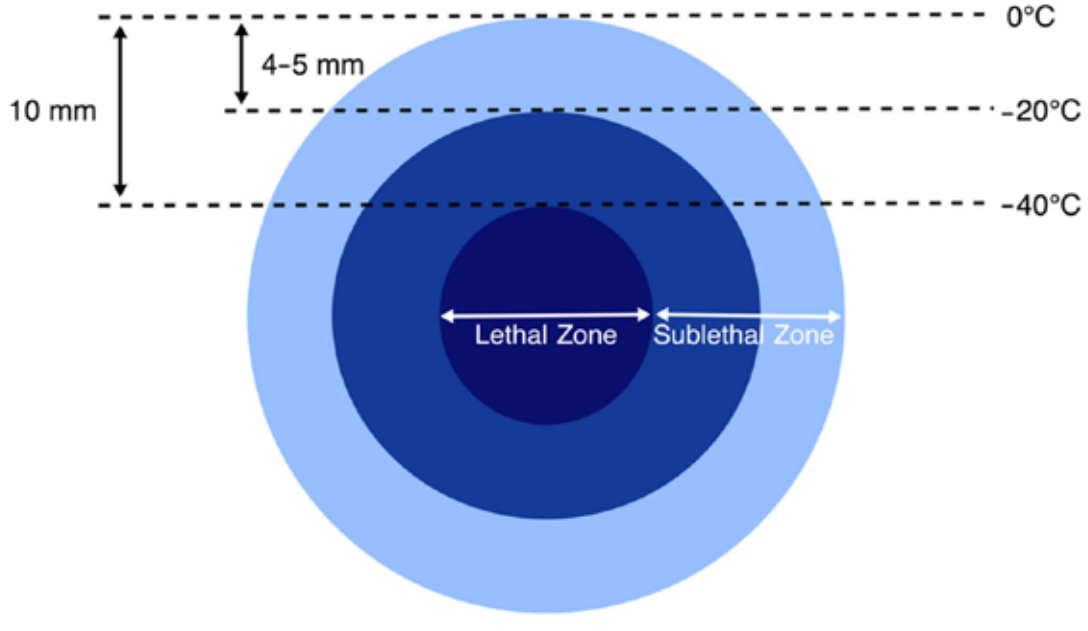
Cryotherapy

Mechanism of action

Cryoablation consists of two consecutive cycles of rapid freezing, where cells are exposed to lethal temperatures (below –40°C) followed by slow thawing. During the rapid freezing phase, the ice formation in the extracellular space causes severe extracellular hyperosmolarity, which ultimately results in intracellular dehydration and cell membrane damage.[56] Simultaneously, the ice formation in the intracellular space results in direct cell membrane disruption and cellular necrosis.[57,58] In addition, microvascular endothelial damage leads to thrombosis, ischemia, and coagulative necrosis.[59]

During the gradual thawing phase of the extracellular ice crystals, the hypotonic extracellular environment leads to the accumulation of water in the cells, edema, and further membrane damage.[58,60] Reperfusion injury is mediated by free radicals, which augment the process of enzymatic degradation and cell necrosis.[59] Several hours after the completion of cryotherapy, the process of apoptosis peaks within the sublethal zone (–10°C to ≤ –40°C), expanding the tissue necrosis zone (≤ –40°C) beyond the direct lethal effect of cryotherapy itself (**FIGURE 1**).[59,60] The antigen release during and following cellular destruction can elicit an immune reaction, leading to cytotoxic T cell–mediated death of tumour cells.[61,62] This may potentially impact the immune-mediated resolution of residual local or metastatic disease.[61,62]

FIGURE 1 Lethal and sublethal zones during cryotherapy. At temperatures between 0°C and –20°C, extracellular ice forms, leading to fluid shifts and cellular dehydration. As temperatures continue to cool, intracellular ice forms and is a major mechanism of cryoinjury. At temperatures between –20°C and –40°C, intracellular ice formation progresses, leading to disruption of the cell and interruption of all metabolic processes. The –40°C and –20°C isotherms are approximately 1 cm and 4–5 mm inside the leading edge of the ice ball, respectively.

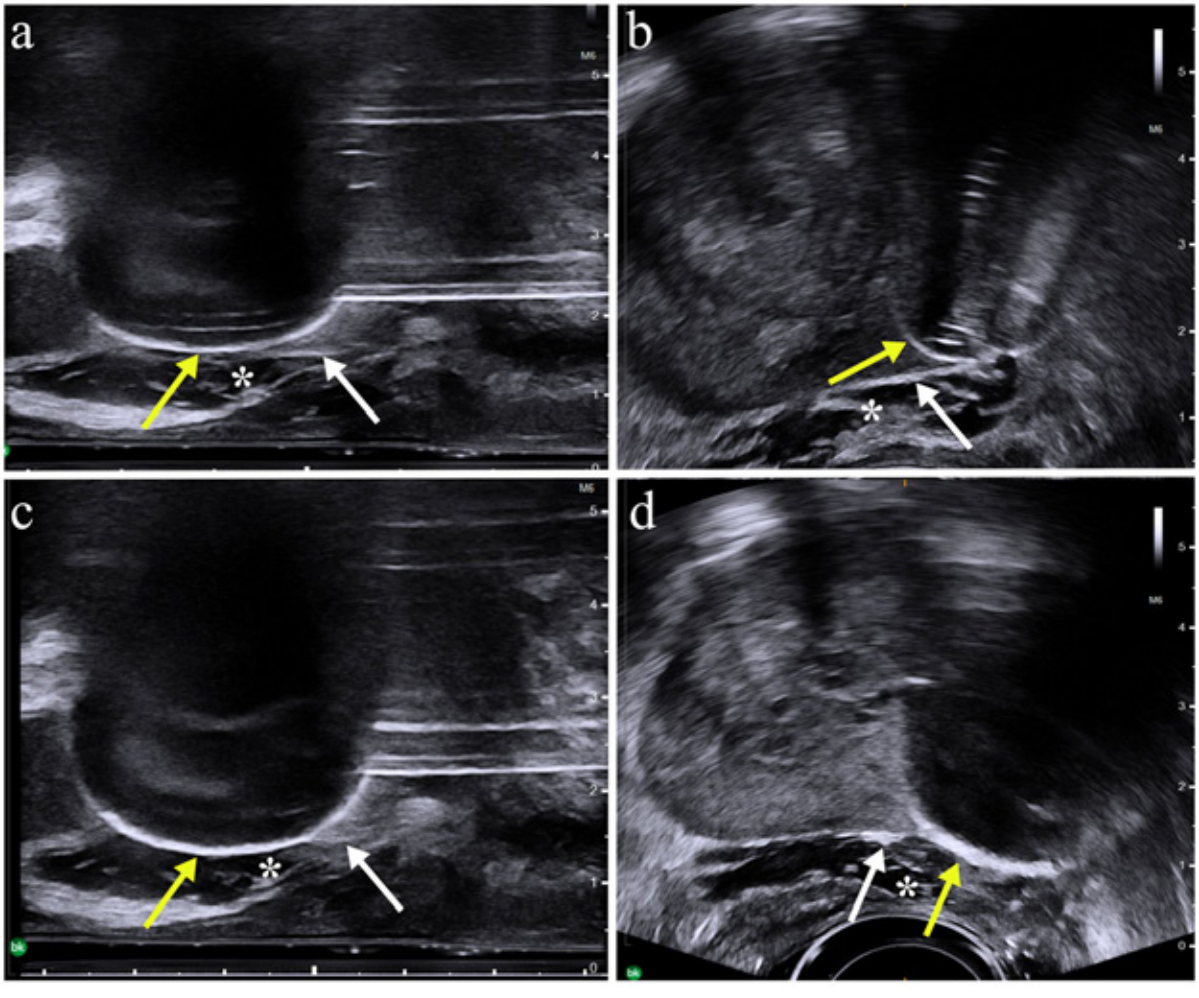


Procedure

Focal cryoablation for PCa is performed preferably under general anesthesia but local anesthesia and/or sedation have been utilized. The patient is placed in the dorsal lithotomy position. All the cryoprobes that deliver the treatment are inserted transperineally in the treatment area through the cryotherapy grid under real-time TRUS guidance. A free-hand approach (no grid) may be also used. Thermocouple probes are placed in the proximity of the Denonvilliers' fascia and external sphincter for real-time temperature monitoring. After that, a flexible cystoscopy is performed to confirm the absence of probes traversing into the urethra or bladder neck. A urethral

warming catheter is then passed over a super-stiff guidewire. Two consecutive cycles of rapid freezing (with argon gas or liquid nitrogen) and slow thawing (with helium gas) are performed. The progress and growth of the ice ball around each cryoprobe are monitored under TRUS guidance in both axial and sagittal planes with special attention to the rectal wall and urinary sphincter (**FIGURE 2**). At the end of the procedure, the thermocouples and cryoprobes are removed while the urethral warmer is sterilely replaced with a Foley catheter for temporary bladder drainage due to acute post-procedural prostatic edema, which typically resolves in a few days.

FIGURE 2 During rapid freezing, real-time monitoring of each cryoprobe shows the ice edge (**a-d**) that eventually coalesces and expands into a single ice ball shown in both sagittal (**a, c)** and axial (**b, d**) planes. White arrows point to the hyperechoic rim of the ice ball representing 0°C, and yellow arrows point to the prostatic capsule. The ice ball is generally allowed to expand into the Denonvilliers' space just shy of the anterior rectal wall (*). This margin should be well appreciated in both sagittal (**c**) and axial (**d**) views and determines when the operator completes freezing.



High-intensity focused ultrasound

Mechanism of action

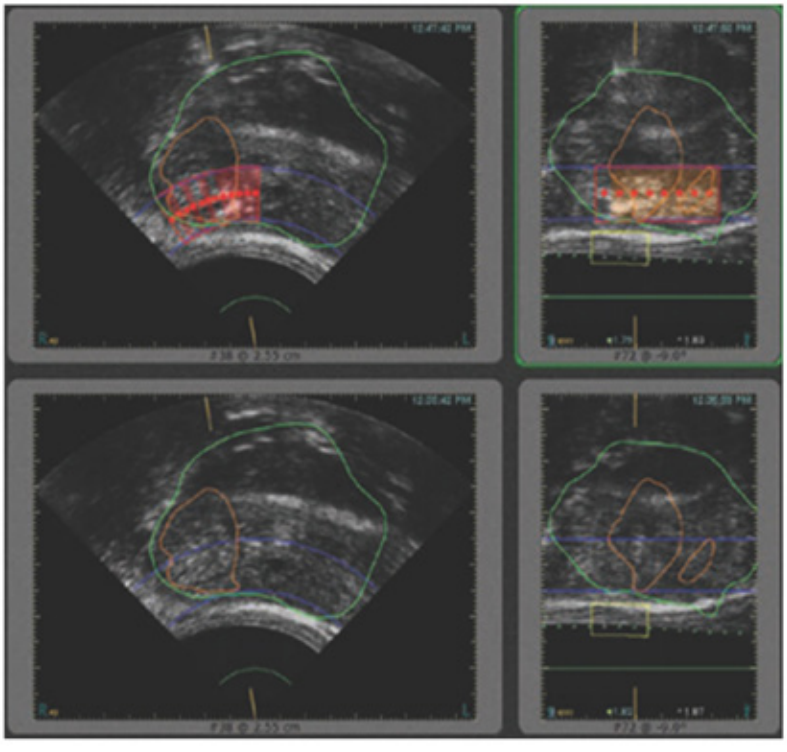
Ultrasound consists of mechanical vibrations produced by a crystal or transducer. These vibrations are produced by applying an alternating voltage across piezoelectric materials, which oscillate at the same frequency as the alternating current. A diagnostic US is of relatively high frequency (1–20 MHz) and results in insignificant, harmless energy deposition. Conversely, HIFU uses lower frequencies (0.8–4 MHz) at a high intensity (> 5 W/cm^2) and can cause selective thermal-mediated tissue destruction if delivered in a focused manner and maintained for an adequate amount of time.[63]

Tissue damage during HIFU occurs via two methods: hyperthermia and cavitation. Hyperthermia damage is obtained when thermal energy reaches temperatures up to 80°C and causes protein denaturation, disruption of the lipid cell membrane, coagulative necrosis, and irreversible cell death. Cavitation occurs when acoustic intensities are high enough to create microbubbles that interact with the acoustic field. As the microbubbles grow, they implode, resulting in shockwaves and microjets that can mechanically damage tissue. The following inflammatory response generated by both methods then leads to fibrosis and scar tissue deposition.[64,65]

Procedure

Focal HIFU for PCa is performed under general anesthesia although spinal anesthesia has also been described. A urinary catheter is placed to ensure urine flow during the procedure. Depending on the device used, the patient is placed in the dorsal lithotomy or right lateral position. The HIFU probe is placed into the rectum, and the gland is imaged. Using the HIFU control panel to review the images, the treatment zones are defined and logged into the treatment computer. Fusion of preoperative mpMRI images over real-time TRUS is used to overcome the differences between the acquisition plan of the two imaging modalities. After the target zone has been established, treatment is executed by the machine (**FIGURE 3**). The treatment can be paused, and the planning adjusted, if, during the ablation, the focal pulse points fall outside the contour of the target lesion on the TRUS images. Throughout the entirety of the procedure, rectal thermal injury is prevented with the use of a cooling system utilizing chilled, degassed water. A focal HIFU procedure can take between 1 to 2 hours, depending on the size of the treated area. At the end of the procedure, a urethral Foley catheter is placed into the bladder for some days.

FIGURE 3 Focal HIFU of an intermediate-risk right peripheral zone cancer. The green line is fused to the contours of the prostate at mpMRI using elastic registration. The orange contour represents the MRI lesion.



Abbreviations: HIFU, high-intensity focused ultrasound; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging.

Focal laser ablation

Mechanism of action

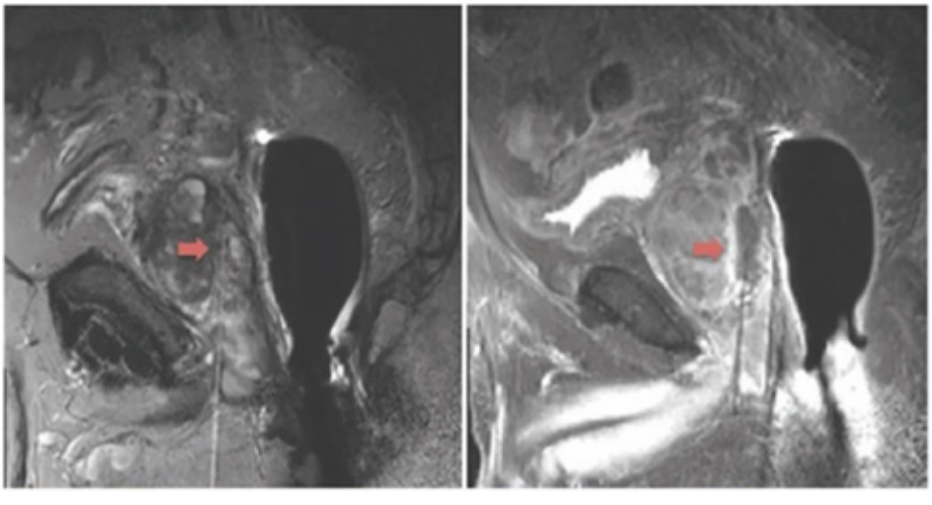
FLA causes thermal destruction of prostatic tissue by laser. Its action, based on a photothermal effect, results from the absorption of radiant energy by tissue-receptive chromophores inducing heat energy in a very short time (a few seconds).[66,67] This increased temperature causes cell death. At a temperature of more than 60°C, coagulation is quasi-instantaneous and irreversible protein denaturation also occurs.[68] The area subjected to 42°C and 60°C undergoes thermal damage with longer heating periods, developing coagulative necrosis in 24 to 72 hours after the treatment.[69,70]

Procedure

FLA can be performed in general, spinal, or local anesthesia depending on the treatment approach. The patient is placed in the lithotomic or dorsal lithotomy position based on the surgical approach (transperineal or transrectal). A US probe is placed into the rectum for intraoperative guidance. The identification of the target(s) on TRUS

images is typically made with an MRI-fusion or in-bore approach (**FIGURE 4**).[71–73] Then, a small 12/14 Fr cannula containing the laser fibre applicator with a 400–600 μm fibre contained within is positioned in the treatment area. Once an appropriate location is confirmed, the sheath overlying the laser fibre is withdrawn revealing the diffusing laser fibre tip. Additional temperature probes can be placed adjacent to critical structures to ensure the temperatures of sensitive tissues do not exceed a safety threshold of 50°C.[74,75] The laser is then activated until the desired volume of prostate destruction is obtained. Typically, the laser is set to 8–15 W, and ablation times of 1–2 minutes are selected to obtain ablation spheres/ellipsoids of various sizes. Multiple abutting ablations are often needed to completely ablate lesions of larger size. A urinary catheter can be placed at the end of the procedure for a few days.

FIGURE 4 MRI images before (left) and after (right) FLA. The tip of the trocar/laser can be visualized by the red arrow.



Abbreviations: FLA, focal laser ablation; MRI, magnetic resonance imaging.

Vascular photodynamic therapy

Mechanism of action

WST-11 (Padeliporfin, TOOKAD® Soluble; Steba Biotech SA, Luxembourg, Luxembourg) is the most widely used photosensitizer for vascular PDT.[76] It is a water-soluble agent circulating with serum albumin until hepatic clearance, with a half-life of 30–60 min in humans.[77] Its rapid elimination from the body implies the need to avoid sunlight just for a limited time after treatment. Illumination of WST-11 at 753 nm leads to the intravascular generation of free radicals with complete vascular arrest of tumour-feeding arteries and draining veins.[77–79] This results in a profound ischemic injury and subsequent non-thermal coagulative necrosis of the target tissue, with minimal to no thermal dispersion to surrounding tissues.[78,80] Importantly, because it is confined to the circulation, the wave of damage evoked by photoexcitation does not impact the collagenous scaffold of the connective tissue.[81]

Procedure

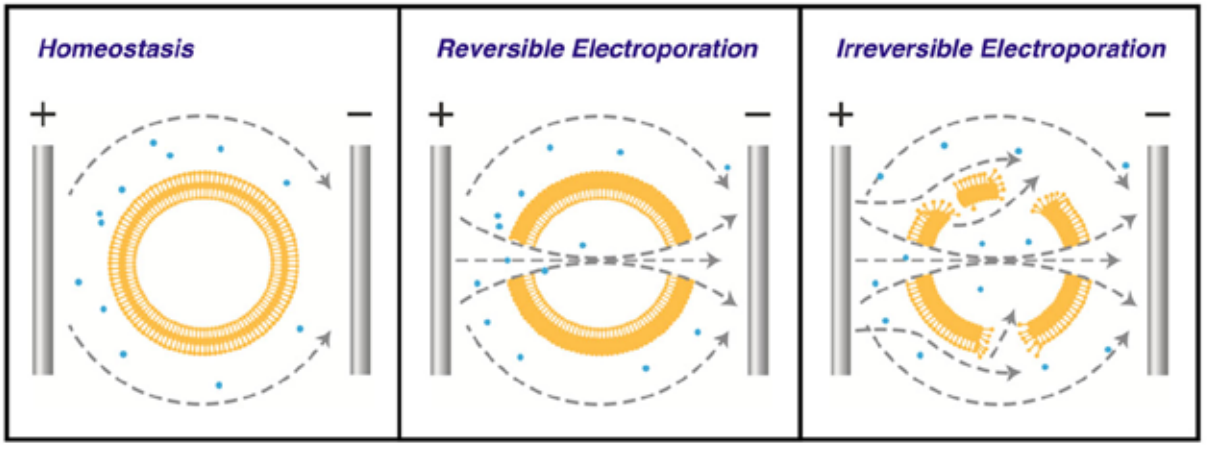
Vascular PDT is typically performed under general anesthesia. The patient is in the lithotomic position. After the insertion of a urethral Foley catheter, hollow transparent needle catheters are inserted transperineally through a brachytherapy grid at the target sites under TRUS and mpMRI guidance.[15,82] Optical fibres with cylindrical diffusers of specific lengths are inserted within the catheters to deliver targeted light doses to the prostate. The length of the diffusing part of the fibre is based on the TRUS images according to the tumour volume and geometry. A light-detecting probe is also placed into the rectum to ensure that the light dose is sufficiently low to minimize energy delivery to areas outside of the prostate. The photosensitizer, typically WST-11, is then administered intravenously over a 10-minute infusion. It is thus activated locally by a specific wavelength of light (753 nm) applied over about 22 minutes.[82] The entire procedure takes approximately 1.5 to 2 hours to complete. Afterward, the fibres are removed, and the patient recovers for some hours in a low-level lightroom. The urethral catheter is removed the day after. The patient is discharged on the day of treatment with instructions to avoid direct sunlight for 24 hours.

Irreversible electroporation

Mechanism of action

Electroporation is a phenomenon in which a series of bipolar electric pulses, traveling between two electrodes at a time, are used to create nanopores in cell membranes. These pores allow molecules to pass into the cell. Above a certain threshold, the nanopores become permanent, causing cell death due to the inability to maintain homeostasis causing IRE (**FIGURE 5**).[83,84]

FIGURE 5 Schematic illustration of reversible electroporation and irreversible electroporation. With *reversible electroporation*, the electric field temporarily disturbs the phospholipid bilayer, allowing molecules to pass through the cell membrane into the cell. With *irreversible electroporation*, the electric field passes through the cell membrane, resulting in permanent permeabilization of the cell, loss of homeostasis, and apoptotic-like cell death.

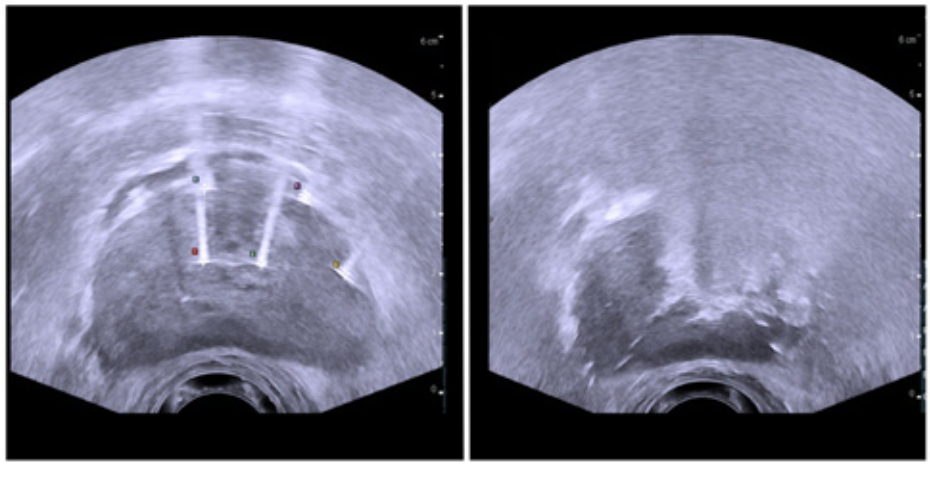


The peculiarity of IRE is that it is a non-thermal treatment.[85,86] This results in connective tissue structure preservation and minor damage to blood vessels, neural tissue, or other vital structures.[87–89] In the context of PCa, this results in potential lower toxicity of neurovascular bundles, rectal wall, sphincter, and urethra and tissue distortion.[85,90]

Procedure

IRE is performed under general anesthesia and deep muscle relaxation (curare-induced muscle blockade) to avoid the induction of strong contractions that could alter or displace the US or electrode probe placement. The patient is placed in the lithotomy position. A transurethral Foley catheter is inserted. Treatment volume is identified by merging mpMRI and real-time TRUS findings via a cognitive- or software-based MRI-US fusion system. Then, the 19 Fr unipolar electrode needles are inserted transperineally under continuous TRUS guidance using a brachytherapy grid. A minimum of two monopolar electrodes are needed, and up to six can be placed. For a 1-cm lesion, a three-electrode configuration can effectively cover the target volume. For larger lesions, four needles are the best option, in either a square or diamond configuration, depending on the shape and location of the target volume (**FIGURE 6**). The active part of the electrode is exposed by retracting an isolating sheath of the necessary length. Finally, the short-duration, high-voltage direct current is released to destroy the area. By default, direct current pulses of 1,500 volts/cm by 90 µs are delivered. To obtain IRE, a direct current at the intensity of 30–40 Ampere should be administered between each pair of electrodes. Volts/cm and pulse length can be adapted following the feedback graph provided by the software. The treatment is then launched by 90 electric pulses between each electrode pair. The duration of IRE is around 30 to 60 minutes from Foley catheter insertion to needle ablation. At the end of the procedure, electric feedback charts are verified, and electrodes are pulled out. The patient can generally be discharged in the first 24 hours and the catheter is removed in less than 3 days.

FIGURE 6 Ultrasound images before IRE (left), needles in place and relative distances are measured; after treatment (right), ultrasound shows artifacts mainly due to electrophoretic gas generated by high-voltage current.



Abbreviation: IRE, irreversible electroporation.

Procedural tips and tricks

Regardless of FT energy, correct probe placement is essential. MRI/US software–based fusion systems or in-bore MRI can assist in the coregistration of images in this phase, especially in large glands. Some software enables pretreatment planning mimicking the extension of the ablation, allowing the urologist to check for proper cancer coverage before treatment delivery. Any intraparenchymal landmarks, such as cysts or nodules of adenoma and/or calcifications, can be used to confirm the location of the tumoural lesion.

If the ablation involves the positioning of more probes, such as cryoablation or IRE, these should be placed taking care that no cancerous tissue between the probes is left uncovered. Checking the extent of the ablation on the sagittal and axial planes on real-time TRUS allows one to easily avoid this problem. Specifically, for cryoablation, probes delivering energy may be activated asynchronously to control the formation of the ice balls according to the needs of the procedure.

Including the urethra in the ablation region can result in urethral slough and/or urethral strictures. To avoid this scenario, it is prudent not to place the probes or to direct the treatment in the areas near the urethra/sphincter, especially along the sagittal axis where the urethra can be s-shaped. With cryoablation, this problem is limited by using the thermal catheter. In this light, the correct functioning of the circulation pump should always be checked: the temperature of the water must be at 40–42°C and no descent of the water level in the bag should be observed, as this suggests the presence of a leakage, which often is caused by probes repositioning with the catheter already inserted.

The inclusion of the rectum in the ablation zone can cause a rectal fistula. For transperineal techniques, such as cryoablation and FLA, this risk can be limited by reducing the pressure of the TRUS probe on the rectal anterior wall or releasing the grid from the stepper once the probes are secured and placed in the optimal position. Alternatively, injecting saline (intraoperatively) or a biodegradable hydrogel spacer (generally 2 weeks before the procedure) placed between the prostate and the rectum is another useful option. Temperature monitoring with thermocouple probes is also important. For transrectal techniques, such as HIFU, rectal cooling is essential.

Intraprostatic calcifications shield the energy conducted by HIFU, resulting in inadequate tissue heating or reflecting energy back toward the rectum. The removal of these calcifications by transurethral resection of the prostate (TURP) is an option to overcome this limitation. Suboptimal treatment can also occur during the treatment of transition and anterior lesions in large glands, as a large distance from the transrectal probe may compromise effective energy delivery. Here, preoperative treatment with 5-alpha reductase inhibitors or, more anecdotally, “debulking” TURP may be used to reduce gland size. Alternatively, the choice of a different type of energy may be considered.

FT is a minimally invasive treatment that can be performed under different anesthesia regimens. While local anesthesia puts the patient at a lower risk for complications, under this regimen, the patient is more inclined to movement, which can impair the precision of the treatment. Therefore, the type of anesthesia should be carefully considered balancing between the risk for anesthesiologic complications and that of suboptimal treatment due to the patient’s movement.

Investigation therapies—update

Nanoparticles ablation

Mechanism of action

Nanoparticle ablation is a type of targeted photothermal therapy.[91] Nanoparticles are composed of a dielectric core with a metallic outer shell, most commonly a silica core and gold shell (AuroShells; Nanospectra, Houston, Texas, USA). Inert on their own, these 150-nm diameter particles can be excited by absorption of laser-emitted near-infrared light, converting it into thermal energy. This process is known as surface plasmon resonance, wherein particular frequencies of light result in collective oscillation and excitation of the nanoparticle surface electrons, ultimately causing hyperthermia.[92] AuroShells must accumulate at sufficient concentrations within the target lesion. Due to the faulty vascular systems of solid tumours, these molecules can leach out into surrounding tissues, allowing AuroShells to amass preferentially within tumours, to be finally cleared or sequestered via the liver-spleen axis.

Procedure

Patients are intravenously infused with the AuroShell solution at a concentration of 7.5 mL/kg the day before the planned procedure to allow adequate time for concentration within the tumour. Under general or regional anesthesia, trocars are guided transperineally into the target lesions using the previously obtained images from the MRI-TRUS fusion biopsy as a roadmap. Through these trocars, infrared laser fibres are introduced. Whenever activated, the laser excites the AuroShells causing thermal ablation of the tissue surrounding the trocars, ultimately leading to cell death.

An ongoing trial (NCT04240639) is evaluating long-term results of this modality.

Transurethral ultrasound ablation—TULSA

Mechanism of action

The mechanism of cell destruction of transurethral ultrasound ablation (TULSA) is similar to that of HIFU.[93]

Procedure

The patient is under general anesthesia in a lithotomic position.[94] The TULSA procedure is performed under real-time MRI guidance. The US applicator is placed in the prostatic urethra and the rectal cooling device adjacent to the prostate. The correct placement of both devices is verified using MRI. Anatomical MRI images are acquired to plan and delineate the treatment areas on the treatment delivery console. Then, the US applicator, guided by a robotic arm, is used to apply heat to the specified prostate regions. Typically, the system can deliver heat up to 30 mm from the US applicator to the periphery. The treatment delivery is checked under the guidance of continuous MRI thermometry and temperature control in a closed loop. Based on real-time MRI thermometry, the system automatically adjusts US power to prevent both under- and overheating.

An active clinical trial (NCT05438563) is assessing this modality for intermediate-risk PCa.

Focal microwave ablation

Mechanism of action

Microwave is a novel thermal ablation modality using radio waves. High- or medium-frequency currents cause frictional heating between ions, increasing kinetic energy. Radio waves destroy tissue when temperatures rise above 50°C for about 5 min, causing cell membrane damage, denaturation of protein, and direct cytodestruction.[95] Usually, temperatures above 60°C are used for ablation. Microwave propagation depends mainly on the permittivity of the medium rather than the thermal conductivity or tissue impedance and causes coagulative necrosis in a more predictable and controllable way in comparison to other energy sources.[96]

Procedure

In general or regional anesthesia, a 17-G treatment needle is inserted transperineally or transrectally into the prostate via a dedicated grid. This phase is generally performed under fusion MRI/TRUS guidance. The fusion system allows for virtual simulations of the elliptical treatment area according to the needle position and microwave settings. Once the virtual simulation is satisfactory, the microwave energy is delivered to the target area. The microwave power is generally set to 12 W based on a preclinical predictive ablation chart, while the duration has to be decided according to the area to be treated.[97]

The FOSTINE trial (NCT03023345) is investigating the results of this FT modality.

Water vapour ablation

Mechanism of action

Water vapour ablation is a technology utilized as a minimally invasive treatment for benign prostatic hyperplasia. Recently, this concept has also been applied to treating localized PCa. Via a device inserted through the urethra, sterile, high-pressure steam is directed into the prostatic lesion. The steam condenses and transfers thermal energy (up to ~103°C) directly into the targeted tissue, causing coagulative necrosis.[98]

Procedure

The procedure is carried out under general anesthesia in an outpatient setting. A handheld delivery device deploys a temperature-resistant needle transurethrally into the prostate under cystoscopic and TRUS guidance. Water vapour is then delivered through the needle and visualized with real-time TRUS. Water vapour is delivered in 10-second treatments, causing irreversible thermal ablation. The needle is then either repositioned along the same path for additional vapour cycles at adjacent sites or retracted and repositioned for treatment in another area of the prostate. After the procedure, patients are discharged with a urethral catheter.[98]

The VAPOR 2 Study (NCT05683691) is an ongoing clinical trial currently evaluating the oncological and functional safety of this FT modality.

Treatment Planning and Execution

Role of multidisciplinary teams in treatment planning

The role of a multidisciplinary team in planning FT for PCa is critical to achieving optimal success. It should bring together the expertise of several figures including urologists, radiologists, pathologists, anesthesiologists, and specialized nurses. The urologist has the crucial role of proposing this treatment option to well-selected patients and contributing with their surgical knowledge of prostate anatomy when performing the treatment. The radiologist provides the interpretation of the prostate mpMRI and real-time TRUS to accurately localize cancerous lesions and critical structures such as the urinary sphincter, rectum, and neurovascular bundles. The pathologist contributes by analyzing the samples of preprocedural biopsy—to confirm the presence and grade of PCa and its location—and follow-up biopsies to evaluate treatment response. The anesthesiologist can assist the urologist with local anesthesia block or offer spinal or general anesthesia, in IRE cases with deep muscle relaxation (full paralysis 0-twitch), when indicated. Specialized nurses support patient care and education, ensuring the patient is well informed and prepared for the procedure. By integrating diverse professional perspectives, multidisciplinary teams ensure a thorough evaluation and a tailored treatment plan that aligns with the patient's specific clinical needs and personal preferences.

