Received: 18 January 2025 | Revised: 1 March 2025 | Accepted: 5 March 2025

DOI: 10.3322/caac.70020

REVIEW ARTICLE

The contemporary management of prostate cancer

Deep Chakrabarti MD[1] | **Peter Albertsen MD**[2] | **Aidan Adkins MA**[3] | **Amar Kishan MD**[4] | **Vedang Murthy MD**[5] | **Chris Parker MD**[1,6] | **Angela Pathmanathan MDRes**[1,6] | **Alison Reid PhD**[1] | **Oliver Sartor MD**[7] | **Nicholas Van As MDRes**[1,6] | **Jochen Walz MD**[8] | **Alison Tree MDRes**[1,6]

[1]Uro-Oncology Unit, The Royal Marsden National Health Service Foundation Trust, Sutton and London, UK

[2]UConn Health, Farmington, Connecticut, USA

[3]Europa Uomo, Antwerp, Belgium

[4]Ronald Reagan UCLA Medical Center, University of California-Los Angeles Medical Center, Santa Monica, California, USA

[5]Tata Memorial Hospital and Advanced Center for Treatment Research and Education in Cancer, Homi Bhabha National Institute, Mumbai, India

[6]The Institute of Cancer Research, London, UK

[7]Mayo Clinic Comprehensive Cancer Center, Mayo Clinic, Rochester, Minnesota, USA

[8]Institut Paoli-Calmettes Cancer Center, Marseille, France

Correspondence
Alison Tree, Academic Urology Unit, The Royal Marsden NHS Foundation Trust, Downs Road, London SM2 5PT, UK.
Email: alison.tree@icr.ac.uk

Abstract

Prostate cancer is the most common cancer in two thirds of the world, with an expected doubling in both incidence and mortality in the next two decades. No strong environmental associations exist for the development of prostate cancer; therefore, lifestyle measures are unlikely to mitigate this increasing burden. The last three decades have seen rapid developments in the diagnostic and therapeutic landscape of prostate cancer, including multiparametric magnetic resonance imaging, positron emission tomography, robotic surgery, image-guided hypofractionated and stereotactic radiotherapy, novel anti-androgens and radioligand therapies. Prostate cancer is unique in that not everyone with a diagnosis needs treatment, and active surveillance is the preferred option for some. This review discusses the contemporary management of all stages of prostate cancer in the light of these modern developments, enabling holistic individualization of treatment, and describes the promise of future research to further improve outcomes.

KEYWORDS
medical oncology, prostate neoplasms, radiation oncology, survivorship, urology

EPIDEMIOLOGY

Incidence and mortality

An estimated 1.5 million individuals are diagnosed with prostate cancer and almost 400,000 die from it worldwide each year. Prostate cancer is the most commonly diagnosed cancer in two thirds of the world's countries and has a positive correlation with a country's wealth as measured by the human development index. The highest age-standardized incidence rates (per 100,000 males) are observed in Northern Europe (82.8), Australia/New Zealand (78.1), the Caribbean (73.8), and North America (73.5), whereas regions in Asia and Africa have the lowest overall rates but the highest annual increases.[1–3] Prostate cancer mortality rates do not correlate with incidence rates most likely because of disparities in screening, diagnosis, and treatment between wealthy and poorer countries. Prostate cancer is the leading cause of cancer death in men in 52 countries, including countries in the Caribbean, sub-Saharan Africa, Central and South America, and Sweden in Europe.[1] Wealthier countries in Asia, such as Japan and South Korea, have a lower incidence than Western countries with a similar human development index.[4] Worldwide, the number of new cases of prostate cancer will likely double from 1.4 million in 2020 to 2.9 million in 2040, and the annual number of deaths will increase from 375,000 in 2020 to approximately 700,000 by 2040.[5]

Risk factors

Few known environmental or lifestyle factors have a concrete association with prostate cancer. The only established risk factors are advancing age, African/Caribbean descent, a positive family history, and certain genetic mutations. More than 70% of all prostate cancers are diagnosed in individuals older than 65 years.[6,7]