Lesion targeting and margin

Lesion targeting

The standard of care for identifying the tumoural lesion is mpMRI.[3] Similarly to MRI-targeted prostate biopsy, for FT, the cancer lesion can be identified through a cognitive, MRI/US software–based fusion, or in-bore approach. The fusion and in-bore approaches, being less operator dependent than the cognitive one, can tailor the treatment of the index lesion more precisely and potentially guarantee better functional outcomes while maintaining safe oncological control.

HIFU typically involves a software-based MRI/US-fusion approach. Other FT energies, such as cryoablation and IRE, can be performed in a cognitive or software-based MRI/US fusion. FLA can be performed under real-time MRI thermometry. TULSA is typically performed under in-bore MRI.

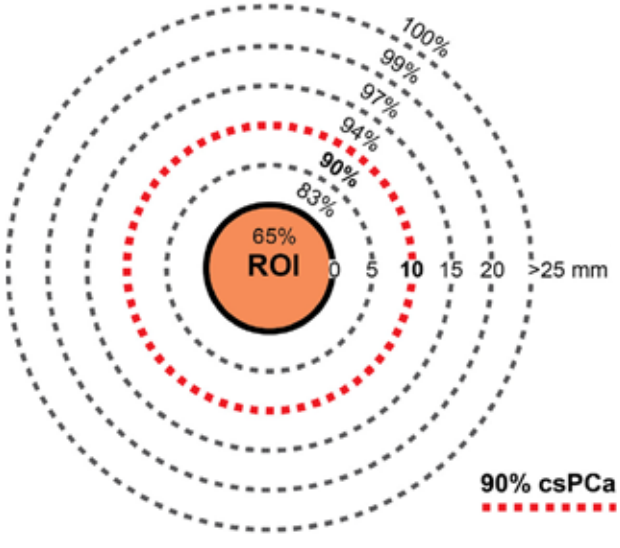
While in-bore FT is extremely precise and expensive, cognitive FT may result in an excessively wide treatment area, potentially compromising functional outcome. In this light, the MRI/US software–based approach may be the ideal compromise for an FT program. Today, the market offers several software devices that allow for 3D surgical navigation of the pelvic anatomy and visualization of needle trajectories of the prior biopsy, providing a comprehensive understanding of the tumour location and extension and its relationship with surrounding structures.

Margin

The adoption of an adequate surgical margin surrounding a tumour is common in all organ-conserving surgery, such as partial nephrectomy, partial penectomy, and partial ureterectomy. Compared to these treatments, FT for PCa has some challenges to overcome due to the absence of a postoperative specimen to evaluate margin status.

Multiparametric MRI is a valuable tool to guide the urologist during FT. However, it has been shown that mpMRI tends to underestimate tumour volume, despite its wide variability (4%–97%).[99,100] In a study by Sorce *et al.*, significant underestimation was reported between the volume at mpMRI and that at RP, especially in the low volume range (< 2 mL), where the volume at RP almost doubled that at mpMRI.[101] More recently, Brisbane *et al.* found that up to 90% of csPCa can be present within a radius of 10 mm from the nearest MRI-visible lesion (**FIGURE 7**).[102]

FIGURE 7 Diagrams showing the overall cumulative distribution of biopsy cores containing csPCa (% of total) in and around MRI lesion (region of interest, ROI). Note that 90% of csPCa cores are found within a 10-mm radius from ROI surface (dashed red line), but only 65% are within ROI. Percent of csPCa (95% CI) within: ROI, 65% (63–67%); 5 mm, 83% (81–84%); 10 mm, 90% (89–91%); 15 mm, 94% (93–95%); 20 mm, 97% (96–98%); and 25 mm, 99% (98–99%).



Abbreviations: CI, confidence interval; csPCa, clinically significant prostate cancer; MRI, magnetic resonance imaging; ROI, region of interest.

Source: *Reprinted from* Eur Urol, *82/3, Brisbane WG, Priester AM, Ballon J,* et al.*, Targeted prostate biopsy: umbra, penumbra, and value of perilesional sampling, pp. 303–310, Copyright 2022, with permission from Elsevier.*[102]

Therefore, an additional margin exceeding the MRI-visible index lesion to ensure adequate treatment coverage is the standard of care when performing FT. According to a consensus meeting by Donaldson *et al.*, a margin of 5–10 mm is generally enough to guarantee complete tumour coverage and optimize oncological outcomes, without negatively impacting functional outcomes and complications rate.[8] This balance of precision and comprehensiveness in treating the targeted lesion and its immediate surroundings is vital for the long-term success of FT.

Real-time monitoring and feedback

Real-time monitoring during treatment delivery is paramount during FT and is carried out under TRUS guidance. For the majority of FTs, the prostatic parenchyma generally reacts to the treatment becoming hyperintense (popcorn effect). The urologist can monitor the complete coverage of the treatment area by checking the extension of this hyperintensity. Conversely, for focal cryoablation, treatment is monitored by checking the extension of the ice ball along the prostate. In this regard, the integration of sagittal, coronal, and axial planes of TRUS is essential to obtain an oncologically safe treatment.

Less commonly, FT can be performed under intraoperative MRI guidance. This method increases not only treatment precision but also its costs. Several studies have reported the use of this technique with HIFU,[16,103] FLA,[71,104] and TULSA.[93,105] However, to date, there is no evidence supporting its superiority.

Some FT energies, such as FLA, HIFU, and TULSA, use MRI thermometry to provide real-time temperature feedback to ensure accurate tumour ablation and preservation of the surrounding tissues.[106] This option does not apply to cryoablation because free water shifted into ice crystals does not contribute to the MRI signal but the ice ball can be easily visualized.[107,171]

Anesthesia considerations

FT can be performed under different anesthesia regimens according to the modality used.

HIFU is generally performed under general anesthesia, although it can also be carried out under spinal or epidural anesthesia. IRE should be conducted under general anesthesia and deep muscle relaxation to avoid the short pulses of direct electrical current that cause muscle contraction. Also, PDT is typically performed under general anesthesia. FLA and cryoablation have the best anesthesiologic safety profiles and can potentially allow for in-office treatment with local anesthesia and mild sedation/nitrous oxide.

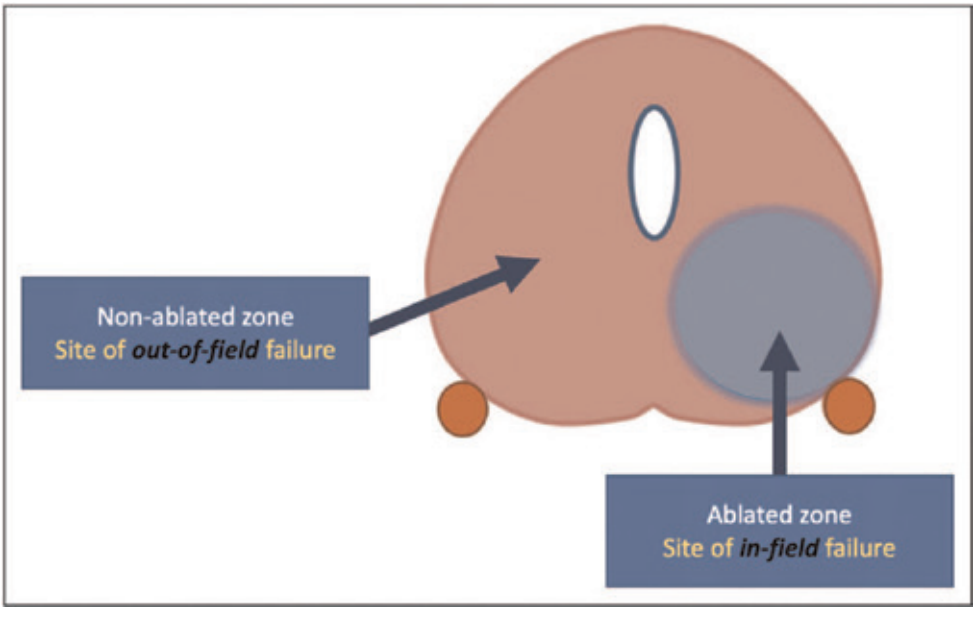
While reducing the patient's degree of consciousness increases anesthesiologic risk and costs, it may impair the alignment between MRI and TRUS and correct probe positioning due to patient movement, thus potentially compromising cancer control. Therefore, the choice of local or spinal/general anesthesia should be balanced between several aspects, including FT modality requirements, patient needs, and challenges due to patient motion.

Focal Therapy Outcomes and Follow-Up

Evaluation of treatment efficacy

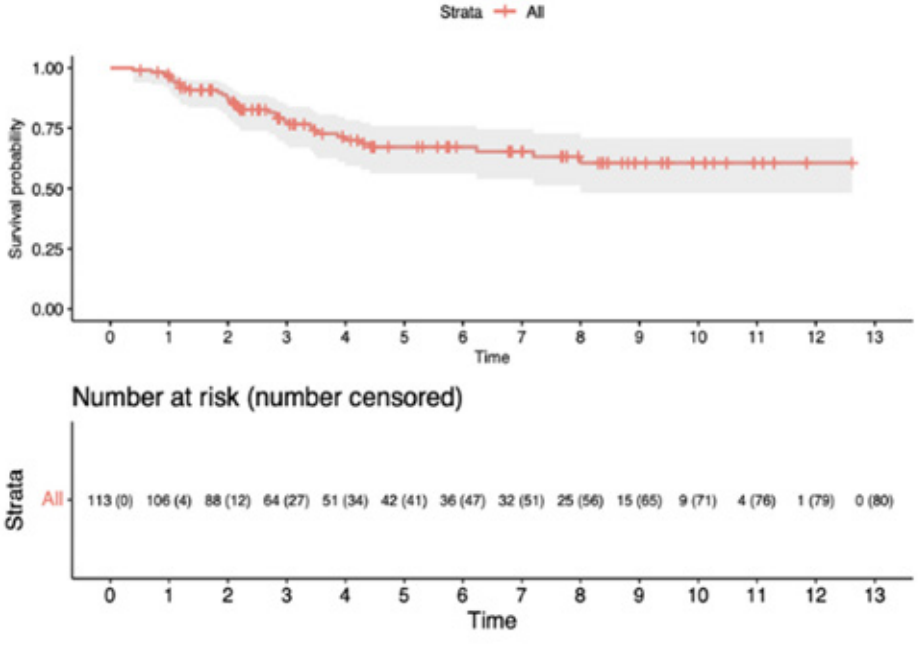
Evaluation of treatment efficacy is based on primary endpoint reporting medium- to long-term oncological outcomes of survival free from csPCa (in-field and out-field) recurrence and salvage whole-gland treatment at follow-up intervals. Results are illustrated with Kaplan Meier Curves (**FIGURES 8 and 9**).

FIGURE 8 Pattern of focal therapy failure.



Source: *Reprinted from* Curr Opin Urol, *32(3), Kotamarti S, Séguier D, Arcot R, Polascik TJ, Assessment after focal therapy: what is the latest?, pp. 260–266, Copyright 2022, with permission from Wolters Kluwer Health, Inc.*[110]

FIGURE 9 CsPCa in-field recurrence-free survival rates at 1, 3, 5, 7, and 10 years are 0.96 (95% CI, 0.90–0.98); 0.78 (95% CI, 0.68–0.85); 0.67 (95% CI, 0.56–0.76); 0.65 (95% CI, 0.54–0.74); and 0.60 (95% CI, 0.48–0.71), respectively (HIFU series *n*=114).



Abbreviation: HIFU, high-intensity focused ultrasound.
Source: *Titecat P. et al. HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

Standardization of pretreatment patient selection and post-treatment follow-up could benefit FT by reducing the risk for disease progression. Items to be collected and allowing for outcomes of survival free from csPCa recurrence are shown in **TABLES 1, 2, and 3**.

Secondary endpoints are aimed at evaluating adverse pathology results at salvage RP, biochemical recurrence, and metastatic progression in patients treated by quadrant or hemi-ablation HIFU for unilateral localized PCa. These endpoints will be addressed in another chapter.

Regarding follow-up protocols, there is a lack of standardization after focal treatment, in contrast to the well-structured follow-up inherent in AS. While most studies rely on PSA kinetics, MRI, and biopsy for surveillance, there is no consensus on the timing for these exams.[108,109]

TABLE 1 Pretreatment: Clinical, mpMRI, and Biopsy Data

Item*	Type/Values
Date of Birth	DD/MM/YYYY
Biopsy Imaging and Clinical	
Pretreament Biopsies	
Number of systematic biopsy	Numeric
Number of systematic biopsy positive	Numeric
Number of targeted biopsy	Numeric
Number of targeted biopsy positive	Numeric
Treated Lesion	
Grade group index lesion	1–5
Maximum cancer core length	mm
Percentage of grade 4	Percentage
Positive sextants at biopsy	Yes(1)/No(0)
Positive biopsy at base	Yes(1)/No(0)
Positive biopsy at mid	Yes(1)/No(0)
Positive biopsy at apex	Yes(1)/No(0)
Positive lobe at biopsy	Yes(1)/No(0)
Positive biopsy at left lobe	Yes(1)/No(0)
Positive biopsy at right lobe	Yes(1)/No(0)
Second CS-treated lesion (outside primary CS-treated area)	Yes(1)/No(0)
Untreated non-CS lesion (outside treated area)	Yes(1)/No(0)
Imaging	
MRI	Yes(1)/No(0)
Visible lesion on MRI	Yes(1)/No(0)
MRI PI-RADS score	1–5
MRI lesion positive at targeted (or systematic) biopsy	Yes(1)/No(0)
MRI lesion largest diameter positive at biopsy	mm
MRI lesion location at base (PZ)	Yes(1)/No(0)
MRI lesion location at mid-gland (PZ)	Yes(1)/No(0)

Abbreviations: 5-ARI, 5-alpha-reductase inhibitors; ADT, androgen deprivation therapy; CS, clinically significant; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; N/M, lymph node/metastasis stage; PI-RADS, Prostate Imaging–Reporting and Data System; PSA, prostate-specific antigen; PZ, peripheral zone; RP, radical prostatectomy; US, ultrasound.

Source: *Titecat P,* et al. *HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

TABLE 1 Pretreatment: Clinical, mpMRI, and Biopsy Data *(Cont'd)*

MRI lesion apex location (PZ) (within 6 mm from apical surface)	Yes(1)/No(0)
MRI lesion posterior location (posterior to 17 mm from rectal surface)	Yes(1)/No(0)
MRI lesion anterior location (anterior to 17 mm distance from rectal surface)	Yes(1)/No(0)
MRI (or US) prostate volume	cc
Clinical Data	
Pretreatment hormonal use (5-ARI or ADT)	Yes(1)/No(0)
Prebiopsy PSA	ng/mL
PSA density (PSA/vol)	ng/mL/cc
Stage cT1C	Yes(1)/No(0)
Stage cT2	Yes(1)/No(0)
Stage cT3/T4 or metastatic (N/M)	Yes(1)/No(0)
Patient fitted for RP	Yes(1)/No(0)
*Date should be collected for each exam, event, or treatment (DD/MM/YYYY).	

Abbreviations: 5-ARI, 5-alpha-reductase inhibitors; ADT, androgen deprivation therapy; CS, clinically significant; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; N/M, lymph node/metastasis stage; PI-RADS, Prostate Imaging–Reporting and Data System; PSA, prostate-specific antigen; PZ, peripheral zone; RP, radical prostatectomy; US, ultrasound.
Source: *Titecat P,* et al. *HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

TABLE 2 Treatment: Clinical, mpMRI, and Biopsy Data

Treatment*	
Age at treatment	DD/MM/YYYY
Energy	
Focal	Yes(1)/No(0)
Quadrant ablation	Yes(1)/No(0)
Hemi-ablation (< 50% of prostate volume treated)	Yes(1)/No(0)
Subtotal (50%–70% of prostate volume treated)	Yes(1)/No(0)
Treatment only of visible lesion at MRI	Yes(1)/No(0)
Treatment of both lobes	Yes(1)/No(0)
Treatment of all CS cancer lesions	Yes(1)/No(0)

Abbreviations: BPH, benign prostatic hyperplasia; CS, clinically significant; DRE, digital rectal examination; ISUP, International Society of Urological Pathologists; mo, months; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PSAv, prostate-specific antigen velocity; TURP, transurethral resection of the prostate.
Source: *Titecat P.* et al. *HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

TABLE 2 Treatment: Clinical, mpMRI, and Biopsy Data *(Cont'd)*

Treatment report (safety distance to apex; distance to base; treated volume)	
Treatment failure	Yes(1)/No(0)
Associated pre- or per-ablation session TURP	Yes(1)/No(0)
Cancer in BPH material	Yes(1)/No(0)
ISUP stage of cancer in BPH material	1–5
Follow-up	
PSA	
PSA at 3, 6, 12, 18, 24, …120 months	Numeric (ng/mL)
PSA nadir	Numeric (ng/mL)
PSA density post-treatment	Numeric (ng/mL)
Biochemical progression Definition: nadir+2 ng/mL / PSA nadir of 1.0 ng/mL at 12 mo and 1.5 ng/mL 24 to 36 mo	Yes(1)/No(0)
PSAv > 0.5 ng/mL/yr	Yes(1)/No(0)
Biopsy/MRI	
MRI per protocol (6–18 mo post-treatment)	Yes(1)/No(0)
Suspicious lesion at per-protocol MRI	Yes(1)/No(0)
Biopsy per protocol (6–18 mo post-treatment)	Yes(1)/No(0)
Cancer at per-protocol biopsy	Yes(1)/No(0)
CS cancer at per-protocol biopsy	Yes(1)/No(0)
Same items MRI/biopsy per protocol (> 18 mo post-treatment)	Yes(1)/No(0)
MRI for cause	Yes(1)/No(0)
Suspicious lesion at for-cause MRI	Yes(1)/No(0)
Biopsy for cause (PSA elevation or suspicious DRE)	Yes(1)/No(0)
Biopsy for cause	Yes(1)/No(0)
Cancer at biopsy for cause (for each biopsy)	Yes(1)/No(0)
CS cancer at for-cause biopsy (for each biopsy)	Yes(1)/No(0)
Post-Treatment BPH surgery	
Cancer in BPH material	Yes(1)/No(0)
ISUP stage of cancer in BPH material	1–5
*Date should be collected for each exam, event, or treatment (DD/MM/YYYY).	

Abbreviations: BPH, benign prostatic hyperplasia; CS, clinically significant; DRE, digital rectal examination; ISUP, International Society of Urological Pathologists; mo, months; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PSAv, prostate-specific antigen velocity; TURP, transurethral resection of the prostate.

Source: *Titecat P.* et al. *HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

TABLE 3 Outcomes: Clinical, mpMRI, and Biopsy Data

Oncological Outcomes	
Histological recurrence at biopsy in treated area (in-field)	
Any cancer recurrence in treated area	Yes(1)/No(0)
CS cancer recurrence in treated area	Yes(1)/No(0)
Maximum cancer core length at recurrence	mm
Grade group at recurrence	1–5
Anterior location of recurrence in treated lobe	Yes(1)/No(0)
Apical recurrence in treated lobe	Yes(1)/No(0)
Visible MRI lesion in treated area	Yes(1)/No(0)
Histological recurrence at biopsy in untreated area (out-field) treated lobe	
Same items as in treated area	
Histological recurrence at biopsy in untreated area (out-field) untreated lobe	
Same items as in treated area	
Stage Progression	
Extraprostatic progression T3a or T3b	Yes(1)/No(0)
Metastatic progression (pelvic nodes)	Yes(1)/No(0)
Metastatic progression (distant metastasis)	Yes(1)/No(0)
Salvage Treatment	
Salvage partial treatment	
Partial salvage treatment	Yes(1)/No(0)
Retreatment in treated area/lobe	Yes(1)/No(0)
Retreatment in untreated area/lobe	Yes(1)/No(0)
Salvage whole-gland treatment	
Post-treatment hormonal use	Yes(1)/No(0)
Radical treatment RP/RT	Yes(1)/No(0)
Second/third salvage	Yes(1)/No(0)
Death	Yes(1)/No(0)
All-cause death	Yes(1)/No(0)
Cancer-related death	Yes(1)/No(0)

Abbreviations: CS, clinically significant; MRI, magnetic resonance imaging; RP, radical prostatectomy; RT, radiotherapy.
Source: *Titecat P.* et al. *HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

TABLE 3 Outcomes: Clinical, mpMRI, and Biopsy Data *(Cont'd)*

After Salvage Treatment	
Pathological stage at radical prostatectomy	pT2a(1)pT3b(5)
Grade group at radical prostatectomy	1–5
Biochemical recurrence after whole-gland treatment	Yes(1)/No(0)
Second and Third Recurrence	
Second/third recurrence-treated area/untreated area	Yes(1)/No(0)
Any recurrence-treated area	Yes(1)/No(0)
CS cancer recurrence at biopsy	Yes(1)/No(0)
Maximum cancer core length recurrence	mm
Grade group recurrence-treated area	1–5
Visible MRI lesion in treated area	Yes(1)/No(0)

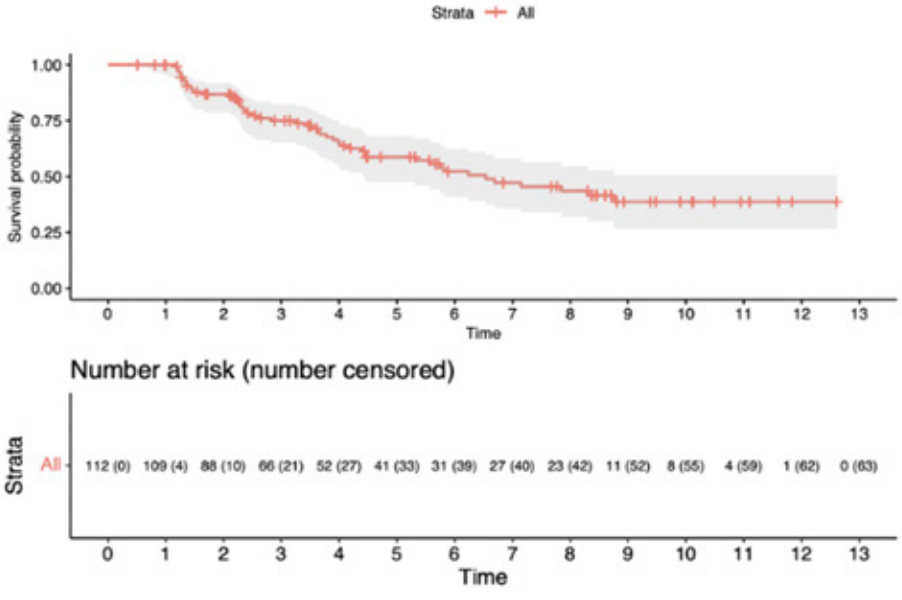
Abbreviations: CS, clinically significant; MRI, magnetic resonance imaging; RP, radical prostatectomy; RT, radiotherapy.
Source: *Titecat P.* et al. *HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

Oncological outcomes

Defining focal therapy failure

Understanding treatment failure after focal HIFU for PCa necessitates recognizing patterns such as in-field failures (IFFs) and out-of-field failures (OFFs) (**FIGURE 10**).[110] IFFs arise from potential inadequacies in energy delivery or targeting precision, leading to the persistence of cancer cells despite negative MRI scans. These are considered as real FT failures, especially in the presence of clinically significant disease (GS > 7) and are mainly due to incomplete ablation of the tumoural lesion. For this reason, they are also called ablation failures. Conversely, OFFs include progression in preexisting undiagnosed tumours or the emergence of new malignancies, potentially reflecting suboptimal initial patient evaluation. These are also called selection failures (or staging failures)—terms referring to inappropriate initial treatment choices, typically revealed by the emergence of significant local disease progression following ablation.[111]

FIGURE 10 Radical treatment–free survival rates at 3, 5, 7, and 10 years are 0.75 (95% CI, 0.65–0.82); 0.58 (95% CI, 0.47–0.68); 0.47 (95% CI, 0.35–0.58); and 0.38 (95% CI, 0.26–0.50), respectively (HIFU series *n*=114).



Abbreviation: HIFU, high-intensity focused ultrasound.
Source: *Titecat P. et al. HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished].*

Oncological control

In a systematic review of 72 studies, the oncological effectiveness of primary FT performed with eight energy sources in 5,827 patients with localized PCa was evaluated.[108] Almost all studies reported that they performed control biopsies, but most did not report on csPCa. Clinically significant PCa in the treated area was described with a median of 14.7% for HIFU, 8.5% for IRE, 10% for PDT, 15% for cryoablation, and 17% for FLA. The follow-up was relatively short, making the assessment of oncological control potentially inaccurate.

A total of 649 patients across 11 UK sites receiving focal HIFU or cryotherapy between June 2006 and July 2020 reported within the UK-based HEAT (HIFU Evaluation and Assessment of Treatment) and ICE (International Cryotherapy Evaluation) registries were evaluated.[112] The primary outcome was failure-free survival (FFS), defined as the need for more than one focal re-ablation, progression to radical treatment, development of metastases, systemic treatment, or PCa-specific death. This was compared to the FFS in patients undergoing radical treatment via a propensity score-weighted analysis. Median follow-up was 24 months (IQR, 12–41). Sixty percent of patients had intermediate-risk disease and 35% had high-risk disease. A total of 113 patients (17%) required further treatment. Sixteen had radical treatment and 44 required systemic treatment. FFS was 82%

(95% CI, 76%–87%) at 5 years. Comparing patients who had radical therapy to those who had FT, the 5-year FFS rate was 96% (95% CI, 93%–100%) and 82% (95% CI, 75%–91%), respectively ($p<0.001$). Ninety-three percent of those in the radical treatment arm had received RT as their primary treatment with its associated use of androgen deprivation therapy (ADT), thereby leading to potential overestimation of treatment success in the radical treatment arm, especially given the similar metastases-free and overall survival rates seen.

A systematic review and meta-analysis on IRE and HIFU was recently conducted, with 55 publications ($n=22$ IRE; $n=33$ HIFU) included.[113] In the meta-analysis, IRE patients had lower mean percent PSA level reductions, higher mean rates of in-field negative post-treatment biopsy, and higher rates of potency maintenance than HIFU patients.

Another recent study enrolled 50 patients between 2014 and 2020 with grade group (GG) ≤ 2 PCa proven by combined MRI-TRUS fusion biopsy.[114] All patients were treated with focal HIFU and underwent control 1-year MRI and biopsy. The median follow-up was 42 months. Seventy-four percent of patients had a 1-year control biopsy, revealing PCa in 23 of 50 patients (46%), of which 20 had in-field cancer. CsPCa was found in 6% to 26% (depending on csPCa definition) within the whole gland, and our results are in line with this, showing 21% csPCa in any area at 1 year (Titecat P. *et al.* HIFU partial gland ablation for localized PCa. Long-term oncological outcomes at 7 years. Lille, France [unpublished]).

Stabile *et al.* reported the results of a cohort of 1,032 patients treated with primary focal HIFU.[115] Most patients (83%) had a Gleason score of 3+4 or below. The median follow-up was 36 months. The primary endpoint was freedom from biopsy failure, reported as 84%, 64%, and 54% at 24, 60, and 96 months, respectively. These results may underestimate the presence of residual PCa for two reasons. Firstly, control biopsies were performed for only 40% of patients. Khandwala *et al.* highlighted that MRI alone might be insufficient to rule out residual cancer in a population treated with focal HIFU.[116] In their study, 73 men were included; among the 19 men with persistent GG ≥ 2 disease, 58% (11 men) had no visible lesions on MRI. Among the 14 men with PIRADS 4 or 5 lesions, 50% (7 men) had either no cancer or GG 1 cancer at biopsy. The importance of control biopsies after focal HIFU is highlighted by Rompré-Brodeur *et al.*'s study, which identified up to a third of csPCas in systematic biopsies performed 6 months after focal HIFU treatment in a series of 77 patients.[117] Secondly, freedom from biopsy failure was defined as the absence of Gleason 3+4 or higher, which did not consider the presence of residual Gleason 3+3 cancer. However, it represented nearly 20% of the initial sample.

Functional outcomes

Among the energy sources used for FT, all have their own specificity regarding results, with a specific impact on urinary, sexual, and intestinal functions. As the literature evolves, we gain valuable insights into the efficacy and outcomes of focal therapies. No technique stands out for having a smaller functional impairment; instead, they all exhibit low toxicity in terms of functionality.[118,119] Moreover, recent reviews contribute to the confirmation of these findings, highlighting the stability of such results (**TABLE 4**).[108,120]

TABLE 4 Summary of Functional Outcomes

Technique	Ablation	Incontinence	ED
HIFU	Thermal	< 5%	[–3.7; –1.6]
Cryoablation	Thermal	< 1%	[–2.0; 0.1]
IRE	Non-thermal	< 1%	[–3.2; 0.4]
Laser ablation	Thermal	< 1%	[–2.7; –1.5]

Abbreviations: ED, erectile dysfunction; HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation.

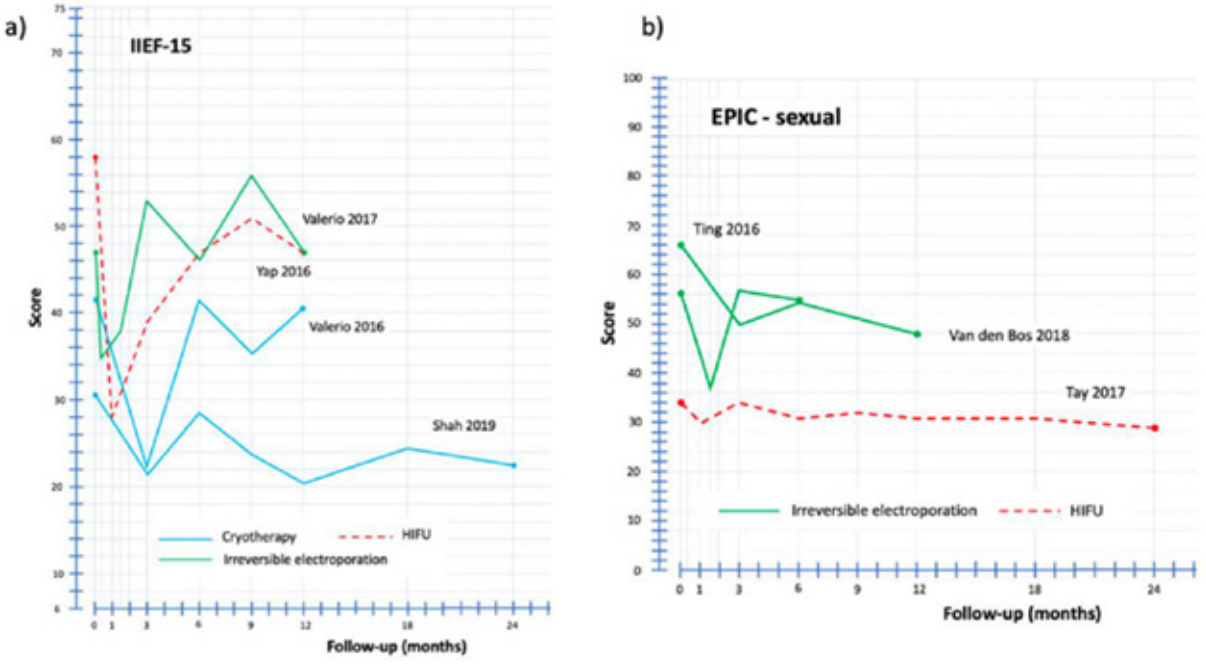
Sources: *Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years?* Eur Urol. *2022;81(1):5–33. doi:10.1016/j.eururo.2021.08.005*[108]

van der Poel HG, van den Bergh RCN, Briers E, et al. *Focal therapy in primary localised prostate cancer: the European Association of Urology position in 2018.* Eur Urol. *2018;74(1):84–91. doi:10.1016/j.eururo.2018.01.001*[120]

Compared to these results, radical treatments showed worse functional outcomes and a high rate of complications. Men undergoing RP have a considerable risk for postoperative urinary incontinence (10–30%) and erectile dysfunction (48–83%), while those undergoing RT are at risk for urge incontinence (3–6%) and rectal toxicity (5–16%).[121–123]

The use of validated questionnaires is advocated (**FIGURE 11**).[118] These instruments offer a structured and standardized approach to assessing specific domains of interest, including erectile function and overall QoL. By using these validated tools, clinicians can obtain comprehensive and reliable data on patient-reported outcomes, helping them to understand the impact of treatment and tailor interventions where necessary.

FIGURE 11 Evolution of mean/median IIEF-15 (a) and EPIC-sexual domain (b) scores.



Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; IIEF-15, International Index of Erectile Function.
Source: *Reprinted from* Eur Urol Focus, *8/4, Fiard G, Chowdhury A, Potter AR,* et al., *Detailing sexual outcomes after focal therapy for localised prostate cancer: a systematic review and meta-analysis, pp. 926–941, Copyright 2022, with permission from Elsevier. doi:10.1016/j.euf.2021.09.009*[118]

Indeed, the use of symptom-specific questionnaires tailored to the treatment modality is essential in guiding clinical decision-making. By adding instruments that analyze the various treatment-related symptoms, such as hyperactivity, clinicians can effectively monitor patient outcomes and optimize post-treatment QoL.