Smoking, being overweight or tall, consuming higher quantities of dairy products and calcium or diets with low levels of vitamin E or selenium may increase the risk of prostate cancer.[8–12] Gut microbiomes may also play a role in the development of castration resistance by the modulation of signaling pathways by dietary polyunsaturated fatty acids and metabolism of dihydrotestosterone and testosterone.[13–15] Specifically, commensal gut micriobiota can convert androgen precursors into active androgens and thereby provide an alternative source of androgens, which confer endocrine resistance.[16]

The increased incidence in the Caribbean countries or in countries of sub-Saharan Africa likely reflects increased genetic susceptibility in those of West African descent.[17,18] Those with low testosterone have a reduced risk, whereas testosterone-replacement therapy does not appear to increase the risk of developing prostate cancer.[19,20] Ejaculation frequency during adulthood (≥21 compared with four to seven ejaculations per month) may reduce the chance of a prostate cancer diagnosis.[21] Unfortunately, there are no strong modifiable risk factors for this disease.

Genetic predisposition

Prostate cancer correlates strongly with a family history of any cancer. Nine percent of individuals with prostate cancer have a family history of cancer and present six to seven years earlier than those with nonhereditary disease.[22–24] Those who have a first-degree relative with prostate cancer have a two-fold increased risk of diagnosis. The risk is highest if a family member was diagnosed before the age of 60 years.[25] If a man has more than one first-degree with prostate cancer, his risk of diagnosis increases to more than three-fold and depends on the relatives involved: father and a brother (relative risk [RR], 5.5), two brothers (RR, 7.7), three brothers (RR, 17.7).[22,25,26] Prostate cancer is called familial if an individual has more than three affected relatives, three successively affected generations, or two affected relatives diagnosed before the age of 55 years.[27]

Germline (inherited) mutations confer an increased risk of developing prostate cancer and include the following genes: BRCA1, BRCA2, ATM, ATR, mismatch repair (MMR) genes (MSH2, MSH6, and PMS2), CHEK2, RAD51D, NBS1, and PALB2.[28] The incidence of germline mutations mediating DNA repair is higher in those who have metastatic disease versus localized prostate cancer.[29] Germline BRCA1/2 mutations are present in approximately 6% of patients with prostate cancer.[30] The mutations that confer the highest risk of developing prostate cancer are those in BRCA2[29,31] (eight-fold) and HOXB13[32–34] (three-fold).[33,35] More than 170 single nucleotide polymorphisms (SNPs) have been associated with prostate cancer, but their contribution to cancer development is poorly defined.[36]

SCREENING

Prostate-specific antigen (PSA) is a glycoprotein enzyme secreted by the epithelium of the prostate gland. PSA helps break down large proteins in semen, thereby decreasing seminal viscosity and improving sperm motility and fertility.[37] Normally, only a small amount of PSA diffuses into the bloodstream. However, conditions that disrupt the prostate microarchitecture (i.e., trauma, prostatic inflammation, or malignancy) cause an increased diffusion of PSA into extracellular space and consequently into the bloodstream through lymphatic channels that can be detected by a serum assay. PSA levels may be increased in benign conditions like benign prostatic hyperplasia and prostatitis or after perineal trauma, ejaculation, and in cancer.[37] Certain drugs may lower PSA levels, and these include thiazide diuretics, nonsteroidal anti-inflammatory drugs, statins, and, more significantly, 5-alpha-reductase inhibitors.[37]

Theoretically, prostate cancer is a good target for screening because of high global mortality rates and the availability of a convenient blood test to measure PSA. The primary aim of PSA screening is to identify cancers earlier, when their natural history can be altered by effective treatments.[38]

However, PSA is an unreliable marker for prostate cancer; most individuals with elevated levels do not have prostate cancer, and a

normal PSA test does not rule out having the disease.[39] Compared to an unscreened population, a single PSA test does not improve mortality after 10 years and only marginally improves prostate cancer mortality after 15 years (0.09%). PSA testing does lead to an increased diagnosis of low-risk prostate cancer cases.[40,41] The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (ClinicalTrials.gov identifiers NCT00002540, NCT01696968, NCT01696981, and NCT01696994), which recruited 76,693 men from 10 American centers identified no mortality benefit from screening with PSA and digital rectal examination (DRE). However almost all men in the control arm also received a PSA test, which reduced the trial's power to detect a clinically meaningful benefit.[42,43] A secondary analysis of the data established that a baseline PSA level could serve as a long-term risk factor for clinically significant disease. Those with PSA levels <1 ng/mL likely need no further screening.[44]

The European Randomized Study of Screening for Prostate Cancer (ERSPC) identified a 20% reduction in prostate cancer mortality but also noted that 570 men needed to be screened and 18 men needed to be diagnosed to prevent one prostate cancer death, although these numbers were reduced with longer follow-up.[45–48] Unfortunately, the risk of overdiagnosis was substantial. Forty percent of men had low-risk disease identified that might never have become clinically apparent.[49] The Rotterdam cohort of the ERSPC study demonstrated a reduction in progression to metastatic disease by 24% and a reduction in prostate cancer mortality by 31% with screening. The Göteborg randomized trial also recorded a 29% reduction in prostate cancer mortality; however, 221 men needed to be invited and nine needed to be diagnosed to prevent one death from prostate cancer.[50] A Cochrane meta-analysis of older clinical trials failed to detect a clinically significant reduction in prostate cancer-specific mortality.[38]

Prostate cancer screening based solely on PSA risks overdiagnosis and overtreatment of indolent disease, psychological effects, including anxiety or depression, and the potential complications associated with biopsy or overtreatment.[51,52] Therefore, although there is a possible reduction in prostate cancer mortality, the risks of overdiagnosis and overtreatment have deterred widespread adoption of screening. Several modifications, including models incorporating clinical variables, PSA dynamics, magnetic resonance imaging (MRI), risk calculators, and genetic markers (including SNPs) may lower these risks.[53–55] A screening algorithm with PSA and MRI followed by MRI-directed, targeted biopsy reduced the diagnosis of clinically indolent disease by half.[56,57]

The European Union has now invited countries to pilot screening using PSA and MRI for risk assessment.[58] The PRAISE-U project encourages early detection and diagnosis of prostate cancer through customized and risk-based screening programs.[59] A Swedish cohort of such organized testing has been reported in which 35% of 68,060 invited men underwent PSA testing, and the combined approach of MRI and PSA density avoided a biopsy for >50% men with a PSA of ≥3 ng/mL.[60]

Individuals in families with hereditary cancer syndromes or known carrier mutations for BRCA1/2 may benefit from targeted screening.[61,62] Initial results from studies evaluating targeted screening based in men with higher genetic risk[63,64] have been reported.[63–66] Initial results of a mobile case-finding project piloted in the United Kingdom could potentially lead to raising health awareness and address health inequalities.[67] A large clinical trial from the United Kingdom is due to start recruiting in 2025 to compare the accuracy and cost-effectiveness of potential screening methods, including PSA tests, fast MRI scans, or genetic tests for those at a higher risk.[68]

We do not recommend routine PSA screening of all individuals, and PSA testing should always be guided by an informed discussion between the health care professional and the individual on personalized risk (ethnicity, number of first-degree relatives involved).[27,69–76] MRI before biopsy is likely to play a prominent role in any future studies of screening. Risk calculators that incorporate clinical factors, MRI features, and blood or urinary biomarkers have been described to aid in the detection of clinically significant disease at biopsy but require wider multicentric external validation toward routine adoption in clinical practice.[77,78]