- International Index of Erectile Function (IIEF): Assesses erectile function and sexual satisfaction.
- International Prostate Symptom Score (IPSS): Evaluates urinary symptoms such as urinary frequency, weak stream, and hesitancy.
- Expanded Prostate Cancer Index Composite (EPIC): Measures prostate-related QoL, including urinary, sexual, bowel, and hormonal symptoms. The EPIC-26 and EPIC-CP are also utilized in follow-up.
- Overactive Bladder Questionnaire (OAB-q): Assesses the severity and impact of overactive bladder on QoL.

Assessment of treatment morbidity and complications

Critical factors influencing treatment morbidity

Various factors influence the toxicity and morbidity associated with PCa management. These include the prostate volume, any previous surgery, and any preexisting erectile dysfunction, lower urinary tract symptoms (LUTS), and neurological comorbidities. Using patient-reported outcomes measures is crucial in risk assessment. The status of preoperative erectile function is a prognostic factor in assessing treatment outcomes.

The location of PCa significantly influences post-treatment complications. Lesions located near the urethra, bladder neck, or apical area are associated with higher incidences of postoperative irritative and obstructive LUTS. Additionally, posterior lesions close to the neurovascular bundles may require extended ablation, potentially impacting erectile function.

Treatment intensity must be correlated with the tumour characteristics. However, from an oncological perspective, inadequate surgical margin increases the risk for recurrence. Conversely, extensive treatment may compromise post-treatment QoL. The objective is to treat the lesion while maintaining a safety margin and preserving adjacent anatomical structures.

Complications

Complications related to FT occur mainly in the first month post-treatment and include hematuria, infectious complications, and catheter-related issues such as pain, discomfort, and urethral sloughing. Patients should be adequately prepared for such complications to facilitate coping mechanisms.

Swelling induced by FT often necessitates urinary catheterization for at least 1–7 days, with alpha-blockers potentially aiding in retention prevention, depending on the size and modality of treatment. Urethral sloughing, which can vary in frequency and severity based on energy sources and ablation templates, may lead to acute urinary retention. Furthermore, clot retention may occasionally arise, particularly among patients receiving anticoagulant therapy. LUTS are also common within the first month post-treatment, requiring an active treatment.

Recto-urethral fistula is the most feared complication of FT, which manifests with pneumaturia, fecaluria, and urine leakage from the rectum. While the incidence of recto-urethral fistula remains rare after a primary treatment, this risk increases in salvage treatment settings, mainly when cancer is located posteriorly with extracapsular extension. Initial management typically involves conservative measures, including indwelling catheterization. Surgical management such as temporary colostomy or reconstructive procedures may sometimes be necessary.

Typical complications of RP (intraoperative surgical complications, need for transfusion, urinary leakage, lymphocele)[124] and RT (hemorrhagic cystitis, bladder or colorectal fistula, or cancer)[125] are not observed in patients treated with FT.

The summarized complications and their rates in the primary FT setting are presented in **TABLE 5**.[126]

TABLE 5 Complications and Their Rates in the Primary FT Setting

Type of complication	Rate
Infectious (urinary tract infection, epididymo-orchitis)	0–17%
Hematuria	Very frequent; not reported
Acute urinary infection	0–17%
Urethral sloughing	Frequent; not reported
Urinary incontinence	0–5%
Recto-urethral fistula	0–1%

Abbreviation: FT, focal therapy.
Source: *Rakauskas A, Marra G, Heidegger I,* et al. *Focal therapy for prostate cancer: complications and their treatment.* Front Surg. *2021;8:696242. doi:10.3389/fsurg.2021.696242*[126]

Long-term follow-up strategies

PSA

The interpretation of PSA levels in the context of FT presents both opportunities and challenges in the surveillance of treatment efficacy and recurrence. Commonly, the Phoenix criteria are employed, defining biochemical recurrence (BCR) as a rise in PSA to a level of the nadir plus 2 ng/mL. Other modalities of PSA use such as PSA velocity can be used to monitor post-FT patients. Thus, a suspect PSA elevation can be defined as 2 consecutive rising PSA rates with a velocity > 0.5 ng/mL/year.[127]

Recent advancements suggest refined PSA nadir thresholds at specific post-treatment intervals—1.0 ng/mL at 12 months and 1.5 ng/mL at 24 and 36 months—to better assess treatment outcomes. These thresholds aim to provide a more tailored approach to patient management, facilitating the early detection of treatment failures and guiding subsequent clinical interventions.[128]

Despite PSA's utility, the role of PSA as a primary marker in post-FT disease monitoring remains complex. Current studies indicate no consensus on a standardized method for interpreting PSA levels in the recurrence assessment context.[129,130]

Multiparametric MRI

Following ablation, MRI examinations typically depict the expected alterations, manifesting as heterogeneous and hypointense areas on T2W imaging. These regions often exhibit peripheral perfusion as seen in DCE studies, along with changes in tissue structure. HIFU specifically leads to a notable decrease in the size of the ablated lobe, with additional observations such as midline shifts, fibrosis development, and the formation of fluid-filled cavities.

Early postoperative swelling is typically observed in focal cryoablation and IRE, usually manifesting within the first month. Additionally, ablation cavities are commonly seen emerging during the second month after the procedure.[131–133]

Recurrences in treated lesions are characterized by early enhancement (DCE), hypointensity (T2W), restricted diffusion, and hyperintense signal on high b-value (DWI). DCE plays a crucial role in detecting recurrence across various ablation methods and is particularly sensitive in identifying recurrence post-HIFU and cryotherapy treatments. It also notably demonstrates early enhancement indicative of progression following FLA. Conversely, the utility of MRI following vascular-targeted photodynamic therapy (VTP) is limited, as it presents few reliable indicators on DCE or DWI, potentially leading to undetected small recurrences.[131,133,134]

Overall, mpMRI demonstrates potential in detecting long-term recurrent PCa following FT, though its sensitivity in the early months post-treatment remains limited. This underscores the value of late-term MRI follow-up in providing reliable outcome assessments for treated patients.[135]

To address the challenge posed using mpMRI in post-FT follow-up, Giganti *et al.* have proposed the Prostate Imaging after Focal Ablation (PI-FAB) score, a pioneering scoring system specifically designed for this purpose. PI-FAB employs a structured 3-point scale to sequentially rate MRI sequences: starting with DCE sequences, followed by DWI, which assesses the high-b-value sequence prior to the apparent diffusion coefficient map, and concluding with T2W. Crucially, the system requires that pretreatment scans be available to facilitate accurate comparisons and assessments.[109]

In the same fashion to answer the lack of robust guidance on MRI use after FT for PCa, the Transatlantic Recommendations for Prostate Gland Evaluation with Magnetic Resonance Imaging After Focal Therapy (TARGET) were established. A systematic review and subsequent consensus exercises involving 23 experts from diverse disciplines shaped these guidelines. These efforts culminated in a set of standardized recommendations aimed at improving MRI acquisition, interpretation, and reporting, thereby enhancing the consistency and reliability of post-treatment evaluations.[136]

Alternatives to MRI

PSMA PET/CT has revealed promising results in the detection and localization of cancer in the primary as well as in the salvage settings.[137–139] However, despite these promising results, no evidence exists for PSMA-PET/CT in the context of post-FT monitoring.

PSMA PET/MRI is another new modality offering a radiation-free, higher soft-tissue contrast option.[140] It has been investigated in pilot studies, showing some potential to detect PCa recurrence invisible at MRI.[141,142] Nevertheless, it is associated with high costs and some logistic shortcomings that must be considered, hampering its widespread adoption.

MicroUS and contrast-enhanced ultrasound (CEUS) may be other promising modalities to monitor disease after FT as alternatives to mpMRI. While the first is still not investigated in the post-FT setting, the second showed comparable accuracy to MRI and high concordance with histopathological findings.[85,143]

Control biopsy

Due to the suboptimal performance of PSA and MRI when compared to prostate biopsy, histological confirmation is recommended by most consensus panels on post-FT follow-up.[85,129,144,145]

Control post-FT biopsies, including the sampling of the ablated area and systematic cores, can be performed in the context of a protocol at a predefined time ("for protocol") or in case of clinical (abnormal digital rectal examination [DRE], PSA, or imaging) suspicion ("for cause"). Generally, FT cohorts using "for protocol" follow-up biopsies[146,147] show inferior success rates compared to "for cause" biopsies,[115,148] as imaging and other clinical tools may miss the presence of csPCa. Nonetheless, the approach for post-FT biopsy is still an open debate and depends mainly on institution-based protocols.

The recommended timing for biopsy is around 12 months after FT.[129,145] At this time, the inflammatory effects, which might impact the ability of the pathologist to interpret prostate biopsy specimens, are expected to be resolved with the formation of scar tissue.[129] Subsequent biopsies should follow a risk-adapted approach depending on the clinical suspicion.[145]

Integration of Focal Therapy Into Prostate Cancer Care Pathways

Focal therapy as an adjunct to active surveillance

AS is a strategy aimed at reducing overtreatment rates. Patients with very low–risk PCa can safely undergo observation, with long-term data confirming the safety of this approach for specific individuals. Ten-year cancer-specific survival rates range from 98% to 100%.[149] When intervention is deemed necessary, deferred treatment individualizes the need for therapy and yields outcomes comparable to immediate treatment upon diagnosis. However, observational approaches can induce significant anxiety, and physicians are particularly cautious when recommending this strategy for young, healthy men with a long life expectancy.

FT has emerged as an intermediate option between AS and radical treatments, targeting selectively and destroying specific parts of the prostate gland harbouring the most aggressive cancer foci. FT offers immediate treatment aiming to limit the impact on urinary, sexual, and bowel function.

FT could serve as an alternative to AS for the portion of low-risk PCas that presents a higher risk for progression. For example, it has been demonstrated that tumours visible during AS carry a higher risk for histological

progression and conversion to whole-gland treatment.[150] Stavrinides *et al.* showed that visible disease on MRI at baseline is associated with a higher probability of transitioning to active treatment at 5 years.[151] Some studies have compared AS to FT for low-intermediate risk PCa. The prospective randomized trial PCM301 highlighted that partial ablation of low-risk PCa by PDT significantly reduced subsequent detection of higher-grade cancer on biopsy.[82] Consequently, fewer cases were converted to radical treatment, representing a clinically significant advantage that reduces treatment-related morbidity. Other studies, such as HIFUSA, aim to compare oncologic outcomes of AS to focal HIFU therapy for visible Gleason 6 tumours on MRI (NCT03531099).

FT could also be used as an alternative to AS for intermediate-risk cancers, where the index tumour could be destroyed. Then, the patient is monitored under the same conditions as an AS protocol. This would avoid or delay whole-gland treatment while not causing initial functional complications or increasing specific survival risks for patients. The term "super active surveillance" has been proposed in this situation.[152] The concept of "super active surveillance" refers to any optimization of AS that allows for more extended surveillance periods, with the primary goal of avoiding overtreatment by safely eliminating or postponing radical treatment. Super active surveillance could improve oncologic control with minimal functional impact and quality of life similar to AS, which is safe in well-selected patients. VTP on vessels has pioneeringly shown a significant reduction in upgrading on subsequent biopsies, resulting in fewer cases converted to radical treatment, and any energy source can be applied to the concept of super active surveillance, enabling more men to consider tissue-preserving therapy for PCa.

Focal therapy as a salvage treatment

Although prostate RT for cancer is effective, recurrence occurs in 15% to 20% of cases within 5 years following treatment.[153] The vast majority of these patients receive palliative treatment through ADT, which exposes them to harmful side effects and is only effective for a limited duration. For patients with localized recurrent tumours and no signs of metastatic disease, a local curative treatment seems more rational. However, overall prostate salvage treatments, such as salvage RT or salvage prostatectomy, are associated with significant toxicity and are therefore rarely performed. As recurrences are often localized and unifocal, salvage treatment targeted solely at the recurrent tumour lesion seems rational. Remarkably, considering the treatment effectiveness versus treatment-related toxicity in the context of recurrence, FT offers a promising alternative: a second chance to achieve local control, with minimal burden on the patient in terms of side effects.[154]

To achieve such tumour-targeted treatment, advances in imaging have allowed for better exclusion of metastatic disease and precise discrimination of the tumour. The success of focal salvage treatment starts with adequate exclusion of metastatic disease. Nowadays, PSMA PET/CT is recommended in case of recurrence. High diagnostic accuracy is achieved for intraprostatic lesions as well as nodal and bone metastases, even at low PSA values. After excluding metastatic disease, evaluation of intraprostatic disease is necessary to adequately target the recurrent lesion. Currently, this is possible with the use of MRI and biopsy. Indeed, MRI alone is not sufficient prior to salvage treatment. Light *et al.* showed in the FORECAST study that MRI is accurate in detecting recurrent PCa after RT, with undetected cancers being smaller and of lower grade.[169] Targeting biopsy on suspicious areas on MRI allows diagnosis of cancer in most patients. However, for every 5 men with recurrent cancer, this targeted approach would miss cancers elsewhere in the prostate in 3 of these men. If additional FT of the prostate is

planned, random biopsies covering the entire prostate, in addition to targeted biopsies, should be considered to avoid missing tumours.[155]

Today, focal salvage treatment of recurrent PCa after RT is performed with various techniques: focal cryotherapy, focal HIFU, focal brachytherapy, and stereotactic body RT. The extent of ablation differs depending on the ablation method and between series, ranging from focal to hemi-ablation and subtotal ablation. Valle *et al.* conducted a meta-analysis to compare the efficacy and toxicity of salvage RP, HIFU, cryotherapy, stereotactic body RT, low-dose brachytherapy, and high-dose brachytherapy after RT. A total of 150 studies were included in the analysis. Adjusted 5-year recurrence-free survival varied from 50% after cryotherapy to 60% after high-dose brachytherapy and stereotactic body RT, with no significant differences between any of the modalities and RP.[156]

In conclusion, focal salvage treatment offers a promising alternative for patients with localized recurrence of PCa after RT. Thanks to advances in imaging, precise patient selection and localization of recurrent lesions are possible, allowing for local disease control with minimal side effects. Although initial results are encouraging, further studies are needed to assess long-term efficacy and optimal treatment strategies. Ultimately, focal salvage treatment represents a significant advance in managing recurrent PCa, offering hope and improved quality of life for patients.

Combination approaches: focal therapy with systemic therapies

Previous research has emphasized the synergistic benefits of combining ablative therapies with adjunctive treatments to optimize FT outcomes. While systemic modalities have received considerable attention in past studies, recent investigations have shifted focus toward exploring increasingly innovative combinations of therapeutic approaches, including intratumoural immunotherapy paired with thermal ablation. Here, we highlight some of these evolving strategies.

To illustrate that concept, first Baust *et al.* can be cited as they emphasized the role of protein denaturation and cell membrane damage in cryoablation, suggesting opportunities for combination therapies such as thermophysical adjuvants, chemotherapeutics to promote apoptosis, and immune therapies that stimulate immune responses.[157,158] These adjunctive treatments aim to reduce the survival of tumour cells in the sublethal "border zone" exposed to thermal stress. Immune therapies, in particular, could help eliminate surviving tumour cells in this zone by activating the immune system, potentially leading to an abscopal effect and enhancing immune surveillance against PCa spread. This is especially beneficial for patients with multifocal or higher-risk PCa.[157,158]

Additional adjuncts studied include various forms of chemotherapy, RT (either external or with brachytherapy), TNF-alpha to promote inflammation, and anti-freeze proteins.[160] Another promising approach is the pre-ablation administration of calcitriol, which has been shown to increase tissue lethality at higher temperatures *in vitro* and to activate apoptosis via a mitochondrial pathway.[158] Kimura *et al.*'s *in vivo* studies also demonstrated that intra-tumoural calcitriol injections resulted in larger necrotic areas and reduced cellular proliferation, as indicated by lower Ki-67 levels in immunohistochemistry tests.[159]

Preclinical studies have shown potential in combining ablative therapy with systemic immuno-oncology (IO). Sidana *et al.*'s review summarized the immunologic implications of cryoablation combined with immunomodulators.[162] Yakkala *et al.* noted that combining Toll-like receptor (TLR) agonists with cryoablation improved survival and antitumour responses.[161] Additionally, combining immune checkpoint inhibitors with cryoablation has shown efficacy in experimental models.[161,162]

In PCa-specific models, Waitz *et al.* found that combining cytotoxic T-lymphocyte associated protein 4 (CTLA-4) blockade with cryoablation in a murine model synergistically prevented secondary tumour development.[163] Benzon *et al.* reported that combining cryoablation with a checkpoint inhibitor (anti–CTLA-4) and ADT in a murine PCa model delayed distant tumour growth and reduced mortality more effectively than cryoablation alone.[61] Ross *et al.* conducted a pilot trial combining whole-gland cryoablation, ADT, and pembrolizumab in men with hormone-sensitive metastatic PCa, finding the combination to be well tolerated and effective for local disease treatment, though disease control after testosterone recovery was infrequent.[61,163,170]

Furthermore, recent exploration has been made toward using intratumoural immunotherapy plus focal thermal ablation for localized PCa to explore combining intratumoural immunotherapy with focal thermal ablation as a novel approach to treating localized PCa.[164] This innovative strategy aims to enhance the immunogenicity of prostate tumours, which are typically immunologically "cold," by applying thermal ablation that triggers immunological activation. By injecting immunotherapy agents directly into the tumour, this method may induce a robust, localized immune response that targets the primary tumour and potentially initiate an immune reaction against distant metastases (the abscopal effect). This combination could transform PCa treatment by converting immunologically "cold" tumours into "hot" ones, making them more susceptible to immune responses. The concept is still in the early research stages but offers promising potential for improving therapeutic efficacy and patient outcomes in PCa.[164]

Future Perspectives and Challenges

Advancements in imaging techniques

Great strides have been made in the diagnosis and management of PCa, and this is due to monumental advances in diagnostic imaging techniques. The incorporation of prostate MRI into the evaluation of an elevated PSA levels has paved the way for the acceptance of FT as a viable and efficacious PCa treatment option for appropriately selected patients. The availability of prebiopsy prostate MRIs, along with MRI-US fusion biopsy platforms, now allows clinicians to both accurately target prostatic lesions and create precise ablation treatment plans.

Adding to this, incorporating artificial intelligence (AI) and machine learning into the PCa-detection algorithm has the potential to further revolutionize our approach. Accurate target sampling and ablation planning rely largely upon accurate MRI interpretation. While PI-RADS and the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) scoring systems have helped standardize the reporting of prostatic

lesions, there can be significant inter-reader variability. Many studies are underway to create PCa detection AI models that not only analyze image specifics but also are being taught to consider patient-specific demographics and prior biopsy history, among other parameters, to aid in lesion detection and risk assessment.[165]

Standardization of focal therapy protocols

Currently, there is a lack of standardization among FT protocols. This is noted between different institutions and at the individual provider level. The lack of consistency can be attributed to several factors, including disease heterogeneity and clinical variability. The field of PCa FT is incredibly dynamic, with a continuous evolution of techniques and ingenious ablation approaches. As such, many of the newer techniques lack long-term efficacy data, though short- and intermediate-term data demonstrate favourable effectiveness.

As urologic surgeons gain more exposure and expertise within the FT space and robust, long-term data are analyzed, a greater consensus can be expected. Determining and incorporating a standardized protocol regarding the appropriate FT candidates and follow-up surveillance intervals will allow for more robust clinical studies. This, in turn, will help pave the way for FT to be incorporated into international guideline algorithms for PCa treatment.

Patient education and awareness

In the age of increased awareness and health advocacy, patients with low- to intermediate-risk PCa should be offered all viable treatment modalities, including FT. For decades, RP and RT have been the mainstays of treatment for PCa. As such, patients were presented with no viable treatment courses that offered minimal morbidity in conjunction with high rates of curability.

Increasing patient awareness regarding FT starts at the provider level. It is imperative that the curricula of current urologic training programs include exposure not only to FT treatments but also comprehensive instruction in prostate MRI interpretation. As this happens and more institutions employ urologists trained in multimodal PCa treatment therapies, patients will begin to routinely be offered FT approaches as appropriate. Another necessary step in raising patient awareness about the safety and efficacy of FT is furthering education at the primary care level.

Novel technologies and therapeutic approaches

As FT has gained traction in recent years, a multitude of focal energy modalities has emerged. While cryotherapy and HIFU were the traditional options, other soft-tissue ablation systems have gained traction. New technologies like TULSA, nanoparticles, and water vapour ablation have been discussed in this chapter. Another transperineal FT modality that has been introduced is bipolar radiofrequency ablation. This method utilizes a transperineally placed helical ablation probe that concentrates and confines the produced electrical field.

Current studies of these energy modalities have shown promising results. Continued research on the long-term efficacy of these novel focal technologies will lead to increased personalization of PCa treatment and help decrease overtreatment. Increasing the types of energy modalities offered will allow urologists to provide a more tailored treatment approach based on tumour characteristics and patient-specific factors.

Ethical considerations and cost-effectiveness

As clinicians, we are charged with providing patients with treatment options that offer a high likelihood of cure and incur a low morbidity rate. Additionally, an increased focus is on delivering affordable and cost-effective patient care. Unfortunately, the traditional treatment options of RP and a course of radiation are very costly. An uncomplicated robotic-assisted RP can cost upwards of $50,000,[166] and the average cost of RT for PCa is $18,000.[167] In contrast, a European study by Reddy *et al.* demonstrated that over 10 years, either cryotherapy or HIFU is more cost-effective than RP or external beam RT.[168] While FT treatment modalities offer a significantly lower up-front treatment cost when compared to robotic prostatectomy, it is important to factor in the cost of long-term surveillance, which will include interval MRI evaluation as well as fusion biopsies. Despite this, FT remains an excellent treatment modality for well-selected patients and should be considered a viable curative option.

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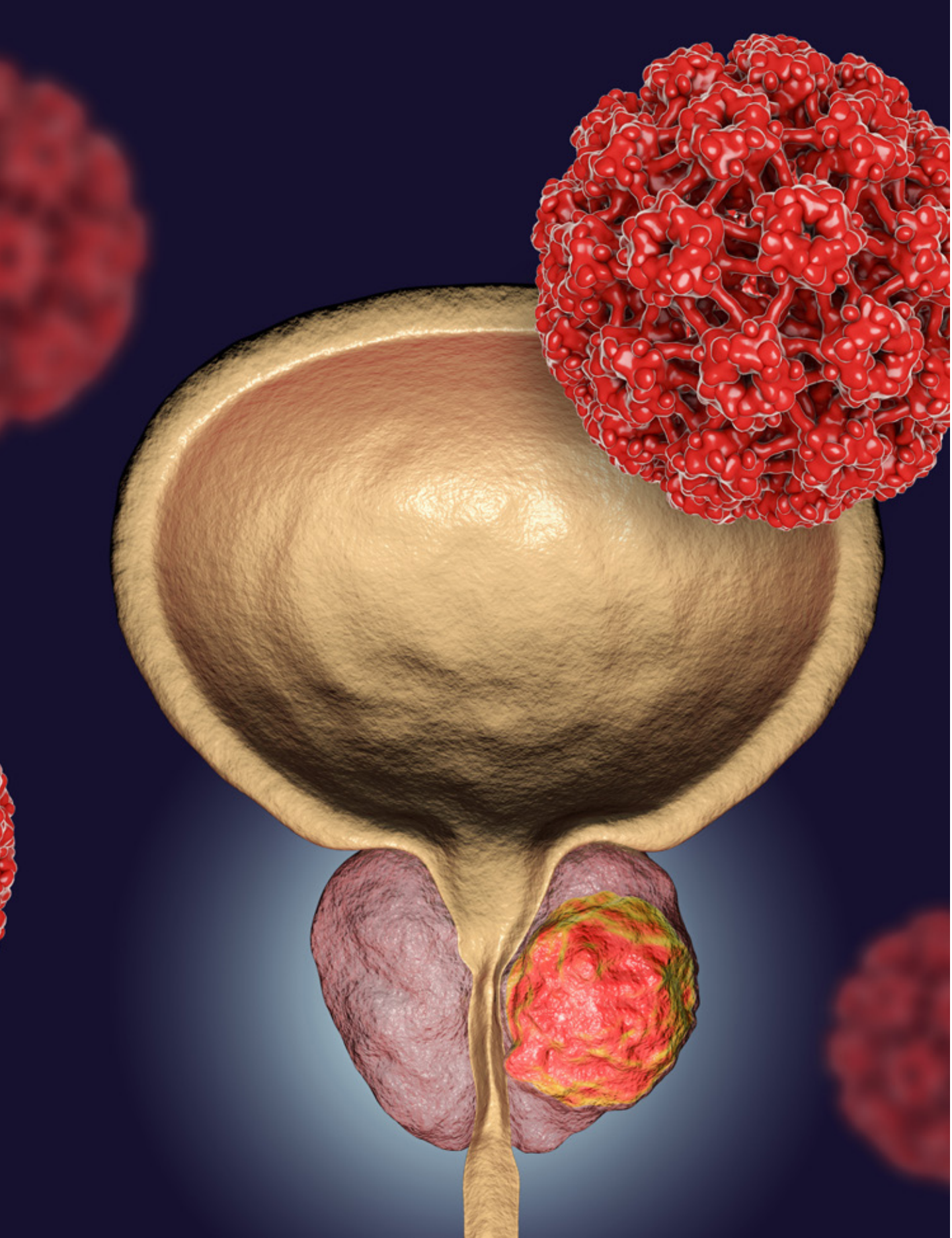

COMMITTEE 14

Focal Therapy for Prostate Cancer: The Technique

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Introduction

Focal therapy represents a significant paradigm shift in the management of prostate cancer, mirroring the targeted/subtotal approach that has been predominant in the treatment of other solid organ malignancies. This approach, akin to the changes seen in kidney cancer treatment, emphasizes a more localized and precise intervention, marking a new direction in how prostate cancer is managed.[1,2]

When discussing focal therapy, the word "technology" immediately comes to mind. This is because what distinguishes focal therapy and makes it unique is its direct connection with technology. This includes utilizing multiparametric magnetic resonance imaging (mpMRI) for precise identification of the index lesion's location and guiding direct targeted biopsies to the lesion that is considered to drive the evolution of prostate cancer toward a lethal metastatic state.[3–5] Looking forward, the development of new, easier, and less-costly imaging modalities, perhaps with equivalent diagnostic accuracy to mpMRI, such as micro-ultrasound, along with the incorporation of prostate-specific membrane antigen positron emission tomography (PSMA PET) scans, promises to further refine lesion localization and staging accuracy. Additionally, the integration of artificial intelligence (AI) stands poised to revolutionize MRI and PSMA interpretation, ushering in a new era of advancements in the field.[6–8]

Technology continues to evolve, and focal therapy evolves in tandem, influencing not only patient selection and follow-up but also treatment planning and delivery. This encompasses delineating treatment boundaries and exploring the potential of employing lesion-targeting methods via cognitive fusion or software-based fusion. Additionally, it involves selecting energy sources based on lesion characteristics, as well as the energy and route of application (transperineal, transrectal, or transurethral). Furthermore, it entails deliberating on the significance of systemic treatments in managing the prostate cancer microenvironment. All these efforts are directed toward improving oncological control while minimizing adverse effects associated with conventional whole gland treatment.[9–12]

Fundamental Focal Therapy Techniques and Strategies Applicable to Every Energy Source

The index lesion

Focal therapy is defined as the targeted application of ablative energy to a specific area within the prostate, most commonly referred to as the "index lesion."

The concept of the index lesion, which forms the theoretical basis of focal therapy, originated 15 years ago when Liu *et al.* examined tissue from both prostate glands and metastatic sites from 30 men with prostate cancer at autopsy as part of the Project to Eliminate Lethal Prostate Cancer (PELICAN). In 2009, the authors discovered

that a single precursor cell was identified in metastatic sites, leading to the conclusion of a monoclonal origin of lethal metastatic prostate cancer.[4] Subsequently, in the same year, Ahmed introduced the concept of the "index lesion" as the site within the prostate with the dominant malignant or metastatic potential.[13]

Although the concept of the index lesion has been challenged and questioned based on the multifocal nature of prostate cancer, a recent systematic review found that metastatic prostate cancer specimens consistently display truncal genomic aberrations, indicating monoclonal metastatic progenitors.[14]

The FLAME Trial (NCT01168479), which investigated whether focal boosting of the macroscopic visible tumour with external beam radiotherapy enhances biochemical disease-free survival in patients with intermediate- and high-risk localized prostate cancer, has recently broadened clinical evidence supporting the concept of the index lesion. The trial randomly assigned patients to receive either standard treatment to the entire prostate or a focal boost arm, in which patients received an additional simultaneous integrated focal boost up to 95 Gy to the intraprostatic lesion visible on mpMRI. Interestingly, the FLAME trial demonstrated that boosting the index lesion is beneficial for patients with localized intermediate- and high-risk prostate cancer.[15,16]

Prostate cancer aggressiveness—International Society of Urological Pathology (ISUP)

The International Society of Urological Pathology (ISUP) grading system for prostate cancer assists in categorizing cancerous tissues according to their aggressiveness.[17] Patients are typically selected for treatment or specific interventions based on the ISUP grade, along with other factors such as prostate-specific antigen (PSA) levels, tumour stage, and overall life expectancy. Typically, higher ISUP grades may indicate the need to exclude synchronous metastases. If these metastases are excluded, a more aggressive intervention with whole gland radical treatments may be warranted, with focal therapy currently contraindicated for high-risk prostate cancer outside of clinical trials.[18]

The seminal question is: Can prostate cells, regardless of whether they are non-tumoural or tumoural and classified as ISUP grade 1 to 5, withstand extreme temperatures, resist irreversible damage caused by electric energy, or repair DNA damage induced by radiation?[19]

There is no definitive answer to this question. While common sense might suggest that a potent energy source could potentially eradicate any type of prostate cancer cell, focal therapy as a treatment for prostate cancer is still under evaluation and primarily reserved for less advanced forms of the disease. Nonetheless, advancements in patient staging accuracy are driving progress in the field, transitioning from treating less aggressive diseases to more advanced ones.[20]

Currently, patients diagnosed with ISUP 2, and some select patients with ISUP 3 disease, rather than ISUP 1 prostate cancer are prioritized for this treatment modality.[21–23]

One concern when treating more aggressive disease is the risk for metastases and micro-metastases. In this regard, the European Association of Urology (EAU), along with the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) guidelines, advocate for imaging to detect any extraprostatic or nodal disease before planning any type of treatment for all patients with ISUP > 2 prostate cancer. Furthermore, intervention on nodal chains is still recommended for cases with a high risk for nodal involvement that is not visible on conventional imaging.[18,24–26] Given that aggressive diseases tend to be associated with non-visible lymph metastases according to conventional imaging, the utilization of focal therapy in this context remains contentious due to the lack of treatment for lymph nodal chains, either through surgical lymphadenectomy or irradiation of the lymph chains.[27] Nevertheless, PSMA PET scan has the potential to revolutionize the landscape of prostate cancer treatment in the near future, as its accessibility continues to expand globally. Hence, patients diagnosed with localized prostate cancer and no evidence of metastases on high-resolution imaging may qualify as suitable candidates for focal treatment, thereby safely broadening its application.

Regarding ISUP 1 prostate cancer, robust randomized controlled trials such as PROTECT have led to the EAU and AUA/NCCN guidelines advocating for active surveillance in patients with low-risk disease, as no discernible benefit has been demonstrated in terms of overall survival.[18,25,26,28] Thus, ISUP 1 prostate cancer outside the index lesion is not a formal contraindication for focal therapy when ISUP2 or ISUP3 is identified within the index lesion.[21,22] Nevertheless, it is important to highlight that studies on active surveillance have shown a more aggressive behaviour of lesions visible on MRI compared to those not visible, with similar treatment risks between visible ISUP 1 lesions and non-visible ISUP 2 lesions. Additionally, worse oncological outcomes have been observed among visible ISUP 2 lesions compared to non-visible ISUP 2 lesions. Further studies are necessary before recommending treatment for visible ISUP 1 and ISUP 2 lesions in patients who would otherwise be candidates for an active surveillance protocol, as the challenge of balancing treatment with curative intent and avoiding overtreatment continues to be a challenge in the management of prostate cancer.[29,30]

Finally, it's important to consider that if, due to patient preferences, treatment is chosen for low-risk or favourable intermediate-risk prostate cancer, even though the patient may be a suitable candidate for active surveillance, it may be reasonable to prioritize focal therapy as the initial option and assess its suitability on a case-by-case basis.

Treatment approach

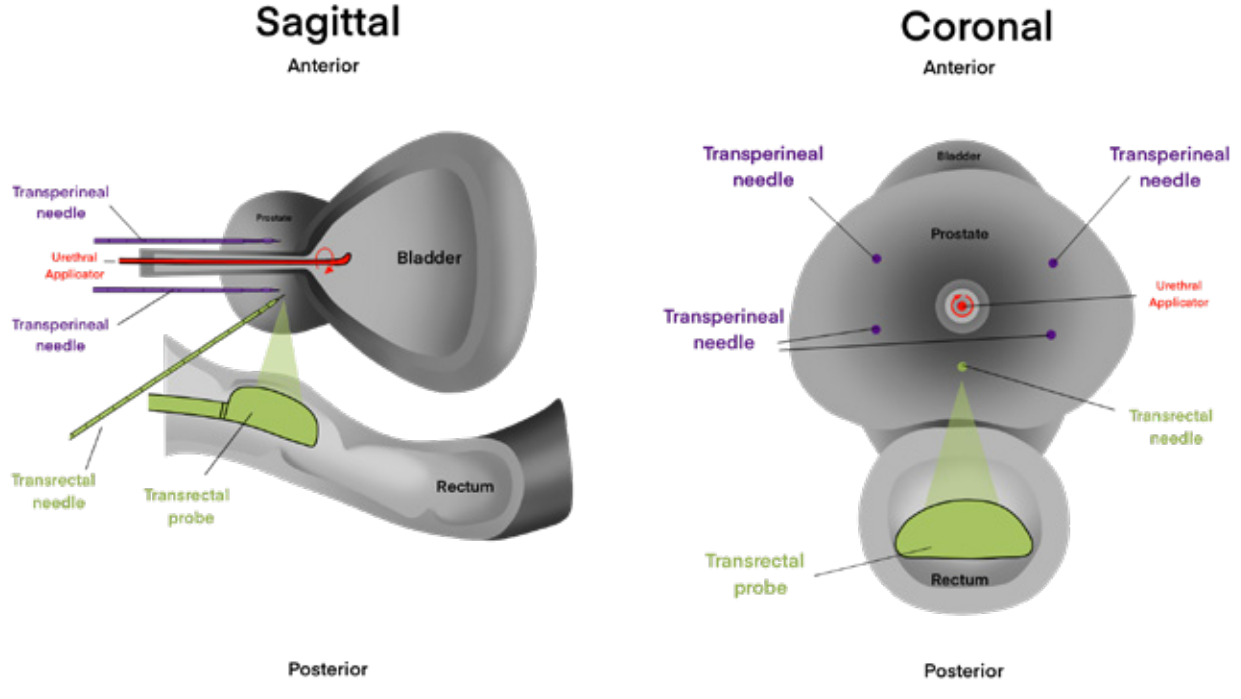
Accessing the lesion for targeted focal therapy

From the outset, it is essential to address the accuracy of biopsy and disease localization. The precision of biopsy is pivotal for accurate diagnosis, as it dictates the treatment course. Moreover, understanding the precise disease localization is crucial for planning effective therapeutic strategies and minimizing the risk for complications. Therefore, dedicating attention to these aspects from the beginning of the discussion is essential to ensure a comprehensive approach to prostate cancer management particularly in the context of focal therapy.

Currently, three primary approaches are available (**FIGURE 1**):

- Transrectal approach: This method involves accessing the prostate through the rectal wall. Techniques such as high-intensity focused ultrasound (HIFU) and focal laser ablation (FLA) can be utilized for treatment.
- Transperineal approach: This approach entails accessing the prostate through the perineum. Techniques including cryotherapy, irreversible electroporation (IRE), and FLA can be employed.
- Transurethral approach: In this approach, the prostate is accessed through the urethra. Transurethral ultrasound ablation (TULSA) and water vapour can be utilized for this approach.

FIGURE 1 Representation of the different approaches for focal therapy in prostate cancer. Green: Transrectal approach; Violet: Transperineal approach; Red: Transurethral approach.



In 2016, a personalized approach, known as the "à la carte" method, was introduced. This approach involves customizing treatment strategies based on the precise location of the lesion. According to this opinion-based strategy proposed almost 10 years ago, transperineal needle-driven energies are optimal for anterior lesions, while posterior lesions can be targeted using techniques accessed via the rectum. Additionally, brachytherapy is recommended for treating apical lesions due to its non-thermal effect and presumed ability to provide better energy delivery control.[32]

Currently, we find ourselves in a significantly altered landscape. First, the integration of transurethral devices such as water vapour and the TULSA device enables access to lesions in a more uniform circumferential manner around the urethra. Second, there have been advancements in non-thermal energies that have shown promising results in treating posterior and apical lesions. Third, surgeons' experience and techniques have progressed, facilitating the treatment of posterior lesions through transperineal and transrectal needle-driven approaches with good functional outcomes and low side effects.[32]

Hence, although an "à la carte" method is very helpful when planning focal therapy, especially during the learning curve, operator experience and the ability to reach the lesion are the cornerstones.

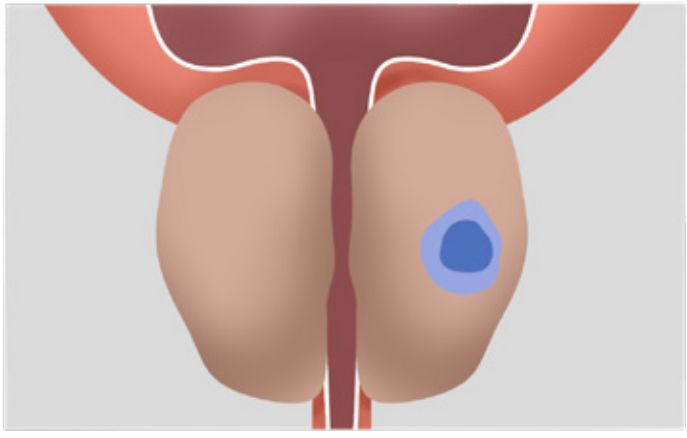
Considering tricks and tips for improving lesion reach, the utilization of debulking prostate surgeries such as transurethral resection of the prostate (TURP) or Holmium laser enucleation of the prostate (HoLEP) prior to HIFU has been proposed. This approach aims to reduce prostate volume, eliminate prostatic calcifications or abscesses that may impede HIFU energy transmission, and decrease the risk for postoperative urinary retention.[33–35] However, further comparative studies or randomized controlled trials are needed to confirm any benefits in terms of oncological and functional outcomes.[36,37]

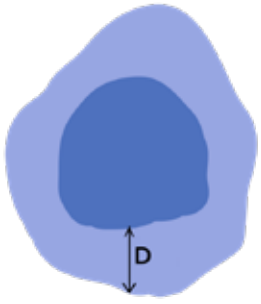
Treatment planning—zone of ablation

The evolution of focal therapy initially encompassed large ablations such as hemi-gland ablation before progressing toward a more precise "focal" approach, targeting specific lesions with a rim of normal parenchyma. However, owing to inherent challenges such as mpMRI identification of lesions and biopsy sampling errors, the field has pivoted toward a middle ground between large ablations and focal treatments.

Consequently, when delineating the zone of ablation, surgeons take into account the lesion's region on the mpMRI and apply a margin. This margin accommodates the tendency of mpMRI to underestimate the size of index lesion (**FIGURE 2**).[38,39]

FIGURE 2 The discrepancy in distance between the lesion identified on magnetic resonance imaging (MRI) and its histological counterpart.





D: Distance between the lesion identified on MRI and the corresponding lesion observed histologically.

In 2015, Le Nobin and colleagues undertook a study to analyze the concordance between prostate tumour boundaries delineated on MRI scans and those determined through histological examination following radical prostatectomy. Their findings indicated a consistent tendency for mpMRI to underestimate tumour dimensions, with an average difference of 1.99 ± 3.1 mm between imaging and histological boundaries. Additionally, they noted that the maximum discordance between radiological and anatomopathological boundaries was notably higher for lesions with a high suspicion level and those of higher grade. The authors observed that employing a simulated treatment volume based on a 9-mm treatment margin resulted in complete histological tumour eradication in all patients studied.[39]

A more recent study by Aslim *et al.* confirmed these findings. The authors found that for tumours measuring up to 12 mm, a 6-mm margin was sufficient to achieve complete ablation of high-grade tumours. They also observed that larger tumours and those containing Gleason pattern 4 or 5 components were more likely to be underestimated in size. Thus, they concluded that the optimal tumour size for focal therapy was less than 12 mm, with an ideal treatment margin of 5–6 mm.[40]

Similarly, Brisbane *et al.* observed that biopsies taken from a 10-mm radius area surrounding MRI lesions contained most cores of clinically significant prostate cancer not present within the lesion itself, introducing the concept of the penumbra area. This suggests that there is a halo/margin around the mpMRI lesion that also contains prostate cancer, which must be addressed if focal therapy is to be delivered successfully.[38]

Lastly, but of equal importance, recent findings from a randomized controlled trial on IRE, comparing focal (including safety margins) versus extended treatment (beyond safety margins), have failed to demonstrate any

difference in the presence of clinically significant prostate cancer on transperineal template-mapping prostate biopsy at 6 months post-IRE. This study underscores the unnecessary expansion of the treatment area. When margins are guaranteed, the treatment can ensure safety in terms of oncological outcomes, rendering larger ablations unnecessary.[11]

In conclusion, evidence strongly suggests avoiding both an extended and an ultra-focal approach. It emphasizes that maintaining a minimum margin of 5 mm is crucial for accurately targeting tumours during focal therapy. However, for larger and more aggressive lesions, a 10-mm margin is justified in certain instances. This has also been confirmed as good practice by an international consensus, the FocAL therapy CONsensus (FALCON).

Intraoperative monitoring

To enhance treatment accuracy and reduce failures within the treatment zone (also referred to as in-field failures) and side effects, intraoperative monitoring techniques are under study.

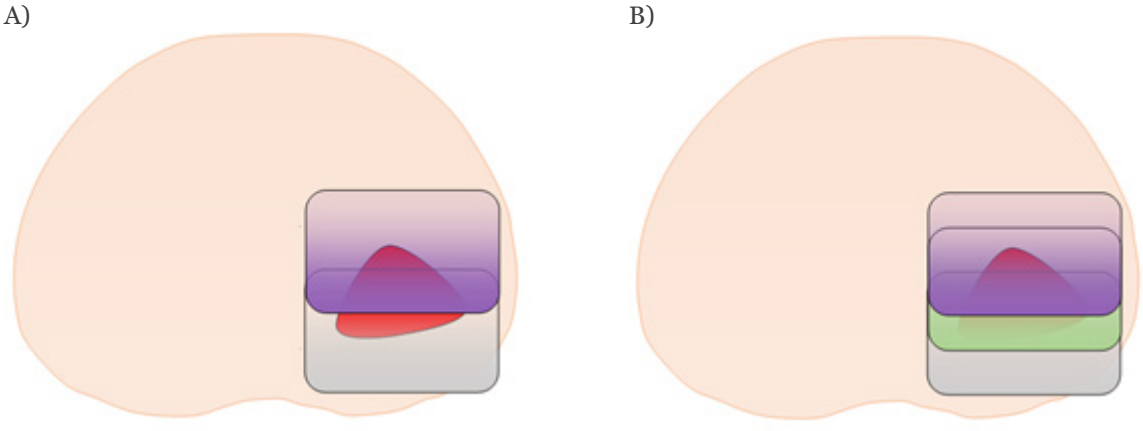
Ehdaie *et al.* conducted a phase 2b multicentre study exploring the role of MR-guided focused ultrasound (MRgFUS). This system combines a transrectal ultrasound device for energy delivery with MRI of the pelvis to visualize the targeted tumour, monitor therapy using MRI thermometry for real-time feedback, and assess tissue immediately post-treatment. The authors observed a higher success rate in treating cancer within the targeted region compared to previous HIFU trials. Nevertheless, comparative studies are required to conclusively determine the utility of this new technology.[10]

Contrast-enhanced ultrasound (CEUS) has also emerged as a promising tool for guiding intraoperative HIFU treatment. Bacchetta *et al.* investigated the efficacy of intraoperative CEUS immediately after focal HIFU. They administered additional energy based on CEUS interpretation to ensure complete ablation in areas deemed undertreated. Subsequent CEUS evaluation after the second procedure indicated no requirement for further HIFU intervention. The authors found significant concordance between CEUS and early MRI (5 to 10 days post-treatment). However, once again, further investigation and comparative studies is needed to determine whether intraoperative CEUS enhances focal HIFU efficacy.[41]

How much energy is enough?

In some instances, achieving optimal dose delivery involves either replicating the procedure within the same session, as observed in cryotherapy, or enhancing overlapping ablative areas during treatment planning and delivery. This latter technique is utilized with specific devices for applying HIFU energy. In cryotherapy, two freeze-thaw cycles are routinely performed per protocol.[42] For HIFU, Huber *et al.* conducted a propensity matching study comparing patients treated with HIFU (Sonablate 500) using either two HIFU blocks or overlapping three HIFU blocks (**FIGURE 3**). They observed significantly higher in-field recurrence (31%) when standard treatment zones (two HIFU blocks) were applied compared to dose-escalation focal HIFU (three overlapping HIFU blocks) (19%).[43] Therefore, the use of three blocks for treatment is currently recommended.

FIGURE 3 Standard 2-block approach (A) vs. dose escalation using 3 blocks (B) of treatment layered approach to focal high-intensity focused ultrasound (HIFU) with Sonablate 500.



On the other hand, the necessity of employing a double-TAP HIFU strategy—where HIFU delivery is administered twice during the same session, either with a secondary treatment boost or by re-treating the same area—when block-guided software is unavailable is currently a subject of debate. To date, no study has conclusively proven that this approach leads to superior oncological outcomes.

Systemic treatments

While the justification for the observed improvement in overall survival by adding androgen deprivation therapy to radiotherapy for intermediate- and high-risk prostate cancer remains unclear and subject to debate, several hypotheses have been proposed:

- Suppression of vascular endothelial growth factor 1 (VEGF1) effects and, consequently, angiogenesis/neovascularization inhibition.[44]
- Reduction in prostate and tumour volume.[45,46]
- Immunomodulation (stimulating factors to enhance the immune system).[47]
- The ability to induce apoptosis in cancer cells—*although it's not clear whether it's due to hormone therapy alone or in synergy with radiotherapy*.[48]
- Control of upregulation of androgen receptors induced by radiotherapy and inhibition of DNA repair machinery.[49]

In the realm of focal therapy, some of the aforementioned hypotheses may shed light on potential improvements in outcomes when combining focal therapy with hormonal treatment. Consequently, several feasibility studies have begun to investigate the hypothesis that integrating the localized effects of focal treatment with the systemic

effects of androgen deprivation therapy could lead to better oncological outcomes. This approach aims to target the mpMRI [and/or PSMA PET?] "visible" index foci with focal therapy while simultaneously addressing "invisible" foci and micrometastatic disease with hormonal treatment.

In this regard, the CHRONOS-B trial is currently randomizing patients between focal therapy alone (HIFU or cryotherapy) and focal therapy combined with neoadjuvant medication (3 months of either finasteride or bicalutamide).[50] As another example of this investigational pathway, the ENHANCE trial is currently investigating, in a single-arm study, the impact on oncological outcomes and side effects of combining one injection of leuprorelin acetate 22.5 mg 1 month before the HIFU treatment.[12] It is important to emphasize that while awaiting results in this area, systemic treatment cannot currently be recommended as neoadjuvant, concomitant, or adjuvant therapy alongside focal therapy.

Integrating focal therapy with prostate radiotherapy

Although the results are still preliminary, it is crucial to highlight a novel avenue of research directly involving focal therapy for prostate cancer. This involves the combination of focal treatment with external radiotherapy similar to the approach used in breast cancer treatment. In breast cancer, focal therapy, such as lumpectomy, is typically complemented with external beam radiotherapy targeting the entire breast.

In this context, the previously mentioned FLAME trial randomized 571 patients with intermediate- and high-risk prostate cancer to receive either the standard treatment of 77 Gy to the entire prostate or the same treatment combined with an additional simultaneous integrated focal boost up to 95 Gy to the intraprostatic lesion visible on mpMRI. With a follow-up of 72 months, the authors demonstrated a benefit in terms of biochemical disease-free survival (bDFS) without impacting toxicity and quality of life.[16] After a 5-year follow-up, the bDFS rates were 92% and 85%, respectively. The standard arm showed a cumulative incidence of late genitourinary and gastrointestinal toxicity grades > 2 at 23% and 12%, while the focal boost arm exhibited rates of 28% and 13%, respectively. Notably, sexual activity in patients without hormonal therapy remained stable, with no deterioration exceeding 5 points from baseline in either treatment arm.

Similarly, RTIRE is a feasibility and safety study that aims to explore the role of IRE followed by stereotactic body radiation therapy (32.5 Gy to the prostate) for patients with ISUP 2 and ISUP 3 prostate cancer.[51] Results from the RTIRE trial are awaited.

Energies

There is a wide range of energy sources available for focal therapy, differing in terms of thermal or non-thermal–based treatment, utilizing a transperineal, transurethral, or transrectal approach, and the characteristics of the energy itself.[52]

Cryotherapy and HIFU are among the most commonly utilized and are well documented in terms of their results. Other known and popular options include IRE and focal brachytherapy. However, the spectrum is much broader with numerous other available energy sources, such as nanoparticles, focal laser ablation, radiofrequency ablation, TULSA, microwave, histotripsy, and water vapour technology.[31]

Next, we will outline some of the main energy sources that have stronger evidence:

High-intensity focused ultrasound (HIFU) and MRI-guided transurethral ultrasound ablation (TULSA)

Energy: Ultrasound waves
Type of energy source: Thermal (60 to 90°C)
Route of application: Transrectal (HIFU) / Transurethral (TULSA)

In HIFU therapy, focused ultrasound waves generate heat in temperatures ranging from 60°C to 90°C, resulting in coagulative necrosis of tissue to which it is applied. Subsequent cavitation, which refers to the formation of microbubbles within the tissue, results and leads to cell death as these bubbles rapidly expand and collapse, generating shock waves and mechanical forces that disrupt nearby cells and tissues. This disruption further contributes to the destruction of the targeted tissue.[53]

HIFU treatment is administered under general or spinal anesthesia, with general anesthesia often preferred to ensure patient immobility during the procedure and it is commonly performed as an outpatient surgery. Prior to the procedure, rectal preparation is crucial to prevent interference with imaging control and ultrasound delivery. Additionally, ruling out intraprostatic calcifications in the treatment area is essential. The upper limit of the lesion and its corresponding treatment margin must be located within 3 to 4 cm (depending on the focal length and recommended distance between the probe and the posterior wall of the prostate of the employed HIFU device) of the treatment site (rectum or urethra) for optimal efficacy. Treatment duration varies depending on the individual case, typically ranging from 1 to 3 hours. After the procedure, patients maintain a urinary catheter for at least 48 hours to reduce the risk for post-treatment urinary retention caused by edema.[31]

As the same type of energy is employed, it is important to mention a novel and promising modality of treatment known as TULSA.

Unlike traditional transrectal HIFU, TULSA utilizes a transurethral probe that has the appearance of a 19-F rigid cystoscope. This device administers HIFU energy from the urethra under real-time MR guidance. To ensure accuracy, any patient movement triggering artifacts on real-time MRI thermometry prompts an automatic shutdown and cool-down mode in the system for recalibration. Therefore, patient paralysis under general anesthesia to minimize motion is required. Additionally, glucagon, a gastrointestinal antispasmodic, may also be administered intraoperatively to reduce rectal wall motion. The procedure can take place in an outpatient setting.

During the procedure, real-time MRI-thermometry monitoring tracks the progression of heat, ensuring precise adjustment of energy delivery to specific tissue segments based on the attained tissue temperature. Additionally, both endo-urethral and endorectal cooling apparatuses are utilized, offering 1–2 mm of preservation and protection for the urethral tissue and rectal wall, respectively. In this manner, TULSA aims to achieve satisfactory ablation of the intended area while safeguarding vital structures.

In summary, notable differences between TULSA technology and traditional HIFU include:

- The heat energy of TULSA originates from the urethra toward the prostate, while for HIFU, it emanates from a rectal probe toward the prostate.
- Image guidance is provided by real-time MRI in TULSA and by transrectal ultrasound in HIFU.
- TULSA delivers a single large directional plane of ablative energy, unlike HIFU, which creates many smaller focused beams.

Several considerations must be addressed when planning TULSA treatment. Patients with non-MRI–compatible implants, such as pacemakers, cannot undergo TULSA due to the indispensability of MRI. Additionally, patients with a hip prosthesis or any metal in the pelvic area may encounter visualization challenges, potentially contraindicating the technique. Apart from MRI compatibility, patients with lesion margins over 3 cm from the urethra, and those with large calcifications or cysts between the urethra and treatment region, should be excluded, as safe energy delivery to the target area may not be feasible, posing risks to untreated areas. Furthermore, patients with a history of urethral strictures should be carefully evaluated before considering transurethral treatment.[54]

Cryotherapy

Energy: Ice ball–extreme cold temperatures
Type of energy source: Thermal (– 40°C)
Route of application: Transperineal

Cryotherapy induces tissue ablation within the targeted area by delivering freezing temperatures targeting less than – 40°C. Ice ball formation during cryotherapy treatments leads to intracellular osmotic dehydration, cell membrane disruption, and ultimately cell death. While immediate cellular damage occurs, delayed vascular injury is considered to play an important role on cell death. Initially, freezing of the tissue leads to stasis within the blood vessels, vasoconstriction, and hypoxia. Upon thawing, blood flow is restored, but damage to the endothelial layer persists due to distension and tearing. This leads to a progressive decrease in vascularization through increased permeability of capillary walls, edema, platelet aggregation, and the formation of microthrombi.[53,55]

Similar to HIFU, cryotherapy can be performed on an outpatient basis under spinal, general, or local anesthesia, with the patient positioned in lithotomy. However, some authors have already described the possibility of carrying out the procedure in the office setting.[56,57]

At the beginning of the procedure, a transurethral warming device is inserted to safeguard against urethral damage. Subsequently, one or multiple cryoneedles (depending on lesion size and type of needle used) are inserted transperineally, guided by transrectal ultrasound. Temperature probes can also be placed throughout the prostate, the urinary sphincter, and between the prostate and rectum to monitor temperature changes throughout the treatment cycles. The standard procedure employs two freeze-thaw cycles. Following treatment, a catheter is left in place for at least 48 hours to mitigate the risk for post-treatment urinary retention.[58]

Focal laser ablation (FLA)

Energy: Laser energy
Type of energy source: Thermal (> 60°C)
Route of application: Transperineal or transrectal

FLA, also known as laser interstitial thermal therapy, utilizes the light emitted by a laser fibre, which, upon absorption by the tissue, induces tissue coagulation through direct heating. Hence, like techniques such as HIFU, TULSA, or cryotherapy, laser ablation acts as a thermal energy source, resulting in irreversible tissue damage by surpassing temperatures of 60°C.[53]

Unlike other modalities of focal treatment, laser energy can be delivered via either a transrectal or a transperineal approach. Another distinguishing feature is that FLA usually utilizes MRI instead of transrectal ultrasound for guidance. This approach offers detailed anatomical visualization crucial for precise treatment planning and targeting. Furthermore, the integration of MRI-based temperature monitoring enables real-time feedback during FLA, enhancing monitoring.[59]

The FLA treatment can be conducted under sedation with a periprostatic nerve block, spinal, or general anesthesia in the operating room. Furthermore, similar to cryotherapy, some authors have also explored the possibility of performing transperineal FLA under local anesthesia in the office with minimal side effects. If this option is chosen, monitoring is not performed by MRI. Instead, MRI-ultrasound fusion, along with a thermal probe adjacent to the laser fibre, is employed for lesion targeting and real-time ablation monitoring, respectively.[60]

During the transperineal approach, the patient is positioned in lithotomy, and an endorectal coil is inserted to aid in stabilizing the prostate. Additionally, a template grid is placed for needle insertion. Once the MRI-compatible trocar position is confirmed, a laser applicator system, comprising a laser-diffusing fibre within a cooled catheter system, is advanced to the targeted area. Following the reconfirmation of the final fibre position, the laser is activated to induce thermal injury.[61]

For the transrectal approach, patients are prepared with saline enemas prior to the procedure, and antibiotic prophylaxis is advised, following the protocol for transrectal biopsies. Positioned in the prone position, a single cooling catheter is inserted into the rectum, directed toward the tumour lesion. After confirming proper alignment, the laser fibre is introduced through the previously mentioned catheter.[62] Regardless of whether the approach is transperineal or transrectal, secondary safety monitors such as thermal probes may be inserted to evaluate the accuracy of magnetic resonance thermometry.[63]

Toward the conclusion of the procedure, the decision to leave a postoperative catheter varies across studies, with recommendations favouring its use in cases of peri-urethral lesions and for a large ablation where an inflammatory reaction is anticipated, potentially leading to urinary retention. Similar to other ablative techniques, patients can be discharged on the same day.[64,65]

Irreversible electroporation (IRE)

Energy: Electrical pulses low-energy direct current
Type of energy source: Non-thermal
Route of application: Transperineal

IRE is a non-thermal technique that utilizes high-frequency electrical pulses (typically 70-90 μs) to induce the formation of pores on cell membranes, allowing an uncontrolled influx of calcium ions. When these pores or water channels persist after the pulse has ended and the external electric field is no longer present, the technique becomes irreversible, leading to cell apoptosis.[66,67]

When performing IRE, the use of general anesthesia is imperative to mitigate the risk for severe muscle contractions and potential epileptic seizures triggered by high-energy pulses. Furthermore, complete muscle paralysis through neuromuscular blocking agents is indispensable to prevent any involuntary movements that could compromise the procedure's success by displacing the needles. Furthermore, it's essential to emphasize that electrical pulses have the potential to induce cardiac arrhythmias. As a result, IRE is contraindicated for patients with epilepsy or preexisting cardiac arrhythmias.[68]

In terms of technique, with the patient in lithotomy, needle electrodes are placed transperineally around the index lesion under biplanar transrectal ultrasound guidance. A maximum distance of 2 cm must be maintained between the electrodes, as longer distances reduce effective currency between electrodes. Following an initial trial with 20 pulses, the actual current between electrode pairs is assessed, and if within the optimal range, the remaining 80 pulses are administered; otherwise, voltage adjustments are selectively made between pairs as needed. Catheter removal is advised starting 48 hours after the procedure.[69]

Focal brachytherapy

Energy: Ionizing radiation
Type of energy source: Non-thermal
Route of application: Transperineal

Ionizing radiation induces cell death through various mechanisms, which can be classified into different types including apoptosis, necrosis, autophagy-dependent cell death, pyroptosis, ferroptosis, immunogenic cell death, and non-lethal processes.[70] When radiation is delivered by placing radioactive material inside the body, it is referred to as brachytherapy.[71]

Focal brachytherapy encompasses two primary modalities: low-dose-rate (LDR) and high-dose-rate (HDR) techniques.[72,73] In both cases, treatment is administered via gamma-radiation sources such as radioactive isotopes (i.e., Iridium-192 for HDR and Iodine-125 for LDR), which are inserted within the patient's body. LDR brachytherapy involves the permanent placement of radioactive seeds in and around the tumour, where they gradually release radiation over several months as the seeds decay. On the other hand, HDR brachytherapy is increasing as an alternative to LDR brachytherapy. In this case, thin needles are temporarily placed into the prostate transperineally, and a high-intensity radioactive source is passed through these needles to deliver a targeted, high dose of radiation. A distinct advantage of HDR brachytherapy is its optimal dose distribution, enabling precise control of the radiation source and the ability to adjust source dwell times during treatment. However, initial capital equipment costs are relatively high, and shielded rooms are required.[74]

New terminology has been proposed for focal brachytherapy, including focal-gross tumour volume (F-GTV), which represents the visibly apparent or clinically demonstrable location and extent of the targeted cancer; focal-clinical target volume (F-CTV), comprising F-GTV plus clinically insignificant disease; and focal-planning target volume (F-PTV), incorporating F-CTV along with a margin to account for uncertainties in image registration and treatment delivery.[74]

To initiate the procedure, patients are administered either general or spinal anesthesia. They are positioned in lithotomy and a bladder catheter is inserted. Utilizing real-time imaging guidance, such as transrectal ultrasound or MRI, the radiation oncologist carefully maneuvers either small, permanent radioactive seeds for LDR or temporary ones for HDR into the specified area within the prostate. The selection and arrangement of seeds are meticulously calculated to deliver the prescribed radiation dose while ensuring the protection of adjacent healthy tissues from unnecessary exposure. After the procedure, patients can typically be discharged on the same day with a bladder catheter, which may need to remain in place for a period ranging from 2 to 5 days.[72,75]

At the outset of this chapter, it's noted that focal therapy is advancing swiftly in tandem with technological progress. Alongside this progress, several devices have been commercialized for the same procedure, each with particularities that might impact outcomes. These should be taken into account, as seen with distal focal or different HIFU devices, which are directly related to the capacity for reaching lesions extending to the mid and anterior gland. On the other hand, new modalities of focal therapy are emerging with promising characteristics.

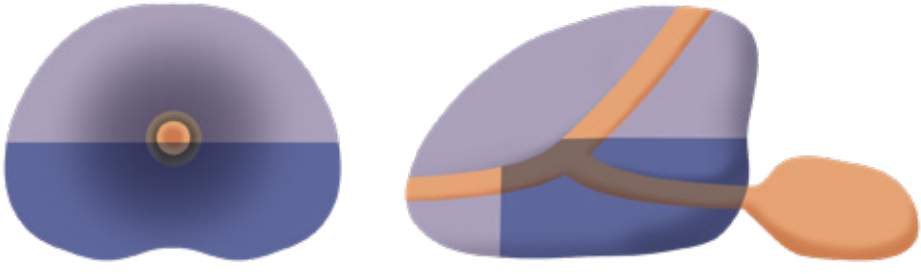
Currently, no energy source can be recommended over others due to the lack of comparative studies conducted thus far. In the following section of this chapter, various energy sources will be elucidated, following a lesion-based approach.[9]

Lesion-Centric Technique Description: Shifting from Energy-Based to Lesion-Based Approaches

Not all surgeries are conducive to robotic technology, laparoscopy, endourology, or open surgery. Surgeons must meticulously evaluate the pathology and select the most suitable approach from the available options. It's imperative to avoid employing a "one-size-fits-all" method. This principle is especially applicable in urology, exemplified by cases of lithiasis. Here, the utilization of a versatile toolbox is imperative for effectively managing the diverse array of calculi that can be found in the urinary system—taking into account their composition, size, localization, and quantity—as well as patient anatomy and both surgeon and patient preferences.[76]

In focal therapy, no single energy source has been proven, with a high level of evidence, to be universally effective and safe for every prostate lesion. Successful treatment requires careful consideration of the energy source and approach used to reach the lesion while minimizing damage to surrounding structures such as the sphincter and the rectum. This emphasizes the importance of having a diverse toolbox in focal therapy to ensure optimal outcomes, as relying solely on one tool may lead to contorting the lesion to fit the tool, whereas it's wiser to tailor the tool to fit the lesion(s). Thus, to provide a more informative approach, it's essential to focus on the specific lesion being treated rather than solely on the energy source employed.[9]

1. Prostate lesions located in the posterior region



High-intensity focused ultrasound

HIFU can be considered a good option for lesions located in the posterior part of the gland, supported by two main reasons. First, and most importantly, energy delivery can be achieved transrectally, facilitating precise targeting of the lesion. Secondly, HIFU and cryotherapy have been the two most utilized energy sources so far, accumulating the most robust evidence base in the field of focal therapy.[31]

It is important to note that one concern in the treatment of posterior lesions is the potential risk for rectal fistula. Nevertheless, according to a systematic review that included more than 1,500 patients, post-HIFU fistula was identified in 16 out of 1,240 patients (1.3%), with complication rates that do not differ from those for established therapies such as radical prostatectomy and radiotherapy.[77]

Transurethral ultrasound ablation

Although no studies have directly compared outcomes using TULSA for different areas of treatment, this modality can be considered a suitable treatment option if the distal part of the treatment area (including the lesions and corresponding margins) is no more than 3 cm away, as this corresponds to the distal focal length of the device.

Cryotherapy

In accordance with the "à la carte" approach, cryotherapy is typically not recommended for posterior lesions due to inherent challenges. These challenges primarily arise from concerns about the risk of inducing rectal damage or potentially undertreating the posterior parts of the prostate while attempting to protect the rectum.[32] However, it's worth noting that the hypothetical risk for rectal damage or undertreatment when cryotherapy is used has not been validated in further research.

On the other hand, multiple studies on hemi-ablation and whole-gland ablation using cryotherapy have demonstrated that achieving good oncological outcomes with favourable functional outcomes and minimal side effects is possible if the surgeon is adept with the transperineal approach, ice ball generation, and the use of different tips and tricks to conduct the procedure safely.[33,78]

In this regard, while a urethral warming catheter is commonly used to protect the urethra, alternative devices have been proposed to safeguard the rectum by heating its wall. Additionally, thermocouple probes near the rectum for temperature monitoring are recommended, providing feedback on any treatment-related changes.[79,80]

As an illustrative example, a systematic review on whole-gland ablation, which inherently involves treating the posterior part of the prostate, revealed that among 16 studies (6 involving cryotherapy and 10 involving HIFU), the rate of recto-urethral fistula was 0.8% for cryotherapy, similar to that for HIFU, which was 0.7%. Therefore, we can conclude that although cryotherapy has traditionally been avoided for posterior lesions, in the hands of experienced practitioners, it can also be considered as a viable treatment option for such lesions.[33]

Focal laser ablation

FLA can be considered a promising technique with great versatility, as it can be applied both transrectally and transperineally. However, there are no studies evaluating the results of the technique based on location so far. In this regard, Eric Walser *et al.* have published the longest series to date of FLA with 120 patients. In this series, the transrectal approach was described with four different locations: anterior 16 (10.8%), central 8 (5.4%),

transition 16 (10.8%), peripheral 108 (73.0%). Although the results by location are unknown, particularly in the apex or posterior part (which were not registered), it should be noted that 2 patients developed transrectal fistulas (1.6%), a relatively high percentage compared to other series of focal therapy.[62] Therefore, while FLA would not be contraindicated for posterior lesions, insufficient evidence remains to support the safety of this approach for peripheral lesions near the rectum unless performed by skilled hands familiar with the technique, especially when other alternatives exist.