DIAGNOSIS

Most cases of early prostate cancer are asymptomatic. Many patients present with unrelated urologic issues that prompt a PSA test. These include urinary symptoms, such as frequency, passing urine at night, hesitancy, incomplete voiding,[79] or sexual side effects like difficulties in achieving an erection.[80]

Advanced or metastatic disease can present with pain, typically back or bone pain. Very advanced disease can lead to metastatic spinal cord compression with radiating back or leg pain, leg weakness, numbness, tingling, paralysis, or incontinence.[81]

The risk of diagnosing a clinically significant prostate cancer depends on multiple factors: age, family history, PSA level, and, when advanced, a DRE. Risk calculators are available that incorporate these factors.[82] The most common finding on DRE is the presence of a hard, fixed nodule. Other findings may include asymmetry or firmness. The presence of a stony, hard prostate on DRE signifies locally advanced disease. If an MRI is to be done, a DRE is not always necessary.[83]

A multiparametric MRI is recommended on clinical suspicion of prostate cancer, prior to a biopsy.[84–87] MRI-directed biopsies are at least twice as accurate in identifying clinically relevant cancer compared with systematic transrectal biopsies alone. MRI also allows >25% of individuals to avoid subsequent biopsies that would likely diagnose insignificant disease.[84,85,88] A suspicious MRI (≥3 according to the Prostate Imaging Reporting and Data System, PIRADS) should be followed by targeted and systematic biopsies. A biopsy can be omitted if the MRI is negative (PIRADS≤2) or with

low clinical suspicion, if high-quality MRI and expertise of reader are provided.[75] MRI before biopsy is always recommended. Global adoption of this strategy with adequate quality control is potentially challenging.[89] MRI provides details about local extent, seminal vesicle involvement, and extraprostatic disease and can help plan surgical techniques to increase negative margins, particularly with regards to neurovascular bundle sparing and excision of potential extraprostatic sites, but leads to stage migration.[90–92]

A histologic diagnosis of prostate cancer is made by assessing the loss of normal glandular architecture and disruption to the basal membrane, loss of surrounding basal cells, and nuclear atypia of luminal cells.[93] The aggressiveness of an adenocarcinoma is reflected in the degree of differentiation on histopathology and is graded using the Gleason score (GS). Several changes have been made over the years, with modifications to grading and reporting.[94,95] The GS on biopsy is a sum of two numbers: the grade of the predominant pattern added to the grade of the highest grade pattern seen. Gleason grades range from 3 (moderately differentiated cancer cells) to 5 (no glandular features, sheets of abnormal cells). If only one Gleason grade is present within the biopsy, then it is doubled.[96–99] Overall grade groups (GGs) have been recommended since 2014 and are as follows: GG 1 (GS $\leq$ 6), GG 2 (GS 3 + 4 = 7), GG 3 (GS 4 + 3 = 7), GG 4 (GS 4 + 4 = 8), and GG 5 (GS 9–10).[100] Commercially available tissue-based biomarkers for risk stratification are now available (e.g., Prolaris [Myriad Genetics], Decipher [Veracyte, Inc.], Oncotype DX Prostate [Genomic Health], ProMark [Metamark Genetics Inc.]) and may help facilitate an individualized approach to treatment.[101]

Most prostate cancers originate from the epithelium and thus are carcinomas. Other rare histologies include sarcoma (derived from mesenchyme) and lymphoma.[102] Pathologically, the most common type of prostate cancer is an acinar adenocarcinoma that originates from the prostatic secretory epithelium in the peripheral part of the gland and accounts for the majority of all newly diagnosed cases.[102] Other histologic subtypes include ductal adenocarcinoma (3.2%, most mixed with acinar adenocarcinoma), preductal adenocarcinoma (0.4%–0.8%), neuroendocrine carcinomas (including small cell neuroendocrine carcinoma, 1%–5%; large cell neuroendocrine carcinoma; and treatment-related neuroendocrine carcinoma), squamous carcinoma (<0.6%), adenosquamous carcinoma, or adenoid cystic carcinoma (basal cell carcinoma).[102–105] Adenosquamous carcinoma is commonly associated with prior treatment.[106–108] Most variant pathologies have a poorer prognosis than acinar adenocarcinoma.[109,110] Treatment-related neuroendocrine prostate carcinoma occurs because of transdifferentiation of a castration-resistant prostate cancer (CRPC) after androgen-deprivation therapy (ADT) and comprises 10%–15% of all CRPCs.[111] Their prognosis is dismal and often less than one year.[112] Focal neuroendocrine differentiation, however, may be a component of adenocarcinomas with a high Gleason grade.[102]

Disease risk stratification[76,113–115] is routinely adopted before the initiation of treatment and after surgery.[113,114,116–118] Patients with low-risk disease (T1/T2 tumor, GS $\leq$6, PSA $\leq$10 ng/mL) do not require further staging. Patients with intermediate-risk disease require further staging investigations (MRI or computed tomography [CT] of the abdomen and pelvis and technetium-99m bone scan), except those with GG 2 disease. For high-risk disease, the cross-sectional imaging should also include the thorax. Those with poor general health who may not be fit for any treatment and those who refuse treatment do not require further staging investigations.[75,113] Predictive nomograms and molecular biomarker tests (e.g., Prolaris, Decipher, Oncotype DX Prostate, or ProMark) improve risk stratification and can help predict local or distant recurrences after radical primary treatment.[119–122]

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is overexpressed on prostate cancer cells, although approximately 10% of all prostate cancers may be PSMA-negative.[123] More than 90% of intraprostatic lesions are PSMA-avid, with avidity corresponding to the grade of the tumor.[124] Therefore, it is an excellent tool in both diagnosis and therapy. PSMA-labeled radiotracers are combined with cross-sectional imaging and are an excellent tool in baseline staging. Early interest based on ^{11}C-choline, ^{18}F-choline, or amino acid metabolism (eg, ^{18}F-FACBC) has been largely succeeded by small polypeptide ligands to PSMA.[125] PSMA-positron emission tomography (PET) scans have greater sensitivity and specificity compared with conventional imaging (CT and bone scan), a lower radiation dose, and reduced scan time, although this has not yet been shown to improve clinical outcomes.[126–128] The presence of nodal disease on a baseline PSMA-PET may predict medium-term oncologic outcomes.[129] Whole-body MRI also has greater sensitivity than conventional imaging and is particularly useful for assessing bone metastases.[130,131] PSMA-PET is recommended as baseline staging in all high-risk patients and can be considered for unfavorable-intermediate-risk patients.[76] A PET scan optimally should be performed before initiating ADT because it may affect detection sensitivities.[113] The global health economic impact of PSMA scans has not been fully determined.[132,133]

Metastatic disease is further classified as high-volume or low-volume based on the CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) criteria (ClinicalTrials.gov identifier NCT00309985). High-volume disease is defined as either four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both. This is based on conventional CT and bone scans.[134] The interpretation of disease burden in light of PET scans is currently unclear. A retrospective study reported similar discrimination based on a PSMA-directed tumor volume of 40 cm^3 on a receiver operating characteristic curve in a cohort of 105 patients from three German centers.[135] Prospective validation is lacking and may be guided by artificial intelligence in the future. PET scans are

more sensitive than conventional imaging for nodal and bone staging and are particularly helpful in the diagnosis of small lesions at low serum PSA levels.[136,137] Diagnostic imaging is represented in Figure 1.

Prostate cancer is currently staged using the 2018 classification (eighth edition) of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (Table 1).[138,139] Risk classification is described in Table 2.