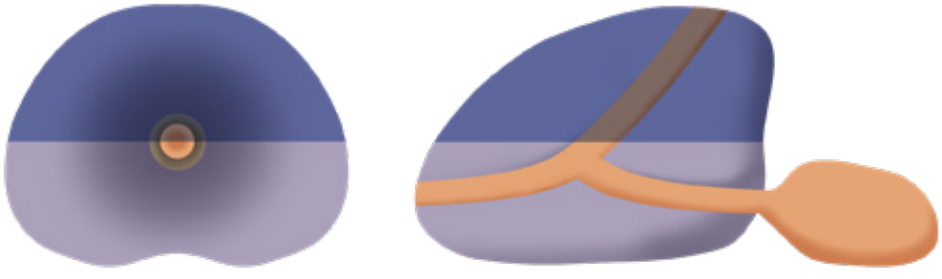
Irreversible electroporation

In the past, transperineal-driven treatments have been suggested to be avoided for posterior lesions. Nevertheless, through meticulous evaluation of the gland's anatomy and ensuring a minimum margin of 5 mm from critical structures such as the rectum, IRE has emerged as a viable option for lesions located on the posterior part of the gland.[69,81] In this vein, Scheltema *et al.* conducted a prospective study aimed at assessing genitourinary function and quality of life subsequent to the ablation of various prostate segments (anterior vs. posterior, apex vs. base vs. apex-to-base, unilateral vs. bilateral) with IRE. After the inclusion of 60 patients, the study concluded that IRE can be safely performed on all prostate segments, as no statistically significant differences were observed between prostate segments concerning genitourinary function and quality of life. Accordingly, with expertise and a thorough comprehension of transperineal biopsy or focal transperineal treatment—particularly acknowledging the nuanced complexities of managing posterior lesions—IRE may be considered a safe option for treating such lesions.[82]

Focal brachytherapy

When considering brachytherapy, most studies focus on the apex-base location of the lesion, as a shorter distance to the base and bladder neck appears to be linked to poorer functional outcomes. Although the series are limited in size, certain authors have reported positive outcomes for brachytherapy in treating posterior lesions. In these instances, inserting a rectal spacer between the prostate and anterior rectal wall may additionally reduce the occurrence of rectal symptoms following focal treatment.[71,83–85]

2. Prostate lesions located in the anterior region



High-intensity focused ultrasound

As previously mentioned, ultrasound waves may effectively treat lesions up to 3–4 cm from the site of treatment (rectum or urethra), necessitating that the distal part of the lesion be positioned at most 4–5 cm (probe-dependent) away from the probe to ensure 10-mm margins. Therefore, transrectal HIFU may theoretically be considered for anterior lesions in cases of small prostates. However, a retrospective study comparing HIFU treatment outcomes for anterior and posterior lesions in small prostates with similar volumes (33 mL vs. 36 mL) found a higher retreatment rate among patients with anterior lesions compared to those with posterior lesions (17/45 [37.8%] vs. 45/222 [20.3%]). This suggests that despite the probe's ability to reach the lesion, there is a significant difference in successfully treating cancers localized more anteriorly compared to those closer to the rectal probe. This discrepancy is likely due to the loss of energy as the pulse traverses multiple tissue planes. There is also a near-field additive energy deposition during HIFU treatment, so posterior tissue accumulates more energy compared to distal tissue overall. Therefore, treating anterior lesions with transrectal HIFU may not be fully contraindicated but may not be recommended, especially when ablative energy can be delivered directly into a desired intraprostatic area by other modalities.[86] If treating anterior lesions is considered, it should be noted that planning treatment solely for the anterior zone is not advisable. Treatment should encompass the posterior part as well, ensuring that the distance between the rectal wall–detected balloon and the bottom of the area to be treated does not exceed 10 mm.

Transurethral ultrasound ablation

Due to the transurethral positioning of the TULSA device and the capability of the robotically driven arm to perform 360-degree treatment within a range of approximately 3 cm from the device, patients with anterior lesions, which may be difficult to access with HIFU due to their distance from the rectal wall, are suitable candidates for TULSA treatment. Therefore, TULSA appears to be an excellent technique for addressing anterior lesions.[54]

Cryotherapy

As one of the pioneering modalities in focal therapy, cryotherapy, like HIFU, has accumulated a considerable body of scientific evidence, although with varying quality, with the majority consisting of retrospective studies and a few prospective. Currently, cryotherapy is considered as a very good option of treatment for lesions situated anteriorly with good oncological and functional outcomes.[32,52]

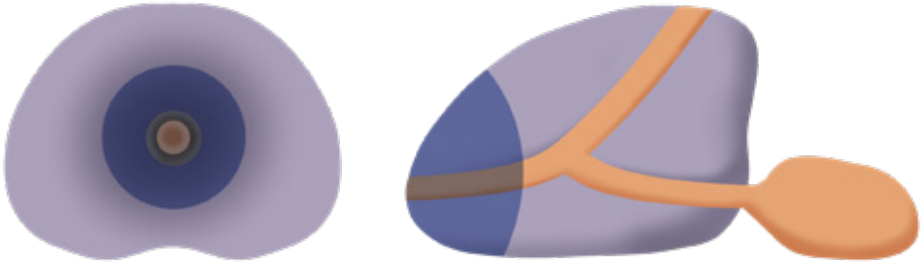
Focal laser ablation

FLA, especially in its transperineal version, like any other energy delivered transperineally, represents a very good treatment choice for anterior lesions. The primary goal when planning focal therapy is to reach the lesion safely.

Irreversible electroporation

Anterior lesions are readily accessible through transperineal needle-based energies, making irreversible electroporation a safe option for treating such lesions. However, it is essential to carefully consider the recommended treatment protocol for individuals initiating treatment with IRE.[69]

3. Prostate lesion located in the apex



Regardless of the energy modality employed, treating the apex is often considered the most challenging area to treat. Notably, following radical prostatectomy, the incidence of positive apical margins can reach as high as 27%, serving as a significant predictor for biochemical recurrence.[87] Moreover, recurrence after radiotherapy frequently involves the apical region.[88]

The first consideration when contemplating the treatment of lesions located in the apex is the definition and anatomical boundaries of the prostatic apex. The apex may be defined as the narrowest part of the prostatic gland, which rests on the superior surface of the urogenital diaphragm and contacts the medial surface of the elevator ani muscles. However, the limits on MRI are not definitive, and when a lesion is described in the apex, it should be carefully evaluated. Sometimes, lesions reported to be in the apex by radiologists are distant from the sphincter and may be suitable for focal treatment.[89]

High-intensity focused ultrasound

Lesions situated in the apex may be safely treated provided there is a minimum distance of 5 to 10 mm between the treatment area and the sphincter. However, it's important to recognize that not all lesions are small, and not all prostates are sufficiently large to accommodate a treatment area with 5–10 mm margins relative to the lesion visualized on MRI, while still maintaining an additional 5–10 mm safety margin with respect to the sphincter. This implies that while there may not be an absolute contraindication, finding suitable candidates for treatment in this area may be rare.[90,91]

Transurethral ultrasound ablation

Presently, there remains insufficient evidence to substantiate the efficacy of treating apical lesions with TULSA and the advantages of MRI monitoring in influencing outcomes. As we await further studies exploring the diverse applications of this technology, it is imperative that patients with apical lesions undergo careful evaluation prior to considering thermal treatment with ultrasound, irrespective of the chosen approach.

Cryotherapy

Following a similar rationale as the HIFU treatment discussed earlier, cryotherapy for treating apex lesions may be considered in highly specific cases where safety margins around the sphincter can be consistently preserved during lesion and margin treatment. In such scenarios, cryotherapy might be deemed suitable in reputable centres, as proposed by some researchers. While retrospective studies have indicated its oncological effectiveness, functional outcomes have not been thoroughly evaluated.[90]

Focal laser ablation

FLA, like any other thermal energy, should generally be avoided for the apex, as controlling the treatment limits may be challenging. Although the use of MRI monitoring may lead to better functional outcomes by improving the accuracy of energy delivery margins, there is still no evidence supporting its safe use for apical lesions.[62]

Irreversible electroporation

IRE has already been tested in apical lesions. Referring to the study conducted by Scheltema *et al.*, where 18 patients received treatment at the level of the prostatic apex (defined as any ablation performed within the mid to upper apex), no differences in genitourinary function and quality of life were observed when comparing apex to base, apex to apex-to-base, or base vs. apex-to-base.[82] Furthermore, Blazevski *et al.* conducted a study involving 50 patients with prostate cancer lesions within 3 mm of the apical capsule treated with IRE. After a median follow-up period of 44 months, no Clavien–Dindo grade ≥3 events were reported, and no significant differences were observed in the Expanded Prostate Cancer Index Composite (EPIC) urinary or bowel quality of life between baseline and 12 months post-treatment. Among the patients who were potent before treatment, 94% remained potent afterward. Only one patient required one pad per day for urinary incontinence at 12 months post-treatment. Lastly, among the 80% of patients who underwent post-treatment control biopsies, only one exhibited an in-field recurrence.[92] In conclusion, preliminary studies on IRE for apical lesions appear to demonstrate that this non-thermal energy can be safely utilized.

Focal brachytherapy

Several retrospective studies have shown that patients who underwent focal brachytherapy at the apex of the prostate experienced significantly less urinary toxicity compared to those treated at the base, with no significant differences observed in terms of erectile function. Nevertheless, series are limited with short follow-ups, and the oncological results are not as favourable as when treating other areas of the prostate. Therefore, it cannot be maintained nowadays that brachytherapy is a superior option for apical lesions with better results compared to other energy modalities.[71,72,93]

In summary, it's clear that no single energy modality is universally applicable in contemporary practice. Rather, embracing a toolbox model, where a range of tools is available and the surgeon selects the most appropriate one considering factors like manufacturer's recommendations, tool availability, surgeon preference, and patient preference emerges as the most prudent choice.

Furthermore, it is anticipated that the rapid evolution and advancement of focal therapy will render this chapter outdated in the near future. Therefore, ongoing vigilance and adaptation are imperative to stay abreast of emerging developments in this field.

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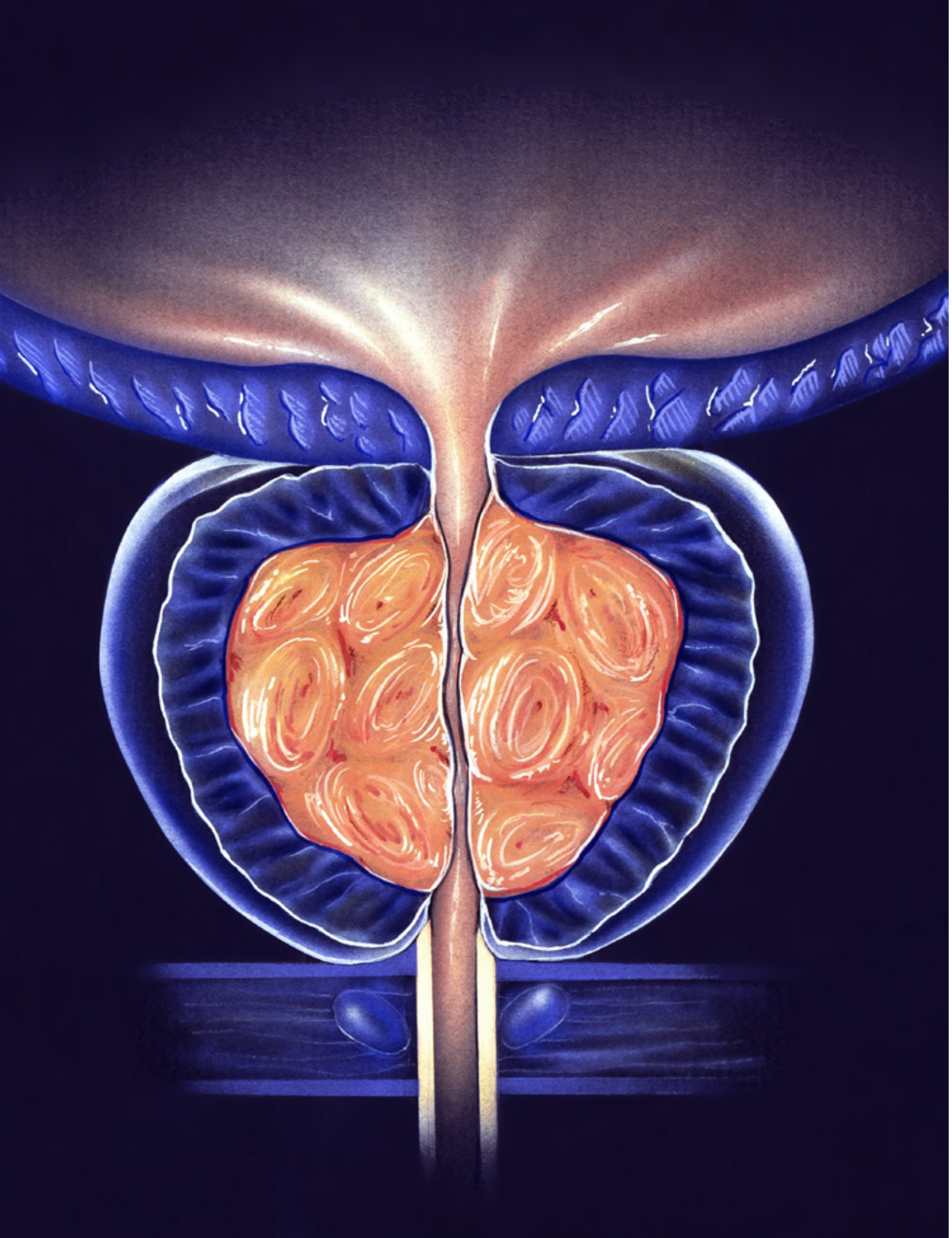

COMMITTEE 15

Management of Lymph Node–Positive Prostate Cancer

CO-CHAIR

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Introduction

Regional spread to the lymphatics is a common and controversial challenge in the management of unfavourable intermediate and high-risk prostate cancer. The precise incidence of lymph node involvement is unknown, with data from large surgical series suggesting that over 10% of men present with lymph node–positive prostate cancer.[1,2] Historically, the presence of metastatic nodal disease was considered indicative of systemic disease, to be managed solely by systemic treatment. However, with advancements in imaging modalities, nodal involvement is increasingly treated as a locoregional spread of prostate cancer rather than a systemic disease, using radical prostatectomy (RP) and/or definitive external beam radiotherapy (EBRT) typically in combination with androgen deprivation therapy (ADT). This chapter covers the diagnosis, significance, as well as the evolving treatment landscape for men with node positive (+) prostate cancer.

Definition

The diagnosis of metastatic nodal prostate cancer depends on how aggressive one wishes to pursue nodal status. Traditionally, in patients treated with RP, the "gold standard" for determining lymph node involvement (LNI) has been standard pelvic lymph node dissection (PLND) or extended PLND (ePLND), providing evidence for pathological staging (pN+). However, in patients undergoing EBRT, nodal involvement may be confirmed surgically (i.e., pN+) or by a radiological definition (cN+), based on nodal size and shape criteria, and more recently, based on prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging. Uniquely, for prostate cancer, there are numerous nomograms based primarily on prostate-specific antigen (PSA) levels, Gleason score (GS), clinical stage, and sometimes the percentage of positive biopsies to predict the probability of pelvic nodal metastasis according to risk stratification, which physicians can use to select patients for prophylactic nodal treatment, when their risk exceeds a certain level (e.g., ≥ 15%).[3,4]

Pathological definition (pN+)

Post RP and PLND

PLND has long been considered the most reliable method for nodal staging in localized prostate cancer, but its accuracy appears to be critically dependent on the number of nodes in the sample and how aggressively the nodes are analyzed.[5] Patients with a preoperative nomogram–based risk for nodal metastasis predicted at > 5% are typically considered candidates for PLND or ePLND, which is considered the "gold standard" when RP is planned.[6] The adequacy of nodal yield and the optimal number of lymph nodes that should be excised are discussed in detail in the surgical management section, though no consensus has been reached on this matter.

Nodal sampling

In an effort to increase the sensitivity for detecting lymph node involvement, sentinel lymph nodal biopsies (SLNBs) have been pioneered by a number of investigators.[7] This approach has been reported in surgical series to have a sensitivity of up to 99% for identifying the location of sentinel nodes.[8–10] An exception to this high sensitivity appears to be in the setting of high-risk patients with lymphatic obstruction caused by tumour.[8] An approach of combining PLND and SLNB has been proposed, although some authors consider this excessive treatment.[11] In the setting of EBRT (drainage areas identified by injecting the prostate in six locations), sentinel imaging has limited utility, as it does not determine *whether* the nodes are involved, but rather where metastases would likely be if the nodes were positive.[10] Although SLNB is not currently a common practice, it remains a highly effective way to identify the areas likely to be involved but unfortunately does not determine whether they are actually involved.[12]

Pathological processing of PLND specimens

It is crucial to establish a consistent approach to the pathological handling and evaluation of PLND specimens. The collaboration between the surgeon and the pathologist is essential for optimizing the staging process. Accurate nodal staging and lymph node count after PLND depend largely on the extent of pathological examination of surgical specimens. Despite these requirements, there are no well-established guidelines for an evidence-based "standard of care" (SOC) for examining the nodal specimens. This leads to considerable variation across pathologists and institutions.[13] The degree with which nodes are dissected (micro-dissection vs. standard) determines the likelihood of identifying involvement of cancer.

The standard approach for isolating lymph nodes from surgical specimens involves manual palpation and dissection from the surrounding fat. Pelvic lymph nodes (LNs) are typically heavily infiltrated by fat and may have an elongated tortuous configuration. An alternative method, serially slicing of the intact specimen, can lead to double-counting of multiple slices from a single LN as separate individual LNs. Thus, careful gross dissection of individual LNs is preferred for accurate LN assessment.[13]

Nodal burden (number and size) and prognosis

The current TNM staging system groups all pelvic node–positive patients into a single category (e.g., N1) and positive nodes beyond the pelvis classified as M1b. From a clinical management standpoint, these authors consider common iliac and para-aortic nodes, and occasionally others higher up in the nodal chain, as suitable areas for inclusion during definitive EBRT.[14,15] Several studies suggest that limited nodal involvement correlates with superior long-term survival compared to more extensive nodal disease, with outcomes also influenced by the sites involved.[16–18] This explains the importance of accurately characterizing the extent of lymph node involvement. In addition to the number of nodes involved, the size of largest metastatic tumour deposit has been considered a prognostic factor by some investigators. For example, in a series of 102 patients, investigators concluded that the size cutoff of 1 cm for the largest metastatic node is the strongest independent prognostic factor of recurrence-free survival, disease-specific survival, and overall survival (OS).[19] Other studies have supported this hypothesis, going so far as to argue that the size of largest metastatic lymph node is much more important than the number of metastatic nodes.[20,21] The significance and definition of nodal micrometastasis in prostate cancer is unclear

or non-uniform among studies and is not incorporated into the TNM staging system.[21] Of note, the prognostic significance of nodal involvement, in terms of long-term survival, appears to be somewhat more favourable than for other types of metastatic spread (e.g., bone, lung, liver).[22]

Clinical definition (cN+)

The clinical diagnosis of nodal metastasis in prostate cancer implies the nodes were detected by radiological imaging criteria. These imaging criteria can be grouped into three types, but ultimately, the detection of metastatic lymphadenopathy in prostate cancer depends on the size or volume of the tumour burden:

A: Anatomical (e.g., CT and T1-2 MRI)
B: Functional (e.g., DW MRI, Dextran-coated ferromagnetic)
C: Molecular imaging (e.g., PSMA PET scan)

A detailed discussion of each of these areas is beyond the scope of this chapter, but a brief review is included in the next section.

Imaging for detection of occult metastatic lymphadenopathy

Accurate information on the presence and precise location of metastatic nodes before definitive local regional treatment (radiation or surgery) can greatly enhance our ability to customize treatment, and potentially save the patient unnecessary morbidity. Unfortunately, this ideal imaging technology does not currently exist. However, in recent years several new methods have been introduced that improve pelvic LN imaging.[23]

Anatomic imaging

Conventional CT

Conventional computed tomography (CT) scans are no longer recommended for routine staging for prostate cancer due to their very low sensitivity in detecting lymph node metastasis and the emergence of more sensitive imaging modalities. The sensitivity of CT scans across studies ranges from 5% to 93%.[24] This variation reflects variability in patient population and study methodologies.[25,26] A study of 55 prostate cancer patients compared the sensitivity of conventional CT and magnetic resonance imaging (MRI) for detecting positive nodes in high-risk prostate cancer patients, confirming the superiority of laparoscopic PLND, over CT, with the latter failing to detect nodal metastases in 9 of 20 node-positive patients.[27] In an older but larger prospective series of 285 patients, the sensitivity, specificity, and accuracy of conventional CT for detecting metastatic lymph nodes were found to be 78%, 97%, and 94%, respectively.[28] A more recent review of the literature involving 23 studies found that the detection rate of CT scans for metastatic lymph nodes was much lower than that of pathological evaluation.[29] The current literature reports that the sensitivity of CT for detecting lymph node metastasis ranges from 0% to 30%, depending on patient characteristics.[27,28]

One key question when using CT scans for detecting lymph node metastasis, is “Should lymph node size on CT scan be a surrogate for presence of lymph node metastasis?”. Arguments against this practice highlight that

micrometastases can be found in about 30% of normal-sized pelvic LNs,[2,3] whereas LNs are often enlarged due to hyperplasia caused by inflammatory or infectious diseases.[30] Tiguert *et al.* found that 56 metastatic nodes had an axial size of less than 1 cm and 20 had a size of less than 5 mm, thus concluding that lymph node size alone should not be used as a surrogate for the presence of lymph node metastases.[31] Certain features such as loss of fatty hilum, irregular or ill-defined nodal margins, round shape in all three dimensions, lower signal intensity on T2-weighted images, and heterogeneous parenchymal signal could help predict nodal metastatic involvement.[32] However, applying these criteria is highly challenging and requires significant expertise.[23]

Magnetic resonance imaging (MRI), multiparametric (mp) MRI

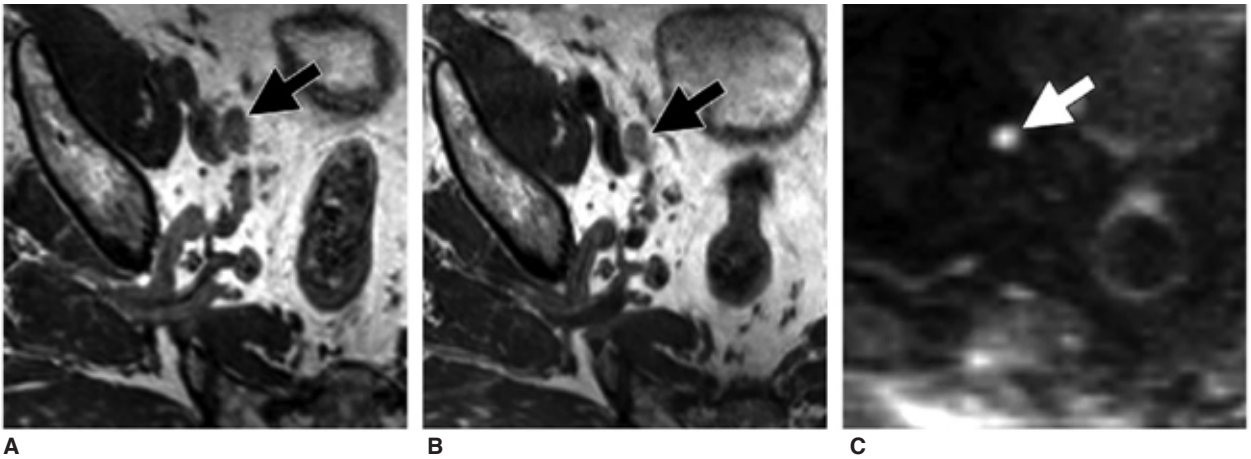
MR imaging has been studied extensively for detecting lymph node metastases by a number of investigators. In an older study, Borley *et al.* reported that MRI identified pelvic lymph node metastases in only 27.3% of patients while missing pelvic lymph node metastases in 72.7% of patients as confirmed by lateral pelvic lymph node dissection (LPLND).[27] Hricak *et al.* found that the accuracy of MRI increased up to 83% when transverse T1- and T2-weighted images were supplemented with additional T2-weighted coronal or sagittal images.[33] However, these results are substantially higher than those reported elsewhere in the literature. For example, a recent retrospective cohort evaluated the accuracy of preoperative lymph node metastases detection by 3T multiparametric (mp) MRI in patients with prostate cancer who underwent RP and PLND. The investigators concluded that mpMRI was superior to CT in detecting lymph node metastasis (LNM) (sensitivity 81% vs. 33%; specificity 99% vs. 97).[34] However, many authors suggest that both CT and even mpMRI have many limitations in detecting lymph node metastasis before RP. A more contemporary large cohort conducted by a group of researchers from Michigan Urological Surgery Improvement Collaborative (MUSIC) assessed the performance of preoperative CT and mpMRI in detecting metastatic LNs. The study found that the majority of pN1 patients had a negative CT or a negative/indeterminate mpMRI prior to RP. For CT, the sensitivity was 8.9%, specificity was 98.3%, negative predictive value (NPV) was 92.1%, and positive predictive value (PPV) was 32.3%, while for mpMRI, the sensitivity was 19.0%, specificity was 97.3%, NPV was 95.9%, and PPV was 26.7%.[35]

Despite the limitations associated with the technique, some experts still recommend conventional imaging, believing that mpMRI is superior to CT scan in detecting metastatic lymph nodes.[36] Therefore, the American Urological Association (AUA) strongly recommends mpMRI in all patients with high-risk prostate cancer (PCa).[37] A meta-analysis by Hovels *et al.* of 24 studies assessed the diagnostic accuracy of CT and MRI for diagnosing LNM in prostate cancer. The study found that for CT, the pooled sensitivity was 0.42 and pooled specificity was 0.82, and for MRI, the pooled sensitivity was 0.39 (95% confidence internal [CI], 0.22–0.56) and pooled specificity was 0.82 (95% CI, 0.79–0.83). The investigators concluded that both CT and MRI showed an equally poor diagnostic accuracy in detecting lymph node metastases from prostate cancer and relying on either CT or MRI will misrepresent the patient's true status regarding nodal metastases, thus misdirecting the therapeutic strategies offered to the patient.[38] To highlight the magnitude of the problem, the rate of LN-positive metastases with negative conventional imaging results varies ranging from 0% and 26%, depending on clinical risk factors. For instance, for low-grade tumours, the rate never exceeds 5%, whereas for high-grade tumours, it can be much higher.[23]

Functional imaging

Functional imaging using ultrasmall superparamagnetic iron oxide (USPIO)–enhanced MR imaging has been investigated for detecting LNM in prostate cancer. Ferumoxtran-10 was the first USPIO used in earlier studies.[39,40] Ferumoxtran-10 is a dextran-coated USPIO that is injected intravenously at a dose of 2.6 mg of iron per kilogram over 30 minutes. After injection, the agent leaks into the extravascular space and is taken up by the lymphatic system. In the lymph nodes, it is engulfed by macrophages within 24–36 hours of injection. The accumulation of intracellular iron oxide within abundant macrophages leads to T2 shortening, resulting in signal decrease on T2 and T2-weighted images. Nodes that are replaced by metastases contain no macrophages, and thus do not take up the agent, exhibiting the same signal intensity as baseline (**FIGURE 1**). Therefore, nodes completely replaced with metastases are both homogeneous and unchanged in signal. In contrast, partially replaced metastatic nodes show heterogeneous signal intensity due to partial uptake of the agent, resulting in a visible defect. The procedure requires a baseline image prior to injection and a follow-up image obtained 24–36 hours after contrast administration.[41]

FIGURE 1 Images in a 64-year-old man with PCa (stage T3bpN1, Gleason score 4+4=8) showing the following: (a) reconstructed axial T2-weighted MRI (640/47) that reveals an LN in the external iliac region on the right (arrow) before and (b) 36 hours after intravenous administration of ferumoxtran-10, with lack of contrast medium uptake (no signal change) suspicious for a LN metastasis. (c) Axial DW (*b* value, 1,000 sec/mm^2) MR image obtained after ferumoxtran-10 administration shows a hyperintense round structure (arrow) corresponding to the LN metastasis confirmed by histologic examination.



Abbreviations: DW, diffusion-weighted; LN, lymph node; MR, magnetic resonance; MRI, magnetic resonance imaging; PCa, prostate cancer.

Source: *Used with permission of* Radiology, *from Functional and targeted lymph node imaging in prostate cancer: current status and future challenges, Thoeny HC, Barbieri S, Froehlich JM, Turkbey B, Choyke PL, Vol. 285, Ed. 3, 2017; permission conveyed through Copyright Clearance Center, Inc.*[23]

A prospective study of ferumoxtran-10–enhanced MR imaging conducted in 80 prostate cancer patients found that surgical nodal metastases were identified in 100% of patients, and a node-by-node analysis had a significantly higher sensitivity than did conventional MR imaging (90.5% vs. 35.4%; $p<0.001$) or nomograms. This study was criticized as patients did not undergo ePLND, which could underestimate the NPV of ferumoxtran-10.[42] Unfortunately, despite studies reporting very high sensitivity and specificity rates, the United States Food and Drug Administration (FDA) declined to approve this agent, and it is only available for research purposes in The Netherlands.

Diffusion-weighted (DW) MRI

DW MR imaging demonstrates that the underlying tissue structure restricts the random Brownian motion of water molecules within the tumour, with restricted diffusion reflecting changes in the volume of epithelium, stroma, and lumen space.[43] In addition, the apparent diffusion coefficient (ADC) is a parameter used to differentiate benign from malignant nodes, with lower ADC values suggesting metastatic nodes. However, the variability of a threshold ADC value used in studies makes establishing of a consistent cutoff very challenging. Overall, studies that use ADC maps to help detect pelvic LN metastases have reported sensitivities ranging from 76.4% to 100% and specificities from 74% to 98.3%.[33] However, some studies show no significant difference in ADC between benign and malignant nodes, with substantial overlap in spite of lower ADC values for malignant nodes; therefore, ADC measurement alone is not recommended for diagnosing nodal metastases.[44] Given the noninvasive nature and high sensitivity of high-*b*-value DW MR imaging, this method is considered highly promising for detecting malignant nodes. Furthermore, it is potentially widely available and does not require injection of an exogenous agent (**FIGURE 4**). However, MRI has fallen by the wayside given the current widespread availability of PSMA PET imaging.

Molecular imaging: the emergence of PSMA PET

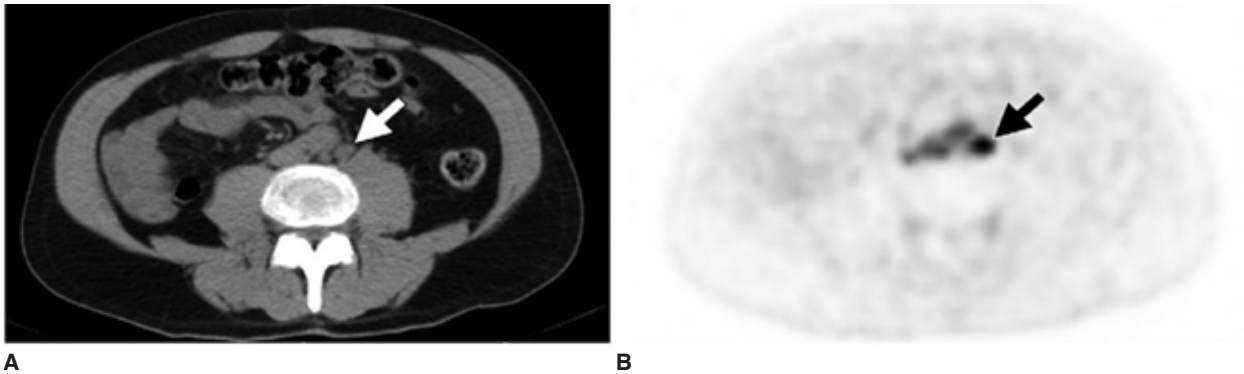
Molecular imaging is the most accurate method for detecting nodal disease in men with clinically localized prostate cancer. ^{18}F-fluorodeoxyglucose (FDG) has limited sensitivity in prostate cancer due to the low glycolytic activity of PCa, and although some PCas take up FDG, most do not.[23] Consequently, FDG PET has not gained popularity for detecting LNM in prostate cancer. Similarly, choline-based (^{11}C and ^{18}F) PET/CT imaging has fallen out of favour with the advent of PSMA PET.

Prostate-specific membrane antigen (PSMA) targeting PET tracers

PSMA is a transmembrane protein that is highly expressed in PCa, with high PSMA expression correlating with unfavourable prognostic factors such as higher grade, castrate resistance, and metastatic disease.[45] Normal prostate tissue and benign prostatic hyperplasia (BPH) exhibit low PSMA expression, making PSMA an excellent target for identifying PCa cells. An ever-increasing list of PSMA PET agents have redefined the SOC for staging newly diagnosed and recurrent prostate cancer. A discussion of the various agents currently available is beyond the scope of this chapter, but suffice it to say overall they are all superior to any conventional imaging approach and relatively comparable to each other, with minor differences. For example, although ^{18}F-based PSMA PET/CT imaging has been reported to have a sensitivity of 92%, the data is limited by the relatively small number of patients and a lack of histopathologic correlation (**FIGURE 2**).[46,47] So-called "second-generation," urea-based, ^{18}F-labelled, PSMA-targeting PET agent 2-(3-(1-carboxy-5-[(6-[18F]fluoropyridine-3-carbonyl)-amino]-pentyl)-

ureido)-pentanedioic acid (^{18}F-DCFPyl) has been reported to have excellent tumour detection in patients with characteristics indicative of PCa recurrence, with a lower background signal and higher PSMA affinity. Although some authors consider this to be a superior agent than N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-l-cysteine (^{18}F-DCFBC) due to its higher affinity and faster background clearance, the clinical relevance remains unclear.[48] One relatively small study (n=9) involving patients with recurrent PCa demonstrated that ^{18}F-DCFPyl detected more lesions compared to conventional imaging modalities (CT, bone scan), most of which appeared negative or equivocal, whereas 139 sites were detected by PET (^{18}F-DCFPyl uptake 138 definite, one equivocal). In contrast, only 45 lesions (30 definite, 15 equivocal) were identified as metastatic with conventional imaging.[49]

FIGURE 2 Images in a 59-year-old 8 years after radical prostatectomy and LN dissection for Gleason 4+3 PCa, with a current prostate-specific antigen level of 11.57 ng/mL. (a) Axial CT image shows subcentimeter LN in the left retroperitoneum (arrow). (b) Axial ^{18}F-DCFBC PET image shows specific uptake in the left retroperitoneal LN with a standardized uptake value of 8 (arrow).



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Abbreviations: 18F-DCFBC, N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-l-cysteine; CT, computed tomography; LN, lymph node; PCa, prostate cancer; PET, positron emission tomography.

Source: *Used with permission of* Radiology, *from Functional and targeted lymph node imaging in prostate cancer: current status and future challenges, Thoeny HC, Barbieri S, Froehlich JM, Turkbey B, Choyke PL, Vol. 285, Ed. 3, 2017; permission conveyed through Copyright Clearance Center, Inc.*[23]

In an analysis using another PET imaging agent, ^{68}Ga and N,N'-bis-[2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid (HBED-CC), involving 42 patients with pathologically confirmed PCa, a higher sensitivity and specificity were observed than with the previously discussed agents. However, this ^{68}Ga-associated PET emitting isotope has a short half-life of only 68 minutes and thus requires an onsite generator. Other small studies incorporating ePLND demonstrated similarly high rates of per-node sensitivity of 94%, specificity of 99%, PPV of 89%, and NPV of 99.5%.[50,51] However, further studies, particularly large-scale, prospective, multicentre trials, are needed to assess the relative merits of these agents for site-by-site nodal staging. Despite these limitations,^{18}F may be preferred over ^{68}Ga for labelling PSMA-targeting ligands due to its longer half-life, making it more practical in the clinic. The need for an onsite generator means that ^{68}Ga may

be feasible only in a high-volume setting. Another factor to consider is that PSMA-targeted PET agents can be limited by their excretion through the urinary system, which may obscure pelvic uptake. This occurs because of blood pooling in areas near anastomoses or the ureters, making it difficult to distinguish from para-iliac nodes, other lymph nodes, or ganglia.[52] Additionally, there are emerging alternative radiolabelled PSMA ligands—such as PSMA-617, PSMA I&T, and MIP-1095—with both imaging and therapeutic capabilities, and only time will tell whether any will be "game changing."[53]

Prediction of nodal metastasis risk in node negative (cN0) prostate cancer

Although current nomograms were developed before the era of modern imaging, they remain relevant due to the reported false negative rates of 30% to 50%, even using advanced imaging technologies. Several nomograms developed in the early 1990s, using clinical factors like PSA, GS, or clinical stage to predict the risk for LNM, are in use. For the purposes of this chapter, we will discuss several nomograms commonly used in clinical practice.

Nomograms predicting risk of lymph node metastasis

Partin nomograms

Partin and colleagues from John Hopkins developed the first well-validated tabular nomograms based on a study performed on 703 patients to predict the final pathological stage in those with clinically localized PCa. The investigators used PSA, GS, and clinical stage to group the final pathological stage into four categories: organ-confined disease, extracapsular disease (ECE), seminal vesicle involvement (SVI), and LNI.[54] However, these nomograms were criticized for being complicated and requiring "look-up" tables, as the data was not easily memorized for use in clinical practice. Additionally, the clinical stage in this series was assessed by a limited number of expert urologists.

Roach equation

Building on previous nomograms, Roach developed a simple equation for estimating the risk for lymph node involvement.[55] This equation relied solely on PSA value and Gleason score, excluding clinical stage due to variability in reproducibility and the assumption that all patients with clinical T3 disease are at high risk for lymph node involvement.[56] The so-called "Roach equation" is as follows:

2/3 PSA + (Gleason score -6) x 10 = risk of + lymph nodes

The main advantage of this equation is that it is easily memorized, eliminating the need to carry nomograms for reference. Patients thought to be below a threshold (e.g., 15%) for lymph node involvement can be spared prophylactic whole pelvic irradiation, reducing both the higher morbidity and the additional cost associated with treatment. We initially validated this equation in a study of more than 200 surgically resected patients from five local institutions.[55] Among patients with a calculated risk of less than 15% (expected range, 0–14%), the observed incidence of positive notes was 6% (expected average, 7). Conversely, among the remaining patients with a calculated risk of 15% or more, the observed incidence of positive nodes was 40%. Thus, using this equation could identify more patients at low and high risk for lymph node involvement than using either the clinical stage, Gleason score, or PSA alone. This and similar nomograms have been used in disease trials evaluating the role of prophylactic nodal irradiation (see **TABLE 1**).

TABLE 1 RCTs Involving Prophylactic WPRT in cN0 Disease in the Primary Setting

Study	Study design	No. of pts	LNI risk	Treatment groups	Outcome
RTOG 9413[87]	RCT	1,322	All > 15% (Roach formula)	2×2 design, neoadjuvant ADT vs. adjuvant ADT—WPRT vs. PORT	Best PFS from WPRT was in GS 7–10, PSA < 30 ng/mL, and Gleason score < 7 and PSA > 30 ng/mL
GETUG-01 trial[88]	RCT	446	45% of pts > 15%	WPRT vs. PORT—4–8 Mo of ADT	No difference in 10-yr OS and EFS. A higher but non-WPRT has better EFS in low-risk subgroup (77.2% vs. 62.5%; p=0.18)
POP-RT trial[100]	RCT	224	All > 20% (Roach formula)	WPRT vs. PORT—24 Mo of ADT	Favours WPRT: 5-yr BFFS was 95.0% with WPRT vs. 81.2% with PORT (HR, 0.23; p<0.0001). WPRT 5-yr DFS (89.5% vs. 77.2%; HR, 0.40; p=0.002), 5-yr OS no difference (HR, 0.92; p =0.83)
Tharmalingam *et al.*[103]	Cohort	812	Not specified	WPRT vs. PORT (with brachytherapy boost)—variable ADT	Favours WPRT: better 5-yr BFFS vs. PORT (84% vs. 77%; p=0.001)
PIVOTAL trial[184]	RCT	124	All > 30% (Roach formula)	WPRT vs. PORT—6–9 Mo of ADT	Confirmed safety of HD-WPRT

Abbreviations: ADT, androgen deprivation therapy; BFFS, biochemical failure-free survival, DFS, disease-free survival; EFS, event-free survival; GS, Gleason score; HD-WPRT: high dose–whole pelvic radiotherapy; LDR, low-dose-rate; LNI, lymph node involvement; Mo, months; OS, overall survival; PFS, progression-free survival; PORT, prostate-only radiotherapy; PSA, prostate-specific antigen; pts, patients; RCT, randomized controlled trial, WPRT, whole pelvic radiotherapy; yr, year.

Using data from the Surveillance, Epidemiology, and End Results (SEER) registry on men undergoing RP for clinical T1c–T4 prostate cancer, some investigators argued that the "Roach equation" overestimated the risk for pelvic LNI.[57] Their erroneous conclusion was most likely due to underestimating the true incidence of positive nodes, as SEER data involved an inadequate number of pelvic lymph nodes being removed.[58]

Abdollah *et al.* analyzed a surgical series of more than 3,000 men undergoing ePLND and validated the Roach equation, reporting an area under the curve (AUC) of 0.803.[59] These authors concluded that the "Roach formula" "does not overestimate" the rate of LNI in contemporary prostate cancer patients if they are treated with ePLND. However, they also concluded that the cutoff of 15% would miss approximately one-third of patients with LNI and argued that "… the cut off should be lowered to 6%."[59] More recently, Koerber *et al.* showed that the Roach equation is a good predictor of the risk for LNI, with an average AUC of 0.781, performing nearly as well as PSMA PET.[60] Notably, this equation has been used in several major randomized clinical trials including RTOG 94-13, 9406, and most recently in 0924, to evaluate the role of elective pelvic nodal irradiation in the definitive management of patients with prostate cancer.[4,58,61]

Briganti nomograms

Briganti and colleagues developed a nomogram for predicting LNI in patients undergoing ePLND based on the PSA, clinical stage, and Gleason score. Their series involved 602 patients, in which LNI was detected in 66. The investigators found the univariate predictive accuracy for PSA, clinical stage, and Gleason score to be 63%, 58%, and 73%, respectively. They concluded that their nomogram—based only on clinical stage, PSA, and biopsy Gleason sum—showed a high predictive accuracy of 76%.[62] Briganti and colleagues subsequently added the percentage of positive cores to the three previously used parameters in an effort to improve predictive accuracy of the nomogram. In univariate predictive accuracy analysis, the percentage of positive cores was found to be the most accurate predictive factor for LNM. The sensitivity, specificity, and NPV of the updated nomogram associated with the 5% cutoff increased to 87.8%, 70.3%, and 98.4%, respectively. However, this update was limited by the relatively small number of patients and absence of external validation.[63]

A further update to the nomogram was made by incorporating the percentage of cores with highest-grade PCa, and the percentage of cores with lower-grade disease into the multivariable model, replacing the previously one of just the percentage of positive cores. Gandagalia *et al.* found that the predictive accuracy of these new factors in their cohort was 90.8%, surpassing the previous two models in predicting LVI.[64]

The investigators then performed a third update to the Briganti nomogram, adding maximum diameter of the index lesion on mpMRI, grade group on targeted biopsy, and the presence of clinically significant PCa on concomitant systematic biopsy. They found that, using a cutoff of 7%, 244 ePLNDs (57%) could be avoided while reducing the number of missed LNIs compared to existing nomograms (1.6% for the new nomogram vs. 4.6% for the Briganti 2012 nomogram vs. 4.5% for Briganti 2017 vs. 4.2% for the MSKCC nomogram).

Memorial Sloan Kettering Cancer Centre (MSKCC) nomograms

Another preradical prostatectomy nomogram was developed using data from more than 10,000 prostate cancer patients treated at Memorial Sloan Kettering Cancer Centre (MSKCC) incorporating PSA values, primary and secondary Gleason scores, and the percentage of positive cores in the biopsy.[65] An external validation on this nomogram, conducted on a cohort of 679 men with clinically localized PCa who underwent RP with PLND, found that using a 7% cutoff would spare roughly 40% of men from PLND with minimal risk (3.2%) of missing LNI.[66]

There are many other nomograms with clinically relevant evidence supporting the predictive accuracy of one over another.[67] However, a major limitation of these nomograms is that they are based on radical prostatectomy series, which were mostly limited to obturator lymph nodes, or sampling of external iliac lymph nodes chains, ignoring presacral and perirectal nodes. The optimal extent of the procedure (standard vs. extended) is still a subject of debate, and this limited sampling may lead to an underestimation of the true incidence of lymph node involvement.[68]

Take-home message:

The definition of positive lymph nodes in prostate cancer is grouped into three categories:

1. Pathologically positive (pN+) lymph node metastasis, confirmed by pathology after PLND, is considered the SOC for diagnosis of positive lymph node disease in prostate cancer or in rare cases through nodal sampling.

2. Clinically positive (cN+) lymph node metastasis, suggested by imaging, with the advent of new nuclear imaging techniques improves the identification in this category. Unfortunately, despite these advances, up to one-third of lymph node metastases are still missed.
3. Clinically negative (cN-) patients with high-risk features for LNI can be readily identified using a host of validated formulas and nomograms.

Management of pelvic lymph node involvement

The selection of treatment modality for pelvic nodal involvement of prostate cancer is influenced by the management approach chosen for the primary tumour. In patients undergoing RP, surgical options include either PLND or ePLND. When radiation in the main treatment modality, whole pelvic radiotherapy (WPRT) with or without nodal boost is considered the standard of care.

Surgical staging management

Pelvic lymph node dissection (PLND) vs. extended pelvic lymph node dissection (ePLND)

The European Association of Urology (EAU) guidelines recommend ePLND for accurately staging of the pelvis in patients with clinically confined PCa with a risk for nodal metastasis greater than 7%.[69] According to the AUA guidelines, PLND is advised for all patients at medium to high risk for nodal metastasis.[70] Fossati *et al.*[71] classified PLND into four types:

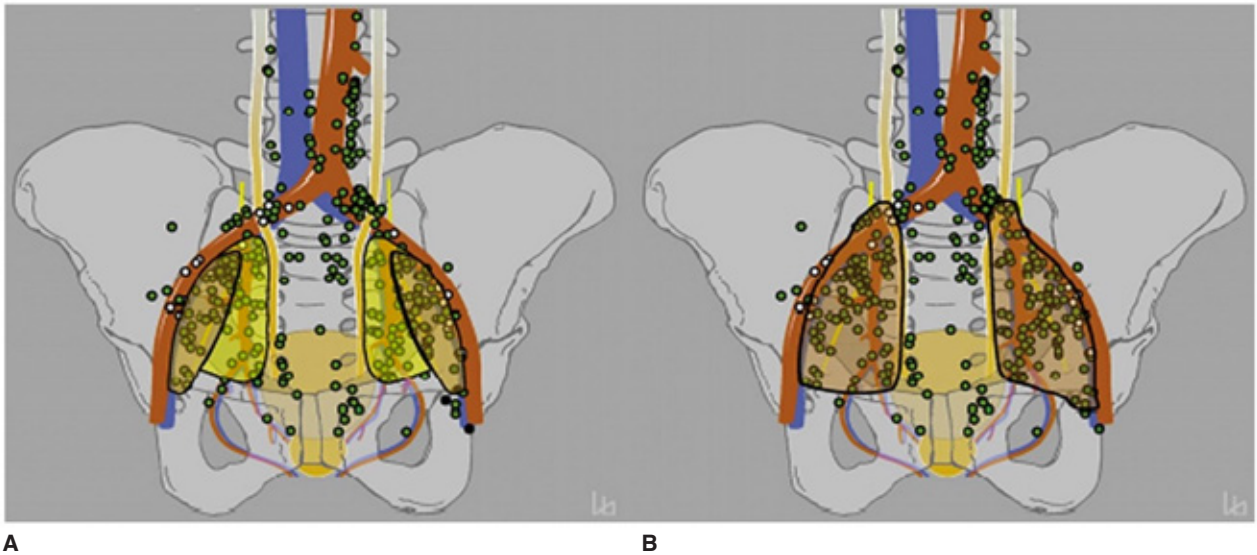
1. Limited PLND (LPLND): Involves the obturator nodes.
2. Standard PLND (SPLND): Involves the obturator and external iliac nodes.
3. Extended PLND (ePLND): Involves the obturator, external, and internal iliac nodes.
4. Super-extended PLND (SePLND): Encompasses ePLND plus common iliac, presacral, and/or other nodes.

The oncologic benefits of PLND for prostate cancer remain controversial, particularly due to the increased risks and complications associated with ePLND. A meta-analysis by García-Perdomo *et al.* compared the effectiveness and safety of SPLND and ePLND, concluding that ePLND was associated with improved biochemical recurrence-free survival (hazard ratio [HR], 0.62; 95% CI, 0.36–0.87).[72] Similarly, a meta-analysis performed by Choo *et al.* reported a significant difference in biochemical recurrence between ePLND and SPLND (HR, 0.71; 95% CI, 0.56–0.90).[73] However, Fossati *et al.*'s large meta-analysis involving 66 studies assessing the impact of PLND found that lymph node removal might not directly improve cancer outcomes; instead, it may lead to more complications.[71] A recent meta-analysis by Zhang *et al.*[74] involving 16 studies with a total of 15,269 participants aimed to evaluate the effectiveness of PLND, identify potential oncology outcomes, and elucidate postsurgery complications across various ranges of PLND. The investigators concluded that "The extension of the PLND range is associated with an elevated lymph node-positive rate; however, it does not improve the biochemical recurrence-free rate and correlates with an increased risk of complications, especially lymphocele."

While there is an established relationship between number of lymph nodes excised during PLND and the rate of detection of nodal metastasis,[75] there is no consensus on the optimal number of LNs that should be examined following PLND for prostate cancer.[13] Two cadaveric studies, one focusing on prostate cancer and the other on urothelial bladder cancer, attempted to define the expected normal lymph node yield from standard PLND; however, both studies revealed significant discrepancies in lymph node counts among individuals.[76,77]

It has been suggested that the extent of pelvic node dissection should be tailored according to risk for lymph node metastasis, with more extensive lymph node dissections performed for those at highest risk.[78] A survey conducted by the International Society of Urological Pathology (ISUP) found that the majority of pathologists (86%) reported finding < 10 LNs on average, while only 8% and 3% reported average yields of 11–15 LNs and > 15 LNs, respectively. These findings indicate a lower average LN yield in routine clinical practice when compared with LN counts documented in the literature.[79] Consequently, the definition of adequate lymph node dissection remains unresolved.[13] While ePLND is more accurate in detecting metastatic lymph node involvement, it may not improve the oncologic outcomes and is associated with an increased risk for complications, particularly lymphocele (**FIGURE 3**).

FIGURE 3 (A) Standard LND area and (B) proposed extended LND for prostate cancer, as described by Mattei and colleagues, targeting nodes extending along the common iliac vessels to the ureteric crossing.



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Abbreviation: LND, lymph node dissection (LND).

Source: *Reprinted from* European Urology*, Vol. 51/Ed. 1, Mattei A, Fuechsel FG, Bhatta Dhar N,* et al.*, The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study, 118–125, Copyright 2008, with permission from Elsevier.*[80]

In general, the surgical management of node-positive disease has been rather disappointing.[81] For instance, in a series by Fossati *et al.*, 75% of the patients experienced biochemical failure within 2 years despite undergoing a salvage lymph node dissection. This unfavourable experience may partially reflect that many patients were initially screened for surgery using C11 Choline rather than PSMA PET. While impressive case reports exist, particularly in patients undergoing PSMA PET imaging, larger series raise concerns about the modest efficacy and significant complications noted.[82,83] However, it is now understood that in selected patients, more favourable outcomes have been reported, and surgical management appears to be feasible in reducing morbidity without compromising efficacy in patients undergoing unilateral resection of nodes, provided they have only unilateral disease as identified by PSMA PET.[84–86] An overview of the available guidelines for managing N1 disease is shown in **TABLE 2**.

TABLE 2 Overview of Available Guidelines for Management of N+ Prostate Cancer

Guideline	cN1M0	pN1M0
EAU[122]	1. Offer local treatment (either RP or EBRT) plus long-term ADT 2. Offer EBRT for prostate + pelvis in combination with long-term ADT and 2 years of abiraterone	1. Offer adjuvant ADT 2. Offer ADT + EBRT 3. Offer observation (expectant management) after LND if ≤ 2 nodes and PSA < 0.1 ng/mL
FROGG[196]	Pelvis and prostate EBRT + long-term ADT	1. Individualized discussion of observation, ADT, or EBRT + ADT 2. Patients should be referred to a radiation oncologist to discuss EBRT + ADT
NCCN[197]	1. EBRT + ADT 2. EBRT + ADT + abiraterone 3. ADT ± abiraterone 4. If < 5 yr expected survival and asymptomatic: observation or ADT	1. ADT 2. EBRT + ADT 3 Observation

Abbreviations: cN1M0 patients, patients with clinically node-positive disease determined via any imaging modality; pN1M0 patients, patients with pathologically node-positive disease in postoperative setting either after initial treatment with RP and LND or after staging LND; ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; LND, lymph node dissection; PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy.

Nonsurgical management (radiation therapy + systemic treatment)

Trials including patients with cN0 at high risk of LNM (i.e., elective nodal irradiation)

For most solid tumours, prophylactic lymph node irradiation is considered a standard of care; however, in high-risk prostate cancer, it remains a debatable practice with no universal consensus. **TABLE 1** summarizes selected trials comparing prophylactic elective nodal irradiation (ENI) versus prostate-only radiotherapy (PORT). A significant part of this controversy comes from the misconception among many physicians that two randomized controlled trials (RTOG 9413 and GETUG 01) yielded "negative" results in terms of both biochemical failure-free

survival (BFFS) and OS. In reality, no trials have demonstrated definitively "negative" results for "prophylactic pelvic nodal radiotherapy." Notably, the GETUG-01 trial did not actually use "whole pelvic" radiotherapy (but rather treated only the "true pelvis") as defined by the RTOG. Additionally, it included too many low-risk patients and was far too small a study to assess any meaningful clinically endpoint.[87]

Phase 3 randomized controlled trials evaluating prophylactic nodal radiotherapy

GETUG-01

Pommier *et al.* studied 446 patients with T1b-T3, N0pNx, M0 prostate carcinoma randomized to received either pelvic node and prostate or prostate-only radiation therapy. Patients were stratified into 2 groups: "low risk" (T1-T2 and Gleason score 6 and PSA < 3× the upper limit of normal [ULN] of the laboratory) (92 patients) versus "high risk" (T3 or Gleason score > 6 or PSA > 3× the ULN of the laboratory).

The investigators concluded that at a median follow-up of 11.4 years, the 10-year OS and event-free survival (EFS) were similar in the two treatment arms. A higher but nonsignificant difference in EFS was observed in the low-risk subgroup in favour of pelvic node radiation therapy (77.2% vs. 62.5%; p=0.18). A post-hoc subgroup analysis showed a significant benefit of pelvic irradiation when the risk for lymph node involvement was < 15%, according to the Roach formula.[88] However, this French trial (GETUG-01) was criticized for its small sample size, with only 45% of participants having a risk for LNI > 15%. Additionally, pelvic field sizes were substantially smaller, with the superior limit set at the level of S1/S2. Furthermore, the number of patients who received neoadjuvant hormonal treatment was not clearly defined.[89]

RTOG 9413

This study enrolled 1,323 patients with risk for LNI > 15% to evaluate the efficacy of WPRT versus PORT and to compare short-term neoadjuvant with adjuvant plus concurrent hormone therapy (HT), with the primary endpoint of progression-free survival (PFS).[90] In the initial report, the neoadjuvant hormone treatment and the WPRT arm demonstrated a PFS advantage compared to the other study arms. Subgroup analysis showed that the greatest PFS benefit from WPRT was observed in patients with a Gleason score 7–10 and PSA < 30 ng/mL, and in those with a Gleason score < 7 and PSA > 30 ng/mL. A post-hoc subgroup analysis, involving only patients treated on arms 1 and 2, compared WPRT with smaller ("mini-pelvis") pelvis radiotherapy versus smallest ("prostate only") PORT and showed that the 7-year DFS was 40%, 35%, and 27% respectively, indicating the importance of pelvic field size and potentially explaining the "negative" results of WPRT in other trials.[91]

Why do the GETUG-01 and RTOG 9413 trials appear to provide contradictory results?

Small pelvic field

Lymphatic drainage of the prostate is complex, with lymph node metastases commonly found in hypogastric and internal iliac nodes (lateral pathway), obturator fossa nodes (inferior pathway), external iliac nodes (ascending pathway), presacral nodes (posterior pathway), and common iliac nodes.[92,93] From a radiation-oncology prospective, this implies the importance of using vascular anatomy rather than bony anatomy, and the inclusion of common iliac nodes has been proposed in published reviews.[15,94] The increasing knowledge of lymphatic anatomy of the prostate has also led to an adaptation of the RTOG delineation guidelines for defining important

pelvic nodal areas.[95] These guidelines emphasize the importance of including the common iliac arteries and veins, as well as the presacral nodes, down to the bottom of the third sacral vertebra.

In the GETUG-01 trial, a smaller pelvic radiotherapy volume (the "mini-pelvis") was used, which, according to a post-hoc subset analysis appeared to benefit only the lowest-risk subset.[88] As a result, the upper border did not include the common iliac nodes or portions of the external iliac and presacral nodes, thus missing major lymph node drainage areas.[93,96] In contrast, the RTOG 9413 trial covered more nodes, with the upper border set at the L5–S1 interspace, although even this may have been insufficient, as some estimates suggest that using a higher upper border (e.g., L4/L5 interspace) would be required to cover > 90% of potentially involved pelvic nodes.[96]

Complex trial design

The complex design of the RTOG 9413 trial made it challenging for many investigators to interpret, with most not recognizing the sequence-dependent interactions between ADT and radiation volume.[87] Additionally, most of the patients included in this trial should be classified as high risk, for which the standard of care is long-term ADT (i.e., 18–36 months) rather than the short-term 4-month ADT (used in RTOG 9413).[97]

Dilution of effect due to inclusion of low-risk patients and low radiotherapy dose

Some authors have suggested that including patients at low risk of pelvic nodal involvement in both GETUG-01 and RTOG9413 may have diluted the benefit of whole pelvis radiotherapy.[93,96] Furthermore, the radiation dose delivered in these two studies was too low to guarantee sufficient local control. Consequently, the rate of local relapse was substantial and led to a second wave of distant metastasis,[98] which further diluted the potential benefit of whole pelvis radiotherapy.[87,88] Results from Sandler and colleagues[99] suggest that whole pelvis radiotherapy may improve outcomes only when the primary tumour is well controlled.

POP-RT trial

This phase 3, single-centre trial focused on node-negative prostate adenocarcinoma, with estimated nodal risk of ≥ 20%. Patients were randomized 1:1 to PORT (68 Gy/25 fractions to the prostate) or WPRT (68 Gy/25 fractions to the prostate, 50 Gy/25 fractions to the pelvic nodes, including the common iliac nodes). The results were as follows: 5-year BFFS was 95.0% (95% CI, 88.4–97.9%) with WPRT versus 81.2% (95% CI, 71.6–87.8%) with PORT, with an unadjusted HR of 0.23 (95% CI, 0.10–0.52%; $p<0.0001$). WPRT also showed higher 5-year DFS (89.5% vs. 77.2%; HR, 0.40; 95% CI, 0.22–0.73; $p=0.002$), but 5-year OS did not differ significantly (92.5% vs. 90.8%; HR, 0.92; 95% CI, 0.41–2.05; $p=0.83$). Distant metastasis-free survival (MFS) was higher with WPRT (95.9% vs. 89.2%; HR, 0.35; 95% CI, 0.15–0.82%; $p=0.01$). The investigators concluded that prophylactic pelvic irradiation for high-risk, locally advanced prostate cancer improved BFFS and DFS compared with PORT, but did not improve OS, although the study was not sufficiently powered to address OS.[100]

Why POP-RT was "positive" trial?

1. Patients with a substantial risk for positive pelvic nodes likely benefit the most from whole pelvis radiotherapy. In the POP-RT trial, nearly half of the patients (109 [49%] of 222) had a Gleason grade group of 4 or 5, almost 50% had a risk for pelvic lymph node involvement exceeding 40%, and the median PSA was 28 ng/mL.[100]
2. The pelvic lymph node coverage in the POP-RT trial was more comprehensive than that of either the GETUG-01 (S1-S2) or the RTOG 9413 (L5-S1) trial, with the upper border set at the L4–L5 junction, thus adequately covering the common iliac nodes and resulting in 93% coverage.[100]
3. The biological dose to the prostate used in POP-RT was higher, potentially reducing the risk for local recurrences. These local recurrences can lead to biochemical failure, which may appear to nullify the benefits of WPRT. Indeed, local control plays an important role in optimizing PFS and MFS[100] and is linked to the dose delivered to the prostate.[101,102]

Tharmalingam *et al.*

This prospective, multicentre study evaluated 812 patients who received high-dose rate brachytherapy (a single fraction of 15 Gy). Before the high-dose-rate boost, group A received PORT (37.5 Gy in 15 fractions) and group B received additional WPRT (46 Gy in 23 fractions). Patients in the WPRT group were treated with ADT for a substantially longer duration (> 18 months) than those who received PORT. After a median follow-up of 4.7 years, high-risk patients who received WPRT had a significantly better 5-year BFFS than patients who received PORT (84% vs. 77%; p=0.001). This benefit was not observed in the intermediate-risk group (91% vs. 90%; p=0.92).[103]

Selected retrospective trials

- Seaward *et al.* found better biochemical control with WPRT in patients at risk for LNI between 15% and 35%.[104]
- Spiotto *et al.* compared the biochemical relapse-free survival (bRFS) among patients receiving WPRT vs. prostate-bed RT (PBRT) after radical prostatectomy. The 5-year bRFS rate was 47% after WPRT vs. 21% after PBRT for patients with a risk for LNI > 15%.[105]
- Pan *et al.* used Partin tables and categorized men into three LNI groups: low, 0–5%; intermediate, > 5–15%; and high, > 15%. A multivariate analysis revealed a benefit for WPRT.[106]
- Aizer *et al.* published a retrospective analysis of 277 patients with ≥ 15% likelihood for LNI. The 4-year bRFS rate was 69.4% in the PORT group and 86.3% in the WPRT group.[107]
- Milecki *et al.* studied 162 high-risk patients assigned to two groups: A (neoadjuvant hormonal therapy [NHT] + WPRT + long-term hormonal therapy [HT]) and B (PORT + NHT). The authors concluded that WPRT combined with long-term HT, compared with PORT for high-risk patients resulted in improvement in cancer-specific survival (CSS).[108]
- Mantini *et al.* examined high-risk prostate cancer patients from Rome, dividing patients based on LNI risk, according to the Roach formula, with cutoff levels of 15%, 20%, 25%, and 30%. For the entire group, the 4-year bDFS rate was similar between the patients who had undergone WPRT versus those who received PORT (90.4% vs. 90.5%, respectively). However, in the cohort of patients with the greatest nodal risk (> 30%), those who had undergone WPRT showed a significant improvement in bDFS, with no differences observed in acute or late toxicity.[109]

Treatment of cN1 disease in the primary setting: Radiotherapeutic options

From a radiotherapeutic perspective, prostate cancer with clinical and/or radiological evidence of pelvic lymph node metastasis is now considered a locoregional disease rather than systemic disease, despite para-aortic involvement being considered M1a by the current American Joint Committee on Cancer (AJCC) guidelines.[15] However, pelvic lymph node metastasis is a strong predictor for systemic spreading, and thus we typically recommend a combination of systemic and local-regional radiotherapy. This recommendation is partly supported by an early report by Granfors *et al.* and by the more recent Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) trial results.[110,111] The inadequacy of ADT alone has been evaluated in patients with locally advanced PCa in a randomized phase 3 trial conducted by the Scandinavian Prostate Cancer Group (SPCG). The SPCG-7 study showed that combining prostate radiotherapy with long-term hormone therapy was superior to long-term hormone therapy alone in terms of overall survival.[112,113] **TABLE 3** summarizes the results of selected studies focusing on patients with N1M0 prostate cancer.

In the RTOG 85-31 trial, a subset analysis of the 173 cN1 patients who were randomized to receive either WPRT alone or WPRT combined with hormone therapy was performed.[114] This study suggested that the PFS of N+ patients was statistically improved at 5 and 9 years with EBRT + ADT (54% and 10%, respectively) compared with EBRT alone (33% and 4%, respectively).