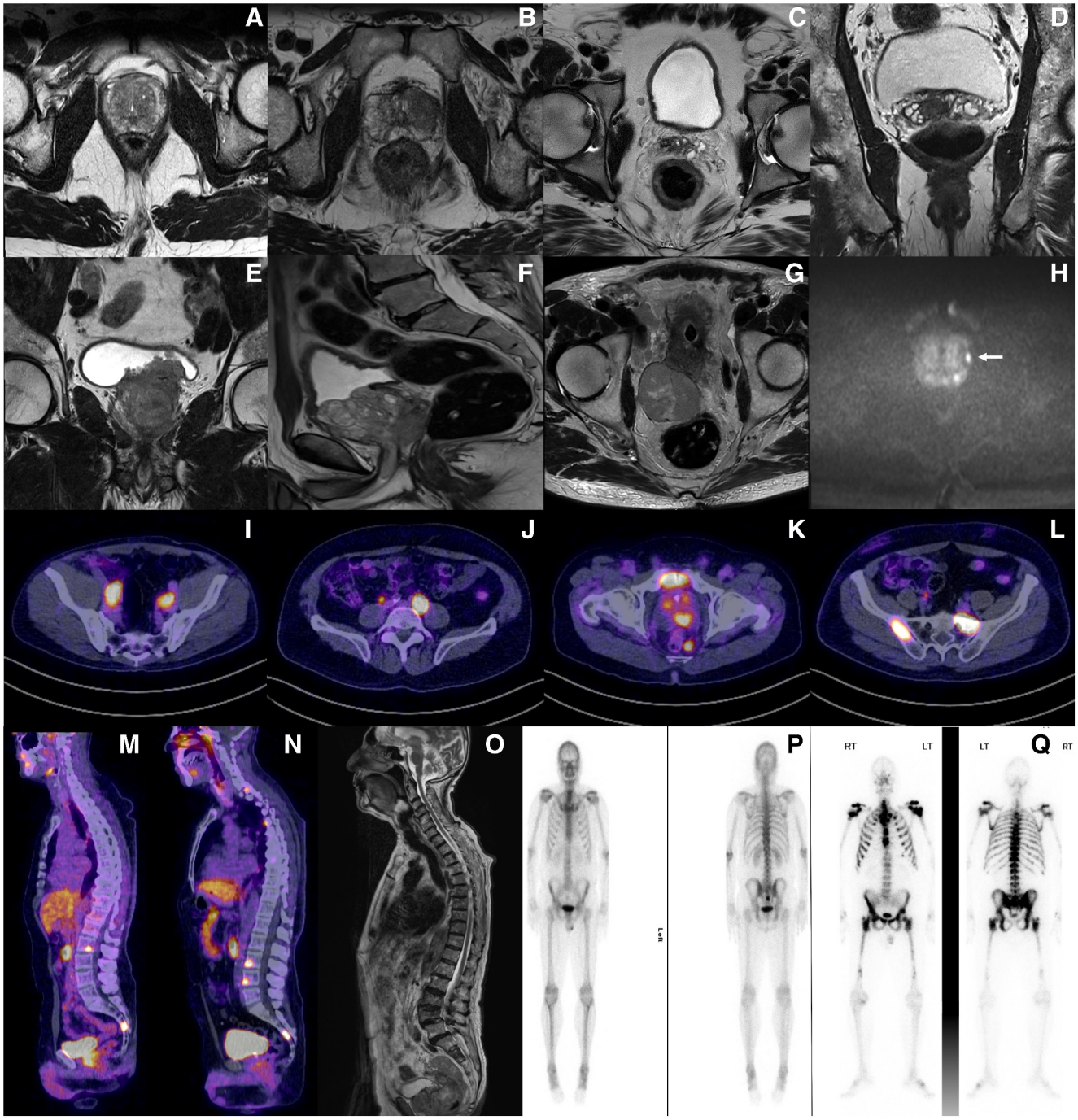

FIGURE 1 Diagnostic imaging for prostate cancer showing prostate MRI (A-H), PSMA-PET (I-N), whole-body MRI (O), and bone scans (P, Q). MRI features of organ-confined disease, (A) T2; capsular bulge and extraprostatic extension, (B) T3a; axial and coronal views of seminal vesicle involvement, (C, D) T3b; adjacent organ involvement, T4, involving (E) urinary bladder, (F) urethra; (G) an exophytic prostatic primary lesion; (H) diffusion-weighted MRI showing restriction in the left peripheral zone; PSMA-PET scan showing bilateral pelvic lymph nodes, (I) N1; common iliac lymph node, (J) M1a; mesorectal lymph node, (K) M1a; pelvic bone metastases, (L) M1b; with (M) low-volume and high-volume (N) bone metastases; (P) bone scan showing isolated uptake in the sacrum with low-volume, and (Q) high-volume bone metastases, *superscan*. Metastatic volume is defined on conventional scans (CT and bone scan) and not PSMA-PET. CT indicates computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

TABLE 1 Prostate Cancer American Joint Committee on Cancer TNM classification (eighth edition, 2018).[a]

Category	Criteria
Clinical T (cT): Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side, but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathologic T (pT): Primary tumor	
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
N: Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
PSA values, ng/mL	Used to assign this category
<10	
≥10 to <20	
<20	
≥20	
Any value	
Histologic grade group	Used to assign this category
1	Gleason score ≤6, Gleason pattern ≤3 + 3
2	Gleason score 7, Gleason pattern 3 + 4
3	Gleason score 7, Gleason pattern 4 + 3
4	Gleason score 8, Gleason pattern 4 + 4, 3 + 5, 5 + 3
5	Gleason score 9 or 10, Gleason pattern 4 + 5, 5 + 4, or 5 + 5

Abbreviation: PSA, prostate-specific antigen.

[a]Used with permission of the American College of Surgeons (Chicago, Illinois). The original source for this information is the American Joint Committee on Cancer's AJCC Cancer Staging System (2023).

TREATMENT

Curative (radical-intent) treatment