In addition, several retrospective and population-based cohorts have confirmed the benefit of adding pelvic nodal radiotherapy to ADT in the cN1 setting.[115] For instance:

- Lin *et al.* analyzed the outcomes associated with treatment of 3,540 prostate cancer patients with cN+ to evaluate the benefits of adding WPRT to ADT. They found that adding radiation to ADT was associated with a 50% reduced risk for 5-year all-cause mortality (HR, 0.50; 95% CI, 0.37–0.67; two-sided $p<0.001$; crude OS rate, 71.5% vs. 53.2%).[116]

- Seisen *et al.* retrospectively compared local radiotherapy plus ADT versus ADT alone in a large cohort of cN+ prostate cancer patients. Their findings supported the use of local radiotherapy due to an overall reduction in mortality compared with ADT alone.[117]

- James *et al.* assessed the role of radiotherapy in nonmetastatic N+ prostate cancer using a cohort from the control arm of the STAMPEDE trial. They found that adding radiotherapy to ADT improved failure-free survival in this subgroup of patients.[118]

TABLE 3 Overview of Selected Studies on N1M0 Disease

Treatment type	Study	Study design	No of pts	Treatment groups	Outcomes
ADT as adjuvant treatment:	Schröder *et al.* (2009)[200]	RCT: EORCT 308846	234	Immediate ADT vs. delayed ADT	NS difference—HR, 1.22 (CI, 0.92–1.62)
	Messing *et al.* (2006)[201]	RCT: ECOG 3886	98	Immediate ADT vs. delayed ADT	Favours immediate ADT—better OS; HR, 1.84; p=0.04
EBRT as adjuvant treatment:	Pilepich *et al.* (2005)[202]	RCT; phase 3 85-31	263	EBRT + ADT vs. EBRT alone	Favours EBRT + ADT, especially high GS, (p=0.002)
	Tward *et al.* (2013)[203]	SEER data observational	1,100	EBRT vs. NO EBRT	Favours EBRT—10-yr CSS: HR, 0.66; $p \leq 0.01$; 10-yr OS: HR, 0.70; $p \leq 0.01$
	Tilki *et al.* (2015)[204]	Retrospective, multi-institution	1,491	Adjuvant vs. early salvage RT	Favours adjuvant EBRT in case of pN1—HR, 0.66 (p=0.04)
	Fonteyne *et al.* (2022)[205]	RCT, PROPER trial	69	PORT (arm A) vs. WPRT (arm B)	No difference in WPRT over PORT; 3-yr bRES: 79% (PORT) vs. 92% (WPRT), p=0.08; 3-yr OS: 92% (PORT) vs. 93% (WPRT), p=0.61
ADT +/- any local therapy	Da Pozzo *et al.* (2009)[206]	Retrospective, single institutions	250	ADT vs. EBRT + ADT	No difference, 10-yr BCR-free survival: 51% (combination) vs. 42% (ADT), p=0.11; 10-yr CSS: 70% (combination) vs. 72% (ADT), p=0.22
	Briganti *et al.* (2011)[207]	Retrospective, two institutions	364	ADT vs. EBRT + ADT	ADT + EBRT—10-yr CSS: 86% vs. 70% (ADT alone) p=0.004; 10-yr OS: 74% vs. 55% (ADT) p<0.001
	Kaplan *et al.* (2013)[208]	SEER data observational	577	ADT vs. EBRT + ADT	No benefit of adjuvant EBRT—OM: 5.35 (EBRT) vs. 3.77 (no EBRT) events per 100 person-years (p=0.193); PCSM: 2.39 (EBRT) vs. 1.3 (no EBRT), (p=0.354)
	Abdollah *et al.* (2014)[209]	Retrospective, two institutions	1,107	ADT vs. EBRT + ADT	Favours ADT + adj. EBRT—8-yr OM-free survival: 88% (ADT + EBRT) vs. 75% (ADT), (p<0.01); 8-yr CSM-free: 86% (ADT = EBRT) vs. 92% (ADT), (p=0.08)
	Rusthoven *et al.* (2014)[210]	SEER data observational	2,991	RT, RP, or both vs. No local Tx	Favours EBRT—10-yr OS: 45% vs. 29, p<0.001; 10-yr PCSS: 76% vs. 53%, p<0.001
	Lin *et al.* (2015)[116]	Observational	3,540	ADT vs. ADT + EBRT	Favours ADT + EBRT, 50% reduction in ACM; HR, 0.50 (p<0.001)

Abbreviations: N1M0 patients, patients with node-positive disease either pathologically or clinically; ADT, androgen deprivation therapy; bRFS, biochemical relapse-free survival; CI, confidence interval; DE, docetaxel and estramustine; cRFS, clinical relapse-free survival; CSS, cancer-specific survival; EBRT, external beam radiotherapy; GS, Gleason score; HR, hazard ratio; NCDB, National Cancer Database; NS, nonsignificant; OM-free, overall mortality free; OS, overall survival; CSM, cancer-specific mortality; PCSM, prostate cancer–specific mortality; PORT, prostate-only radiotherapy; R BCR, biochemical recurrence; RCT, randomized controlled trial; RP, radical prostatectomy; SEER, Surveillance, Epidemiology, and End Results; Tx, treatment; WPRT, whole pelvic radiotherapy; yr, year.

TABLE 3 Overview of Selected Studies on N1M0 Disease *(Cont'd)*

Treatment type	Study	Study design	No of pts	Treatment groups	Outcomes
ADT +/- any local therapy	Jegadeesh *et al.* (2016)[211]	Retrospective	826	ADT vs. ADT + EBRT	ADT + EBRT—improved OS; HR, 0.67 (p<0.001)
	Van Hemelryk *et al.* (2016)[130]	Retrospective—case matched	69	Case matching of pN1 and pN0 after EBRT + ADT	5-yr bRFS: 65% vs. 79% (p=0.08); 5-yr cRFS: 70% vs. 83% (p=0.04); 5-yr PCSS: 92% vs. 93% (p=0.66); 5-yr OS: 82% vs. 80% (p=0.58)
	Poelaert *et al.* (2016)[129]	Retrospective	154	ADT + WPRT	5-yr CSS: 96%; 5-yr bRFS: 67%; 5-yr cRFS: 71%; 5-yr OS: 89%
	Seisen *et al.* (2018)[117]	Observational	1,987	ADT vs. ADT + local Tx	Favours ADT + local therapy
	Bryant *et al.* (2018)[212]	Observational	648	ADT vs. ADT + EBRT	Favours ADT + EBRT—PCSS HR, 0.05; p=0.02; ACM HR, 0.38; p<0.001
	Touijer *et al.* (2018)[213]	Retrospective	1,338	Observation vs. ADT alone vs. ADT + EBRT	Favours ADT + EBRT over ADT alone—HR, 0.46 for OS (p<0.0001); Favours ADT + EBRT over observation—HR, 0.41 for OS (p<0.0001)
	Gupta *et al.* (2019)[214]	Retrospective, 3 institutions	8,074	Observation vs. ADT alone vs. ADT + EBRT	Favours ADT + EBRT over ADT alone—HR, 0.76 for OS (p=0.007); Favours ADT + EBRT over observation—HR, 0.77 for OS (p=0.008)
ADT +/- systemic treatment	Vale *et al.* (2016)[215]	Systematic review, GETUG-12, RTOG 0521, STAMPEDE	945	ADT ± docetaxel	OS, no benefit to docetaxel—HR, 0.87 (p=0.218)
	Ahlgren *et al.* (2018)[216]	RCT, SPCG-12 trial	55/459 — (27 arm A & 28 arm B)	Arm A: docetaxel. Arm B: surveillance	No difference in time to BCR > 0.05 ng/mL (p=0.06)
	Attard *et al.* (2022)[217]	RCT 1: abiraterone trial; RCT 2: abiraterone + enzalutamide trial	774	ADT vs. ADT + abiraterone ADT vs. ADT + abiraterone + enzalutamide	Favours ADT + abiraterone (combination) vs. ADT (alone)—6-yr metastasis-free survival: 82% vs. 69%; HR, 0.53; p<0.0001

Abbreviations: N1M0 patients, patients with node-positive disease either pathologically or clinically; ADT, androgen deprivation therapy; bRFS, biochemical relapse-free survival; CI, confidence interval; DE, docetaxel and estramustine; cRFS, clinical relapse-free survival; CSS, cancer-specific survival; EBRT, external beam radiotherapy; GS, Gleason score; HR, hazard ratio; NCDB, National Cancer Database; NS, nonsignificant; OM-free, overall mortality free; OS, overall survival; CSM, cancer-specific mortality; PCSM, prostate cancer–specific mortality; PORT, prostate-only radiotherapy; R BCR, biochemical recurrence; RCT, randomized controlled trial; RP, radical prostatectomy; SEER, Surveillance, Epidemiology, and End Results; Tx, treatment; WPRT, whole pelvic radiotherapy; yr, year.

Nodal irradiation: Simultaneous integrated boost (SIB) and hypofractionation

Based on previous evidence, WPRT combined with ADT is now considered the standard of care in clinically positive nodal prostate cancer. With the advent of modern biological imaging techniques, such as PSMA PET/CT, it is likely that pelvic nodes will be detected earlier and more frequently. One efficient approach to treat node-positive disease with higher doses than uninvolved nodal areas is using a simultaneous integrated boost (SIB) to PSMA-positive nodes.

Onishi *et al.*[119] retrospectively analyzed 97 patients with cN1 prostate cancer who received intensity-modulated radiation therapy with SIB (SIB-IMRT). The prescribed dosages delivered to the prostate and seminal vesicles, elective node area, and residual lymph nodes were 69 Gy, 54 Gy and 60 Gy in 30 fractions, respectively. After a median follow-up of 60 months, the 5-year BRFS, relapse-free survival (RFS), OS, and prostate cancer–specific survival (PCSS) were 85.1%, 88.1%, 92.7%, and 95.0%, respectively. Acute grade 2 genitourinary (GU) and gastrointestinal (GI) toxicities were observed in 10.2% and 2.1%, respectively, with no grade ≥ 3 toxicities. The cumulative incidence rates of 5-year grade ≥ 2 late GU and GI toxicities were 4.7% and 7.4%, respectively, with no grade 4 toxicities. Therefore, the investigators concluded that SIB-IMRT for cN1 prostate cancer demonstrated favourable 5-year outcomes with low incidences of toxicity.

Recently, Basu *et al.* reported their findings on 22 patients with National Comprehensive Cancer Network (NCCN) high-risk (HR), N+, and oligometastatic (OM) PCa staged using prostate MRI and PSMA PET/CT who received SIB-SBRT.[120] All patients underwent either medical (80%) or surgical (20%) castration. ADT was administered as neoadjuvant, concomitant, and adjuvant therapy for at least 2 years and for oligometastatic patients as second-generation hormone treatment. SIB-SBRT to prostate and pelvic nodal regions (until common iliac level) was 35–36.25 Gy and 25 Gy in 5 fractions, respectively. Post-ADT gross PSMA-avid nodes and skeletal deposits received 30 Gy in 5 fractions. The investigators found that SIB-SBRT for HR, N+, and OM prostate cancer achieved good biochemical control with minimal grade 3 toxicity.

Mizowaki *et al.* reported their experience with 52 patients with T2a-T4N1M0 prostate cancer, who were definitively treated with whole pelvis (WP) SIB-IMRT. Pelvic lymph node metastases were clinically diagnosed based on enlarged lymph nodes seen on diagnostic imaging, which subsequent shrank in size on follow-up imaging after ADT.[121] WP SIB-IMRT was designed to simultaneously deliver 78 Gy, 66.3 Gy, and 58.5 Gy in 39 fractions to the prostate plus seminal vesicles, metastatic lymph nodes, and the pelvic lymph node region, respectively. The investigators reported very promising results, with excellent bRFS, distant MFS, OS, and PCCS (69%, 78%, 88%, and 92%, respectively) at 5 years. In addition, the 5-year cumulative incidence rates for grade 2–3 late GU and GI toxicities were both 2%, with no grade 4 acute or late toxicity. Thus, the use of SIBs has several advantages, including easier plan optimization and the ability to deliver higher radiobiological doses to the affected node(s), potentially improving local control. This approach thus appears to be a safe and effective radiotherapy technique, but larger studies are needed to confirm these findings.

Patients with pN1 disease in the postoperative setting

The EAU guidelines consider ePLND the standard of care and the most accurate staging procedure after RP, despite advancements in molecular imaging techniques.[122] Several retrospective studies recommend adding postoperative WPRT to ADT,[123–125] especially for patients with between two and four positive nodes after nodal dissection.[126] These studies suggest that both PCSS and OS are improved when ADT is combined with WPRT compared with ADT alone.[125–127] However, to date no randomized controlled study has explicitly tested the role of adjuvant RT in node-positive patients after RP and ePLND.

For example, one large retrospective study examined the role of adjuvant pelvic RT in the case of LN involvement after PR and ePLND, focusing on biochemical recurrence (BCR) and PCSS. It compared 121 patients treated with adjuvant standard hormone therapy with 129 patients treated with WPRT combined with HT. In a multivariable model, the inclusion of adjuvant RT significantly improved the predictive accuracy for BCR-free survival and CSS (gain: 3.3% and 3%, respectively; all $p<0.001$).[128]

Another retrospective cohort study of 154 patients with pN1 PCa treated with WPRT and 2–3 years of ADT after RP and PLND investigated the role of adjuvant radiotherapy and reported biochemical recurrence-free survival (bRFS), clinical progression-free survival (cPFS), and CSS. The investigators found that with WPRT, the median bRFS was 88 months and cPFS was 92 months, with acceptable toxicity. Moreover, no relapses were observed in the irradiated pelvic lymph nodes.[129]

In a case-matched analysis of pN1 (≤ 2 positive LNs) and pN0 patients treated with adjuvant IMRT WPRT plus ADT, no significant differences were found in bRFS or cRFS between the two groups. The 5-year PCSS and OS rates were comparable between pN1 and pN0 PCa patients—PCSS, 92% ± 4% vs. 93% ± 3%, $p=0.66$; OS, 82% ± 5% vs. 80% ± 5%, $p=0.58$.[130]

The postoperative salvage setting: N1 disease

Salvage radiotherapy is the only curative treatment in the setting of biochemical recurrence after prostatectomy and no evidence of distant metastasis.[131,132] As pelvic nodes are among the most common sites of recurrence after RP, WPRT is almost a standard of care in the salvage setting, and is supported by numerous prospective and retrospective trials.[131–133]

Song and colleagues found a 20% increase in biochemical progression-free survival (bPFS) with salvage WPRT compared with PBRT in patients receiving salvage radiotherapy after RP (PSA ≥ 0.4 ng/mL).[131]

Ramey and colleagues reported a similar benefit in 5-year bPFS with salvage WPRT.[132] Results from the NRG Oncology/RTOG 0534 SPPORT trial indicate that WPRT combined with ADT is superior to PBRT alone (HR, 0.51 for 5-year distant MFS; $p=0.014$).[133]

The case for nodal recurrence (rN1) patients

ADT is generally considered a gold standard in patients with nodal recurrences after primary treatment for prostate cancer.[134,135] Emerging evidence supports the use of radiation therapy in oligorecurrent nodal disease, especially when combined with molecular imaging for localization of nodal recurrences. As a result, metastasis-directed therapy (MDT) has become an increasingly important treatment option for these patients, based on reports suggesting that local ablative therapy, particularly stereotactic body radiation therapy (SBRT), may be effective in controlling oligometastatic nodal disease.[136]

SBRT in oligometastatic nodal recurrence

Justification and rationale

Oligorecurrent (or "metachronous" oligometastatic) disease typically shows better outcomes than synchronous oligometastases, likely due to its more indolent biology and more lymphotropic pattern of recurrence.[136] Clinical evidence suggests that patients who develop metastases after 2 years or more of the treatment of the primary tumour tend to have better survival rates compared to those with early recurrence, indicating a slower-growing and less-aggressive disease.[137] The studies using molecular imaging modalities have consistently identified the oligonodal region as the predominant pattern for recurrence following primary treatment for PCa.[138,139] Additionally, new recurrence patterns after nodal ablative treatment show that oligometastatic nodal relapses account for 50% of recurrences, with a median time to progression of 19–22 months.[140,141]

Summary of clinical evidence

Although no level I evidence from phase 3 randomized trials exists specifically for oligometastatic prostate cancer, several prospective phase 1 and 2 clinical trials support the use of SBRT in this setting.[142,143] Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) was the first phase 2 randomized trial to show a significant benefit in OS and PFS for SBRT combined with SOC compared with SOC alone, a benefit that persists with long-term follow-up (8-yr OS, 27.2% vs. 13.6%; 8-yr PFS, 21.3% vs. 0.0%).[144] This trial has been criticized for including only 16 patients with PCa, 14 of whom received SBRT.

TABLE 4 summarizes selected phase 2 clinical trials, STOMP and ORIOLE, which provided the best "proof-of-principle" evidence supporting the use of SBRT in oligorecurrent disease. These trials randomized asymptomatic hormone-sensitive prostate cancer (HSPCa) patients with oligometastatic disease (1–3 lesions) to either MDT (SBRT used in 81% of patients in the STOMP trial and in 100% in the ORIOLE trial) or surveillance.[145,146] Despite the small sample size and the short follow-up, both trials found that MDT, compared with observation, was associated with improved treatment outcomes. However, they still share the same limitations of small sample size and relatively short follow-up. SBRT to all visible lesions successfully delayed the initiation of ADT and increased PFS without jeopardizing quality of life (QoL). The long-term outcomes of pooled data from both trials have been published.[147] With a median follow-up time of 52.5 months for the entire group, MDT remained associated with improved PFS compared to observation (pooled HR, 0.44; 95% CI, 0.29–0.66; p=0.001). Interestingly, the PFS beyond 4 years was 15–20% with SBRT, suggesting that a good number of patients will benefit from a durable response with MDT. Although further follow-up is needed, these encouraging results indicate that in

appropriately selected patients, MDT (and specifically SBRT) without systemic therapy might be an alternative approach in well-informed patients wishing to avoid the side effects of ADT.

TABLE 4 Selected Trials of Metastasis Directed Therapy (MDT) in Oligorecurrent Prostate Cancer

Study	N	Imaging/ N° METS	% of nodal lesions	MDT/design	Median FU	Outcome
Harrow *et al.*[144] SABR-COMET—phase 2 RCT[144]	16/99	Conv./1–5		PSOC vs. SBRT + PSOC	5.7 yrs	8-yr OS: HR, 0.05; 8-yr PFS: HR, 0.45
Ost *et al.*[198] STOMP—phase 2 RCT	62	PET-CHO/1–3	55%	Surveillance vs. SBRT	3 yrs	ADTF: 13 vs. 21 mo (HR, 0.06), (p=0.11)
Phillips *et al.*[146] ORIOLE—phase 2 RCT	4	Conv. PSMA-PET 1-3	58%	Surveillance vs. SBRT	19 mo	PFS: 81% vs. 39% (p=0.005) HR, 0.03 (p=0.002)
Siva[149] POPSTAR—phase 1	33	CT, BS, F-PET/1–3	39%	SBRT (ADT in 33%)	24 mo	2-yr Local-PFS: 93%/2-yr DFS: 39%/2-yr ADFT: 48%
Glicksman *et al.*[148] PSMA MRgRT—phase 2	74	PSMA-PET, MR/2	37%	SBRT (87%) or surgery (no ADT)	41 mo	PSA response: median, 21 mo/ PSA-PFS: median, 45 mo
Hölscher *et al.*[150] OLI-P—phase 2	63	PSMA-PET, MR/1 lesion	68%	SBRT 77% CRT 50 Gy 23%—No ADT	37 mo	No grade > 2 treatment-related toxicity; time to ADT: 20.6 mo
Conde-Moreno *et al.*[199] SBRT-SG05—phase 2	67	PET-CHO, MR/1–5	57%	SBRT + ADT	41 mo	Median DPFS: 54.2 mo

Abbreviations: N, number of patients; N° MET: number of metastasis allowed; ADT, androgen deprivation therapy; ADTF, freedom from ADT; BS, bone scan; Conv, conventional; CRT, conventional radiation therapy; CT, computerized tomography; DPFS, disease progression-free survival; F-PET, fluciclovine positron emission tomography; HR, hazard ratio; MDT, metastasis-directed therapy; mo, months; MR, magnetic resonance; OLI-P, Effectiveness and Toxicity of Percutaneous High-dose Radiotherapy in Patients with OLIgometastases of Prostate Carcinoma; ORIOLE, Observation vs. Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer; P, primary; PET-CHO, positron emission tomography [^{11}C]-labelled choline; PFS, progression-free survival; POPSTAR, Patients with Oligometastases from Prostate Cancer Treated with Stereotactic Ablative Radiotherapy; PSAFS, PSA-free survival; PSMA MRgRT, prostate-specific membrane antigen magnetic resonance–guided radiation therapy; PSMA-PET, prostate-specific membrane antigen positron emission tomography; QoL, quality of life; RCT, randomized controlled trial; S, secondary; SABR, stereotactic ablative radiation therapy; SABR-COMET, Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases; SBRT, stereotactic body radiation therapy; SOC, standard of care; STOMP, Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence; yrs, years.

Three prospective phase 1/2 nonrandomized trials—PSMA MRgRT, POPSTAR, and OLI-P—investigated the impact of MDT in oligorecurrent HSPCa staged using novel molecular imaging.[148–150] The MRgRT and OLI-P trials used PSMA-PET in the diagnosis, while the POP- STAR study used sodium fluoride (NaF)-PET/CT. ADT was not allowed in the PSMA MRgRT and OLI-P trials but was administered in 33% of participants in POPSTAR. Most patients enrolled had fewer than three lesions. These molecular-screened trials showed that approximately half the patients achieved a PSA response, resulting in a favourable ADT-free survival rate of around 40–49% at 2 years. A recent meta-analysis of six SBRT studies published between 2013 and 2020 has also confirmed

this pattern.[151–154] Despite variability among studies in terms of baseline imaging, inclusion criteria, and primary endpoints, there is convincing evidence that SBRT can effectively control treated lesions and reduce disease progression in the oligometastatic or oligorecurrent state of PCa with acceptably low toxicity.

Although SBRT has been implemented to delay ADT, in an effort to avoid compromising QoL in a clinically relatively low-risk scenario, most patients may still experience early progression without ADT. This suggests the presence of undetected and disseminated diseases that could benefit from a combined systemic approach. Additionally, systemic therapy with ADT and androgen receptor pathway inhibitors (ARPIs) is a standard of care for metachronous hormone-sensitive low-volume disease,[155] and it remains unclear whether and how these results might impact the treatment strategy for nodal oligorecurrent PCa. The success of MDT in previously described retrospective and prospective studies suggests that we should also consider including all "oligometastatic" sites in low-volume metastatic hormonal-sensitive prostate cancer rather than just irradiating the prostate like in the STAMPEDE trial.

It seems reasonable to suggest that if the primary goals of SBRT in nodal oligorecurrent PCa are to achieve local control, prevent further metastasis, and delay subsequent systemic treatment escalation in selected patients, we should define our endpoints accordingly. A relevant issue that deserves further investigation is whether metastases-free survival, as measured by conventional imaging, can also act as a proxy for overall survival in patients with hormone-sensitive oligorecurrent PCa detected through molecular imaging.

Combined RT and systemic therapy

Some authors have investigated the use MDT without ADT, despite being the current SOC for nodal oligorecurrence.[155] The results of these studies suggest that this approach could be a reasonable option in well-selected subgroups of patients in whom the main objective is to delay the effects of androgen suppression. However, the omission of ADT may compromise long-term survival.[156] The combination of MDT with ADT has not been adequately studied in this setting. The SABR-COMET trial allowed the combination of both treatments and demonstrated a significant benefit in OS, which persisted with longer-term follow-up.[144] These results were not unexpected, as ADT has been a mainstay of treatment for advanced prostate cancer, and its combination with radiotherapy has consistently shown good results in other disease scenarios. In contrast, the combination of ADT and RP has not been shown to be beneficial in the management localized disease, thus its use in the oligometastatic setting is at least controversial.[157] On the other hand, ADT in combination with EBRT has been widely demonstrated to improve the main oncological endpoints in several randomized prospective clinical trials.[97,158–160]

Preclinical studies suggest that the synergistic effects and anti-neoangiogenic effects of ADT may contribute to normalizing irradiation and oxygenation of the tumour microenvironment, thereby enhancing the effectiveness of RT.[161–166] ADT clearly plays a role in controlling distant micrometastasis and, consequently, reduces the risk for distant failure and improves outcomes in oligorecurrent disease.[163,167,168] Therefore, ongoing phase 3 trials are using the combination to achieve optimal oncological results in a context in which the disease can be well controlled (and potentially curable) with the best available oncological treatment in candidate patients.

In the context of metastatic oligorecurrent disease, MDT directed at visible macroscopic (or PET-identified) disease can provide benefits by consolidating the effect of systemic treatment and improving bRFS. Radiation works through different mechanisms, minimizing androgen-independent clones and delaying the onset of castration resistance.[169] Additionally, by decreasing the overall tumour burden, radiation makes ADT more effective in controlling the disease. Therefore, the combination of SBRT with hormonal manipulation is a highly promising and effective approach that may improve oncological outcomes and allow for the de-escalation and or delay of hormonal treatment in certain cases.

Volume of treatment and RT scheme: SBRT vs. ENRT

It can be argued that using generous lymph node coverage, like elective nodal radiotherapy (ENRT) with an additional SBRT boost, can reduce the likelihood of subsequent pelvic nodal recurrences and thus improve outcomes compared to SBRT alone. Although there is no prospective randomized trial conclusively defining the optimal radiotherapy strategy in oligonodal recurrence, available evidence for use of ENRT is derived from retrospective and nonrandomized prospective studies, with wide variability in radiotherapy doses and schedules.

De Bleser *et al.* compared SBRT alone versus ENRT with or without SBRT boost in 506 patients with hormone-sensitive nodal oligorecurrent PCa (≤ 5 positive nodes) from 15 centres.[170] ADT was used in 23% of the SBRT group and 60% of the ENRT group. All patients had regional (N1) and/or distant (M1a) node metastases diagnosed using either PET/CT (either choline or fluorodeoxyglucose) or conventional imaging (MRI: n=5; CT: n=10). The study supported the notion that ENRT was more effective, with fewer nodal recurrences compared SBRT alone (p<0.001), though it was associated with slightly higher toxicity (16% vs. 5%; p<0.01).

The OLIGOPELVIS-GETUG P07 phase 2 study evaluated the efficacy of high-dose ENRT in 67 patients from 15 centres. ENRT was delivered as 54 Gy in 1.8 Gy fractions administered to the whole pelvis, with a simultaneous integrated boost of 66 Gy in 2.2 Gy fractions to pathological pelvic lymph nodes. This treatment was combined with 6 months of ADT in patients with oligorecurrent (≤ 5) pelvic node relapses in PCa, detected by PET choline imaging.[171] After a median follow-up of 49.4 months, the 2- and 3-year PFS rates were 81% and 58%, respectively. The median PFS was 45.3 months, with ≥ grade 2 GU and GI toxicities occurring in 10% and 2% of patients, respectively, at 2 years.

These studies suggest that ENRT may be more effective than SBRT alone for controlling nodal oligorecurrence. The STORM study, a randomized trial designed to compare both strategies, in addition to a 6-month regimen of ADT, has reported preliminary results indicating similar toxicity profiles, though the final results are awaited to assess differences in PFS.[172]

Therefore, there remain unanswered questions regarding:

- Localized treatment (SBRT) or more extensive radiotherapy (ENRT),
- The combination of these radiotherapies with ADT and/or ARPIs,
- The optimal timing and duration of such treatments.

The "standard of care" for these patients who experience a recurrence in non-regional nodes is the combination of ADT and ARPIs without local therapy. However, recent data has shown definitive radiotherapy in combination with limited ADT is likely to be a more effective strategy.

Ongoing trials and future directions

The number of metastases detected on PSMA-PET currently serves as the selection criteria for the indication of MDT in PCa.[173] Some patients, particularly those who have not received systemic treatment, experience rapid widespread metastatic progression.[147] Fortunately, there is increasing interest in investigating biomarkers that could help identify and select which patients would benefit from treatment intensification.[174]

Ongoing trials are exploring the efficacy of MDT combined with ADT and/or androgen receptor signalling inhibitors (ARSIs), using an intermittent approach instead of continuous one. This approach has the advantage of providing treatment breaks from hormonal manipulation, which positively impacts patient QOL while potentially preventing or delaying the development of widespread metastases.[176]

In a retrospective analysis presented at the 2023 AUA meeting involving 263 patients with oligometastatic PCa who underwent MDT, the addition of ADT to MDT was associated with an improved time to biochemical progression (HR, 0.23; 95% CI, 0.16–0.33; $p<0.001$).[177] The results of ongoing studies, such as the DART trial by Ost *et al.* (ClinicalTrials.gov identifier: NCT04641078) or the START-MET trial (ClinicalTrials.gov identifier: NCT05209243), are still waited to determine the most effective combined strategy of hormonal therapy and MDT.[178]

On the other hand, the phase 2 randomized trial EXTEND involved patients with oligometastatic PCa to investigate whether the addition of MDT to intermittent hormone therapy has a better oncologic outcome compared to intermittent hormone therapy alone.[179] After a median follow-up of 22.0 months, the combined therapy arm demonstrated longer PFS compared to the hormone therapy–alone arm. Although phase 3 trials are essential to confirm these results, this trial suggests that the combined approach could serve as a compelling option for individuals with indolent oligometastatic PCa, as 6 months of intermittent hormone therapy may be inadequate for prolonged control.

An important aspect to consider is that ARSIs are not the sole systemic treatment under evaluation for oligometastatic disease. Several trials are exploring other systemic agents such as immunotherapy, Radium-223, and even Lutetium-PSMA. Another consideration is the distinction between continuous and intermittent systemic treatment based on PSA response. Clearly defining the objectives of these strategies is essential for understanding their purpose and evaluating their effectiveness.

Toxicity of radiotherapy

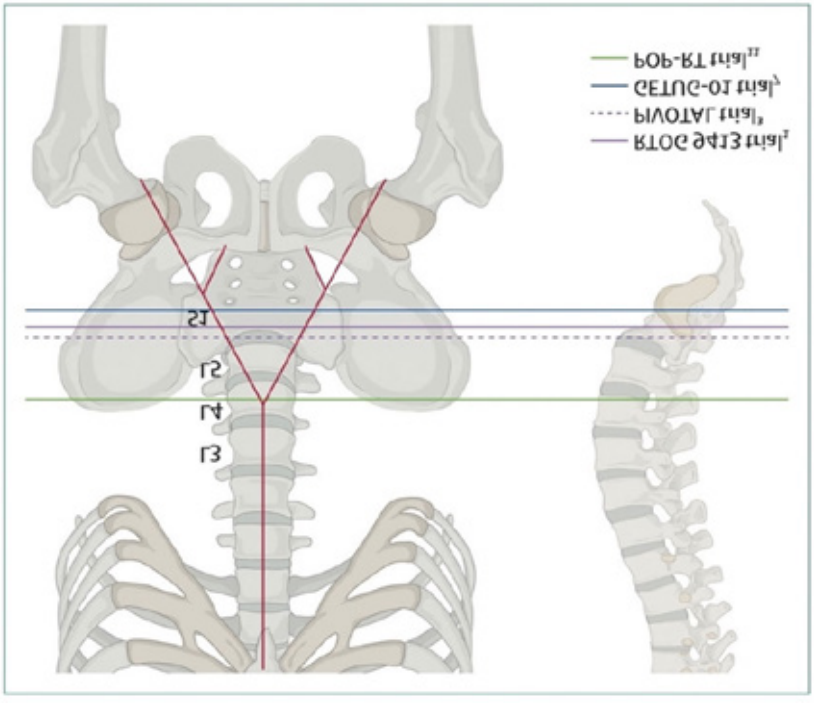
1. **Late GU toxicity:** Theoretically, whole-pelvis radiotherapy may increase toxicity compared with prostate-only radiotherapy.[180] There are discrepancies among studies regarding how much late GU toxicity there is, with some studies using advanced technologies reporting no significant difference in late GU toxicity with PORT versus WPRT at an intermediate dose.[87,88,181,182] In contrast, another study found a 40% increase in late GU toxicity with WPRT.[103]
2. **Late GI toxicity:** Similar inconsistencies exist with late GI toxicity. Although the GETUG-01 trial[88] did not report any excess late GI toxicity, the RTOG 9413 trial[87] found significantly worse GI toxicity with WPRT versus PORT (5.1% vs. 1.9%). Tharmalingam and colleagues confirmed this significant increase in late GI toxicity (≥ grade 2).[103] However, both studies involved patients treated before the routine use of 3D conformal EBRT.
3. **Hematological toxicity:** Data on hematological toxicity is limited, and there were few ≥ grade 3 toxicities reported in the RTOG 9413 trial.[87] WPRT can result in lower absolute lymphocyte and white blood cell counts from baseline 1 year after treatment, particularly in smokers and in patients with low baseline lymphocyte counts. In such cases, the volume of ilium bone marrow receiving 40 Gy is a strong predictor of developing late lymphopenia.[183] WPRT increased late ≥ grade 2 hematological toxicities, although absolute numbers remained low (29 [5%] of 570 patients) compared to prostate bed radiotherapy (27 [2%] of 1,125 patients).[133] Patient-reported toxicity scoring indicated more frequent bowel movements, loose stools, fecal urgency, and gas passage with WPRT.[180]

Impact of using modern radiotherapy techniques on toxicity

Advanced radiotherapy techniques appear to decrease both acute and late toxicity compared to traditional techniques. This was demonstrated in the PIVOTAL, a phase 2 randomized study[184] comparing PORT to WPRT using intensity-modulated radiotherapy. The primary endpoint was to investigate whether modern radiotherapy could further reduce acute and late toxicities. Despite delivering a higher biological dose to the pelvic nodes (55.0 Gy), compared to 50.4 Gy in the RTOG 9413 trial, the PIVOTAL trial, with a median follow-up of 37.6 months, found no difference in late GI and GU toxicities (≥ grade 2) at 24 months between the two groups.[87]

Similar findings were found in the POP-RT trial, which also used IMRT to deliver 50 Gy in 25 fractions to the pelvic nodes, along with a biological dose of 80 Gy to the prostate delivered in 25 fractions.[100] Late ≥ grade 2 GI toxicities were not different between the two groups. Grade 4 toxicities were not observed (according to the Radiation Therapy Oncology Group [RTOG] scale).[100] However, there was a significant increase in late ≥ grade 2 late GU toxicities with WPRT (20% vs. 9% with IMRT; p=0.02). QoL questionnaires did not show any significant change in functional or symptom domains.[185] Notably, upper borders of the treatment fields were defined differently across trials (**FIGURE 4**).

FIGURE 4 Comparison of upper radiation treatment borders in different randomized trials. Figure created with BioRender. The upper borders of the pelvic treatment fields used in different trials are shown. The arterial vasculature of the abdomen and pelvis depicted in relation to the bony anatomy (in red).[186]



Source: *Reprinted from* The Lancet*, Vol. 22 No. 8, De Meerleer G, Berghen C, Briganti A,* et al.*, Elective nodal radiotherapy in prostate cancer, e348–e357, Copyright 2021, with permission from Elsevier.*[186]

In general, trials using IMRT or volumetric-modulated arc therapy (VMAT) report very low rates of severe toxicity, even when applying higher doses to the pelvis.[103,180] The POP-RT trial found a doubling of late GU toxicities, which is associated with the higher doses to the pelvis. However, no ≥ grade 4 toxicities occurred, and grade 3 toxicities occurred in less than 2% of patients (2 of 112), regardless of the treatment group.[100] This low rate of ≥ grade 3 toxicities has been confirmed by other studies. Dosimetric studies showed that intensity-modulated proton therapy significantly reduces the dose to the bladder, small bowel, large bowel, and rectum compared with volumetric arc therapy.[187] However, it is still unclear whether these dosimetric advantages translate into meaningful clinical benefits in terms of reduced late toxicity. A registry study involving patients treated with pelvic proton therapy showed that intestinal and urinary toxicities were infrequent after a short follow-up of 14 months.[181]

Additional Systemic Treatment

Combining ADT with docetaxel or second-generation hormone treatment is well established in the metastatic PCa setting.[188–191] Recently, these drugs have been studied in nonmetastatic PCa, demonstrating promising results.[192] Three trials—the STAMPEDE platform protocol, the NRG Oncology/RTOG 0512 trial, and the GETUG-12 trial—investigated the effect of adding adjuvant docetaxel to ADT. The studies found that adjuvant docetaxel combined with ADT prolonged time to relapse but not MFS or OS. A meta-analysis of these adjuvant docetaxel trials incorporating N0/N1-M0 patients concluded that there was an 8% absolute 4-year survival advantage for docetaxel compared with ADT alone in terms of failure-free survival, without an OS benefit (HR, 0.7; 95% CI, 0.61–0.81; $p<0.0001$).[193] In conclusion, these studies did not find a survival advantage from adding docetaxel to ADT in patients with cN1M0 disease.

More recently, a meta-analysis of two STAMPEDE platform phase 3 trials suggested that adding abiraterone acetate and prednisolone alone or with enzalutamide to ADT was associated with improved MFS in patients with high-risk nonmetastatic (including node+) PCa.[194] Among participants, 39% ($n=774$) presented a cN1 status determined via conventional imaging. Of these patients, approximately 85% received EBRT and ADT as SOC treatment. Metastasis-free survival events occurred in 180 patients in the combination groups versus 306 in the control groups (HR, 0.53; 95% CI, 0.44–0.64; $p<0.0001$). Death occurred in 147 patients in the combination groups versus 236 in the control groups (HR, 0.60; 95% CI, 0.48–0.73; $p<0.0001$). Death due to PCa occurred in 73 patients in the combination groups versus 142 in the control groups (HR, 0.49; 95% CI, 0.37–0.65; $p<0.0001$). These results suggest that the addition of abiraterone and/or enzalutamide could be a promising treatment option for cN1M0 patients, offering potential benefits for overall survival. However, as this analysis is post-hoc, it is crucial to approach these findings with caution when drawing conclusions.[195]

Conclusions

There are growing reasons for optimism about the management of node-positive prostate cancer. With advancements in therapeutic strategies, we are now better equipped to define patients at risk and balance the risks and benefits of aggressive treatment for this population of patients.

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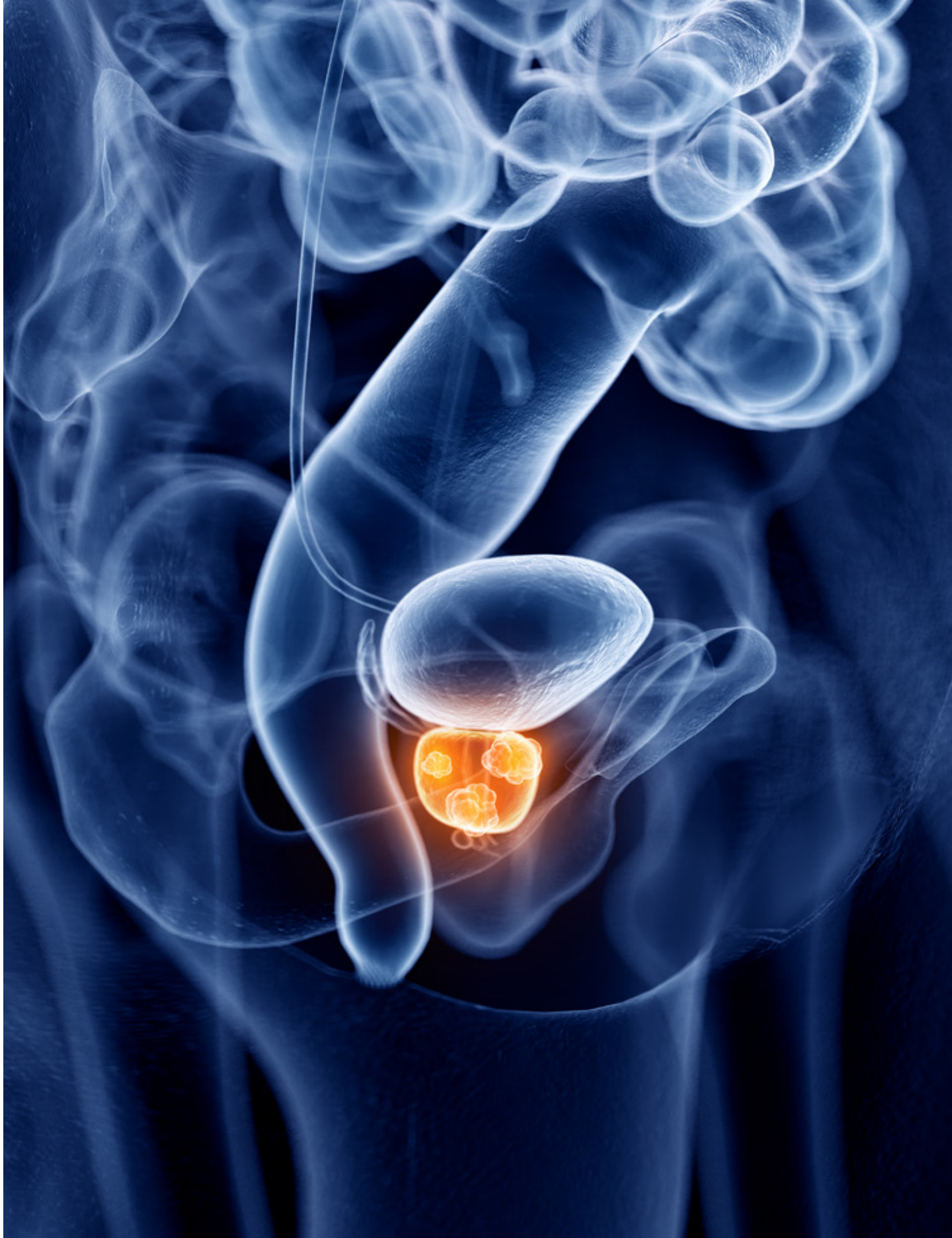

COMMITTEE 16

The Role of Adjuvant and Salvage Radiotherapy Post-Prostatectomy

CO-CHAIR

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Prologue

Envision a 63-year-old, otherwise healthy man with a favourable pathology prostate cancer surgically removed by radical prostatectomy (RP). He breathes a sigh of relief when told that his postoperative prostate-specific antigen (PSA) was undetectable, concluding that he is cured. Unfortunately, this message of success is short-lived: PSA levels rise in nearly a third of patients within only several years of receiving surgery, making these patients candidates for salvage treatment.[1] What should the man do—will he pursue salvage radiation therapy (SRT), embark upon androgen deprivation therapy (ADT), or continue with observation? Everything that is done to him can make a life-altering difference.

This case portrays a decision point that so many prostate cancer patients and their physicians are confronted with in the aftermath of prostatectomy. Among the most controversial current issues in prostate cancer management is when—if ever—to intervene after recurrences.

Introduction

In this chapter, we review the management of biochemical recurrence (BCR) after RP, focusing on the role of external beam radiation therapy (EBRT). We discuss the statistics on the incidence of BCR and controversies concerning the optimal threshold for BCR, as well as issues related to the diagnosis, monitoring, and treatment of recurrent disease. We explore the challenges of identifying patients at risk for BCR in the context of favourable and adverse pathological features based on surgical specimen on one hand, and the need for individualized tailored therapy to attempt to lower the risk for clinical progression after RP. This will be done by focusing on the two major therapeutic options with curative intent. These are EBRT delivered either as adjuvant radiation therapy (ART), which is administered soon after radical prostatectomy, before BCR is defined, or SRT. SRT is employed after detection of BCR following RP. Key landmark trials not only support the efficacy of RT in BCR but also highlight the fact that RT may save some lives—as demonstrated by two early trials, SWOG 8794 (ART) and RTOG 9601 (mostly ART and some SRT). These randomized controlled trials (RCTs) illustrate that there is a chance to improve the outcome of patients with more aggressive cancers postoperatively based on proper risk stratification of patients and an optimum multidisciplinary carefully chosen treatment approach.[2,3] Where possible, we will make sure that our conclusions are based on a critical review of the landmark RCTs and major post-hoc studies that have changed the paradigm shift in treatment approach.

Moreover, the chapter examines advancements in RT methods, including technological enhancements to improve tumour targeting (e.g., image guidance, dose escalation, optimization of treatment volumes), which may contribute to the goal of improving the therapeutic index through greater precision regarding targeting tumoural tissues and minimizing exposure to healthy structures.

Biochemical Recurrence

RP is the most common treatment for localized prostate cancer in the United States, but its failure to cure rate (recurrences) is confirmed by rising PSA levels, indicative of BCR of residual or growing cancer potentially affecting long-term outcomes. BCR after RP is most commonly defined as confirmation of a serum PSA value ≥ 0.2 ng/mL on two successive test measurements.[4,5] However, post-prostatectomy PSA levels can be detected at much lower levels using an ultra-sensitive assay (e.g., < 0.01 ng/mL). The clinical relevance of using these levels has been challenged.[6] In fact, some studies suggest that even PSAs detected at much lower levels may be clinically meaningful.[7] If a PSA is detectable, it is likely caused by one or more of the following mechanisms: local adverse pathology (positive surgical margins), microscopic residual disease, benign residual tissue, or metastatic prostate cancer (local and/or distant) or nonprostatic tissues.[8–10]

Incidence

Historically, a third of patients develop BCR within 5 years following RP.[11] The risk of developing BCR is higher in men with high-risk disease features, that is, patients with extraprostatic extension (EPE) or seminal vesicle invasion (SVI). BCR involves the operative field in around 40% of cases at 10 years after RP, and over 50% at 15 years after RP.[1] Although the rates of BCR were previously estimated to be 20% to 40%, due to improved patient selection and improved surgical techniques, they may now be closer to 15%.[12,13] BCR beyond 10 to 15 years postoperatively is a relatively uncommon event but possible, especially in men with low-grade tumours or in the setting of metastatic disease.[14–16] The extended postoperative risk periods highlight the importance of long-term surveillance strategies for prostate cancer.

Predictive Tools for Decision-Making in Radiation Therapy

Dynamic changes in the PSA, including the doubling time, and velocity are critical in assessing cancer behaviour post-surgery, with faster and shorter doubling times (e.g., under 10 months) indicative of more aggressive tumours and a higher risk for systemic progression (metastasis) and mortality. These PSA kinetics need to be weighed against individual patient factors.[17] Whether these factors (signalling the aggressiveness) should influence the urgency and intensity of clinical treatment decisions is unclear.[18,19] Routine PSA testing for the first several years following surgery should be every 3 to 6 months for 5 years or so. After this time, testing would be annualized depending on individual risk profiles and PSA dynamics according to American Society of Clinical Oncology (ASCO) guidelines, with more frequent monitoring for those with high and aggressive disease features or adverse PSA kinetics.[5,20–22]

Ultrasensitive PSA (uPSA) tests can reliably detect PSA levels as low as 0.01 ng/mL (or even lower) depending upon the specific assay used.[7] Assays have been described that are significantly more sensitive than the standard PSA test, which typically has a lower limit of detection around 0.1 ng/mL, but unfortunately, uPSA assays are no longer widely available. Such assays could in theory allow even for timely personalized interventions, such as salvage therapies (e.g., EBRT ± ADT) that can improve patient outcomes. Early salvage treatment is often associated with a better long-term prognosis compared to delayed treatment.

Preoperative risk factors should be assessed and discussed with patients prior to RP. Patients who are at the highest risk for BCR after RP have multiple clinical and pathological risk factors that collectively lead the individual to a high recurrence risk as well as an increased risk for recurrences after SRT.[12,23] While an elevated preoperative PSA level is a well-recognized factor that is associated with a higher risk for recurrence, a high Gleason score (GS), (e.g., 8 and above) is consistently associated with a higher risk for BCR and death even with organ-confined disease.[11,12,24–27] The increased risk for BCR is also associated with the number of biopsy cores positive for cancer. For example, patients with otherwise what would be intermediate-risk disease who have more than 50% biopsy cores positive for cancer have an increased risk for BCR approaching that of high-risk patients after RP.[28] In addition to the conventional factors mentioned above, some studies suggest that a low baseline serum testosterone predicts an increased risk for recurrence, but this was not seen as a risk factor for patients treated definitively with EBRT.[29,30] Of note, age 70 ± 5 years has also recently been reported be associated with more advanced stage and increased risk for BCR after RP (but not EBRT).[31] Lymph node involvement at the time of prostatectomy portends a very high risk for recurrence and death from prostate cancer.[24] This implies a strong, currently unmet need for adjuvant therapies in selected patients. Taken together, these data suggest that it may be possible to define subsets of patients for whom adjuvant therapy beyond prostatectomy to adequately manage the recurrence.[23,32,33]

Genomic biomarkers have been shown to be useful in assessing the risk for progression and metastasis-free survival (MFS) after RP and may allow for more personalized decisions regarding the use of ART or SRT.[34] For example, a patient with a high post-RP genomic classifier score may benefit more from ART, while those with a low score might be better served with SRT to help reduce distant metastasis, and spare unnecessary treatment, respectively.[35,36] However, as MFS is a relatively uncommon event early in the course of the disease. This data makes it challenging to base actionable decisions regarding management of a potentially curable post-op patient. In other words, early distant metastasis might reflect the presence of systemic disease, which would not be impacted by local RT alone, while those without early metastasis may be the most curable. Therefore, these genomic classifiers may be more helpful in deciding who needs ADT in addition to EBRT, and not whether to give EBRT.

The use of prostate-specific membrane antigen positron emission tomography (PSMA PET) has improved the specificity and sensitivity for detecting the sites of recurrence in the setting of BCR after RP compared to CT scans and bone scans. Use of this modality may enhance personalized decision-making regarding implementation of SRT, even when PSA levels are relatively low (< 0.5 ng/mL).[37,38] With the detection of sites of recurrence(s) by PSMA PET, the delivery of SRT can be personalized by allowing for selected aggressive dose escalation of

locoregional and/or distant metastases, with the addition of systemic therapy if indicated.[39] Several nomograms have been developed for making a personalized estimate of the probability of successful SRT after BCR, with at least one incorporating PSMA PET information.[40–42]

SRT is most effective when the PSA is lowest, with PSMA PET most likely to pick up disease when the PSA levels are higher. Unfortunately, it remains unclear at exactly what PSA level a PSMA PET should be ordered. The challenge is balancing the likelihood of getting a positive scan (at higher PSAs) against the worsening probability of successful SRT, which increases as PSA levels remain low.[40,41]

Expectations with SRT Post-RP Radiotherapy

EBRT delivered as either SRT or ART could potentially eliminate residual/recurrent cancer cells, offering patients a chance for cure or long-term remission. EBRT is the only option proven to provide a long disease-free survival (DFS) with curative intent. If SRT were always successful, potentially all patients treated by RP would be rendered disease free and there would be no need to ever discuss ART. Unfortunately, SRT is not always successful, thus it is important to be familiar with the expected outcomes with SRT and to understand under what circumstances ART might be worth considering. The addition of ADT to SRT has been shown to improve outcomes based on several prospective randomized trials (discussed below) and supported by retrospective studies.[42–46] These trials and nomograms allow us to reach a number of conclusions about SRT. First, long-term success rates are approximately 50%, depending on the prevalence of risk factors, and the details of the intervention (e.g., use of ADT, dose). Secondly, in addition to the PSA level at the time of SRT, several prognostic factors have been identified that are associated with poor salvage rates, including: 1) the use of ADT; 2) Gleason score; 3) the presence of extracapsular extension (ECE); 4) margin status; and 5) SVI; 5) SRT radiation dose. While factors 1) and 5) (i.e., the use of ADT and radiation dose) are actionable, the rest could and should be used (see discussion below) to determine whether ART could improve outcomes compared to SRT.

Why Consider ART?

The goal of ART is to eliminate microscopic disease that might be left by surgery before there is evidence of a recurrence. Using ART to decrease the chance of recurrence applies not only to the classic category of “high risk” that was included in the interpretive guidelines of SPN-1 but also to patients with more subtle signs of high-risk pathologic features discovered at surgery, such as positive surgical margins, EPE, or SVI. The rationale for ART is straightforward. If one can predict persisting disease in high-risk areas of the prostate surgery bed, or regionally, then appropriately aggressive treatment of these areas prior to detectable tumour growth may be more effective. Adjuvant therapy is standard of care for numerous other common cancers including those of the breast and colon.

Major Randomized Trials Testing SRT and ART

The history of RCTs assessing the benefit of ART and/or SRT following RP in patients with high-risk features is worth knowing, as it parallels the progression of treatment in prostate cancer in general.

Early RCTs evaluating the benefit of ART and/or SRT following RP for high-risk features were undertaken between 1988–1996.[1] As usual, the historical context explains the current treatment landscape in prostate cancer (**TABLE 1**).

SWOG 8794 (Southwest Oncology Group) was first of the early major cooperative group trials to evaluate postoperative EBRT.[47] Although, when initially reported out, this trial was considered "negative." With longer follow-up, it demonstrated an improvement in MFS (the primary endpoint) as well as overall survival (OS). In this study, the investigators required that eligible patients have "… clinical T1–2 prostate cancer … within 16 weeks before randomization and must have had at least 1 criterion of pathological T3 disease such as extracapsular tumor extension, positive margins or seminal vesicle invasion … a negative bone scan and … a negative pelvic lymphadenectomy." However, beginning in 1995, lymphadenectomy was made optional for most patients. This trial demonstrated a significant reduction in BCR and improvement in metastasis-free survival and overall survival with the use of ART compared to surgery alone. This was the first trial to show that ART not only reduced BCR but also improved survival outcomes, making it a landmark study for the use of ART in high-risk prostate cancer patients.

EORTC 22911 (European Organization for Research and Treatment of Cancer) was published in 2005.[48] The objective of this trial was to assess the impact of ART on biochemical progression-free survival (BPFS) in men with high-risk features after RP (positive surgical margins, EPE, SVI). The results of the trial showed a halving of the BCR rates with the use of ART compared to surgery alone. Patients who received ART had significantly longer BPFS. The conclusion was that ART significantly reduced the risk for BCR but did not show improvement in overall survival at the time of reporting.

ARO 96-02 (German Cancer Society-Arbeitsgemeinschaft Radiologische Onkologie) was published in 2009.[49,50] The objective of this trial was to compare ART versus early SRT administered at the time of BCR in men with high-risk features after prostatectomy. The results demonstrated a significant reduction in recurrence with ART, but perhaps due to its small size (n=388) this trial did not show improvement in overall survival at the time of reporting.[50]

RTOG 9601 (Radiation Therapy Oncology Group) evaluated the role of ART with the primary objective to determine the efficacy of ART in improving DFS and OS in patients with high-risk features. This trial focused on patients who had undergone RP with rising PSA, high-risk pathological features such as positive surgical margins, EPE, or SVI. This trial also included the use of SRT plus bicalutamide compared to SRT alone.[43] The addition of the antiandrogen improved overall survival and reduced risk for distant metastasis in patients with high PSA level post-surgery. RTOG 9601 is significant for establishing the role of hormone therapy in conjunction

SRT for BCR after RP. The findings of RTOG 9601 helped to establish guidelines for management and timing of ART in specific high-risk patient populations.[3] In a post-hoc, "hypothesis generating study," it was reported that "In patients receiving late SRT (PSA > 0.6 ng/mL, hormone therapy was associated with improved outcomes. In men receiving early SRT (PSA 0.6 ng/mL), long-term antiandrogen treatment was not associated with improved OS."[51] It remains challenging to mechanistically balance the risk-to-benefit ratio in a patient with a rising PSA, and decide not to incorporate the drug. Fortunately, this is a decision that only a well-informed patient can make.

Contemporary Trials on ART vs. SRT After RP

Several more recent RCTs have investigated the optimal timing of ART versus SRT following RP.[1,52–54] RAVES, RADICALS-RT, and GETUG-AFU-17, and the ARTISTIC meta-analysis have provided a relatively consistent picture of this controversial issue. Collectively, these studies showed that it is challenging to predict the event rates for patients expected to be enrolled phase 3 RCTs. They also showed that if post-RP patients are relatively favourable (as were nearly 85% on these trials), SRT was as effective as ART. This suggests that SRT should be considered superior to ART because of the number of patients who could be spared EBRT. Unfortunately, the question concerning the role of ART versus SRT has not been answered for patients with multiple adverse factors (+ nodes, + SVIs, and high GS ≥ 8). Also unresolved is just to whom and for how long ADT should be administered because of somewhat conflicting results and the presence of mostly favourable patients in the RADICALS-HD studies.[55–57]

Technical Considerations for EBRT

When the decision has been made to administer EBRT to a patient, it is critical to accurately determine the appropriate target volume to irradiate. Based on post-BCR biopsies and PSMA PET imaging, the two most important areas to irradiate would appear to be the anastomosis/prostate bed area, and the pelvic lymph nodes.[37,58] The need to address the latter is supported by data from RTOG 0534.[44] Using implanted gold fiducial markers is probably the most accurate way to ensure that the anastomosis is well covered.[59] There are several other therapeutic factors to consider including: 1) the total dose planned; 2) the dose per fraction; 3) and whether drugs should be added to the mix. If drugs are added, which ones and in what sequence and for what duration.

Although traditionally 6 to 7 weeks of EBRT have been used in the post-op setting, shorter courses (e.g., 62.5 Gy in 25 sessions) have been shown to be safe and effective when only the bed is irradiated.[60] The issue remains unresolved but patients with high-grade, high-volume disease should probably receive higher doses, preferably with image guidance.[59,61] The optimal sequence of drugs and radiation, and the duration remain unknown.[22,62,63]

Conclusions Concerning Post-RP Radiation Therapy

A significant number of patients are bound to experience a rising PSA following RP. This event implies that they were not cured. The only curative option for a man who recurs after RP is RT. If patients were appropriately selected for RP, they should be candidates for post-op RT, with the risk- versus-benefit ratio favouring treatment. The most important trials suggest that modern RT should be able to be administered with a low risk for serious complications and a moderate likelihood for success in most patients.

The success of EBRT is highest when it is started when the PSA is relatively low, and should be delivered accurately using image-guided techniques to ensure adequate doses and volumes, even if the PSMA PET is negative.[42–44,54,59,64] The ARTISTIC meta-analysis suggests that patients with relatively favourable postoperative features (GS ≤ 7, negative seminal vesicles and nodes) can be spared ART and offered early SRT when a rising PSA (e.g., > 0.1 ng/mL and rising) is documented.[54] The role of ART in higher-risk patients remains a subject of further investigation but may be wise given their relatively poor prognosis with SRT.[65]

Future work will better define the role of biomarkers in patients who might benefit from molecular imaging, as well as those at long-term risk for metastatic disease.[66,67] Higher doses and larger volumes of radiation may be required in the highest-risk patients, but more studies are needed.[44,61] The use of molecular imaging (i.e., PSMA PET) allows irradiation to be delivered in a personalized way to ensure adequate doses can be delivered to sites of bulky nodal disease.[42,68–70] The addition of next-generation hormonal therapies or other drugs is likely to play an important role in managing these patients going forward.[39]

TABLE 1 Radiotherapy After Recurrence Post–Radical Prostatectomy: Selected Randomized Controlled Trials

Study (reference)	Year#	Population	Intervention	Primary outcome	Key findings	Clinical impact
SWOG S8794[47]	2009	*N*=473: PT3 + SM after RP	ART vs. no ART	MFS	ART improves MFS and OS	Established ART as beneficial
EORTC 22911[71]	2012	*N*=1005, locally advanced prostate cancer after RP	Immediate ART vs. observation	BPFS	ART improves BPFS but not OS	ART delays recurrences
ARO 96-02[50]	2014	*N*=388: pT3-4, No, +/-SM Arm A = WS (Undet PSA) Arm B = ART (Undet PSA)	Arms A + B = 307—Undet PSA ART or WS	CFS MFS OS	After excluding detectable PSA favours ART	Persistent PSA after RP for pT3 indicator for worse OS
RTOG 9601[43]	2016	*N*=725: pT3pNo or pT2pNo +SM, elevated PSA (0.2–4.0 ng/mL)	SRT + Placebo (*n*=377) vs. SRT + AAT (*n*=384) (bicalutamide)	OS at 10 yrs	24 mos. AAT improved OS	ADT and SRT as standard of care in certain HR pts
RTOG 0534[44]	2022	*N*=1792: 3 SRT arms PBRT alone PBRT + SHT PBRT + WPRT + SHT	4–6 mos. ADT + PBRT 4–6 mos. ADT and PLNRT + PBRT	PFS	SRT to lymph nodes + SHT reduced progression after RP prevent progression	Patient stratification important
RAVES[1]	2020	*N*=333 post + RP + SM, EPE, or SVI and undet PSA	ART within 4 mos. ESRT for PSA > 0.2 ng/mL	FFBP	FFBP at 5 yrs: 86% for ART 87% for ESRT (NS)	ESRT can result in fewer side effects
RADICALS -RT[52]	2020	*N*=1396 post +RP+SM, ECE, or SVI PSA ≤ 0.2 ng/mL	ART prior to PSA rise; ESRT only when PSA ≥ 0.1 ng/mL	FFBP	NS diff. in FFBP ART vs. ESRT	ESRT based on PSA results in fewer side effects
GETUG-17[53]	2020	*N*=424: +SM, ECE, or SVI Undet PSA ESRT to prevent overtreatment?	ART within 4 mos. ESRT only when PSA > 0.2 ng/mL	EFS	5-yr EFS: 89% for ART vs. 88% for ESRT (NS)	ESRT provided similar control as ART
RADICALS -HD[55]	2024	*N*=1523; + BCR, PSA < 5 ng/mL, trial within RADICALS-RT	*N*=761, SHT SRT + 6 mos. ADT *N*=762 LHT SRT + 24 mos.	Study of duration ADT: MFS	10-yr MFS: SHT—71.9% LHT —78.1%	LHT + SRT optimal MFS over SRT + SHT
RADICALS -HD[57]	2024	*N*=492: GS <7 (*n*=64)(13%) 3+4 (*n*=229) (47%) 4+3 (*n*=27) (26%) T3b—112 (23%) T4—5 (1%)	No ADT—166 pts 6-mo ADT—164 pts 24-mo ADT—162 pts	MFS, Secondary outcomes: FFDM, OS	10-yr MFS: No ADT—80% 6-mo ADT—77% 24-mo ADT—81%	No diff. in MFS ADT did not improve the outcome

Abbreviations: #, year published; ADT, androgen deprivation therapy; ART, adjuvant radiation therapy; ESRT, early salvage radiation therapy; FFBP, freedom from biochemical progression (absence of rising PSA post-treatment); BPFS, biochemical progression-free survival; CFS, clinical-free survival; EFS; event-free survival; HR, high risk; LHT, long-term hormonal therapy; Mets, metastasis; MFS, metastasis-free survival; mos., months; NS, not significant; OS, overall survival; PBRT, prostate bed radiotherapy; PFS, progression-free survival; SM, surgical margin; PLNRT, pelvic lymph node radiotherapy; pts, patients; SHT, short-term hormonal therapy; SM, surgical margin; Undet; undetectable; WS, wait & see; yr, year.

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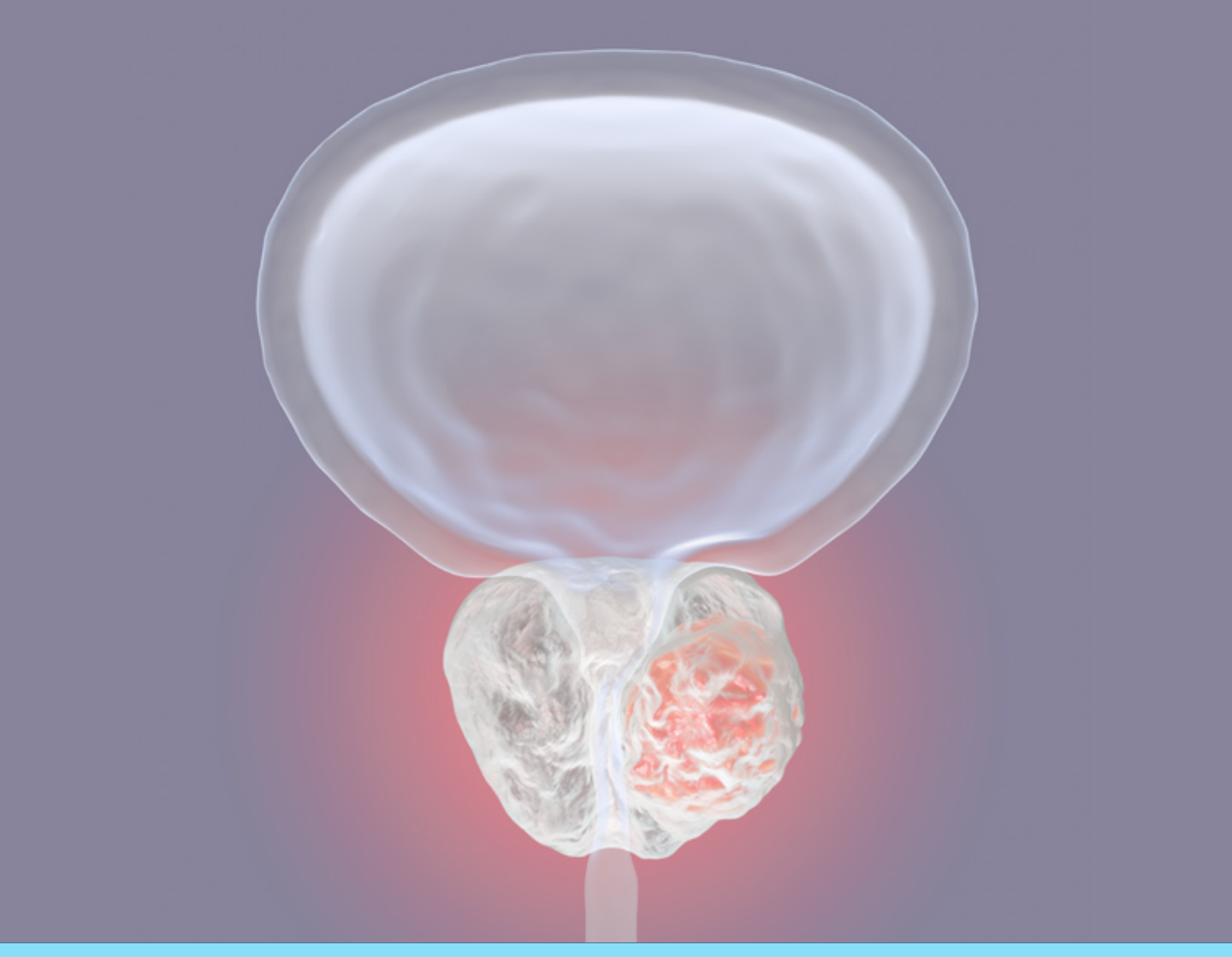

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ISBN 9781068813603