The overall management of localized prostate cancer is based on risk stratification (Figure 2).[75,113,114,116,117] When treatment, rather than surveillance, is indicated, individuals should see both a urologic surgeon and a radiation oncologist to discuss the benefits and risks of each suitable treatment modality. Alternatively, for men in whom the cancer is unlikely to become symptomatic or who need treatment during their natural lifespan, *watchful waiting* can be chosen to avoid treatment in those with a short prognosis (<5 years).

Active surveillance

Active surveillance refers to a policy of close monitoring with low-risk or intermediate-risk disease to defer or avoid curative treatment, balancing cancer control and urinary, bowel, or sexual toxicities. The aim of active surveillance is to detect progression to a higher risk cancer for which radical treatment can be offered.[142] This approach was established in the 1990s after the indolent natural history of many PSA-detected prostate cancers was recognized.[143–147] Early classification systems identifying patients suitable for surveillance were developed.[114,148]

TABLE 2 Prognostic risk groups for prostate cancer.[a]

Risk group	PSA, ng/mL	Gleason score	Clinical stage
Five-tier classification according to NCCN			
Very low risk	<10	≤6 (grade group 1)	T1c
Low risk	<10	≤6 (grade group 1)	T1c–T2a
Intermediate risk	10–20	7 (grade group 2–3)	T2b–T2c
High risk	>20	8–10 (grade group 4–5)	T3–T4
Very high risk	>40	8–10 (grade group 4–5)	T3–T4
Three-tier risk classification according to AUA/ASTRO (Eastham 2022[140]), other proposed three-tier classifications have been described (D'Amico 1998,[114] Tward 2024,[115] European Association of Urology 2024[141])			
Low risk	<10 and	≤6 (grade group 1) and	T1–T2a
Intermediate risk	10–20 or	7 (grade group 2–3) or	T2b–T2c
High risk	>20 or	8–10 (grade group 4–5) or	≥T3a

Abbreviations: ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; PSA, prostate-specific antigen.

[a]Additional clinical and pathologic features are also considered in National Comprehensive Cancer Network (NCCN) risk stratification. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.1.2025. © 2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data become available.

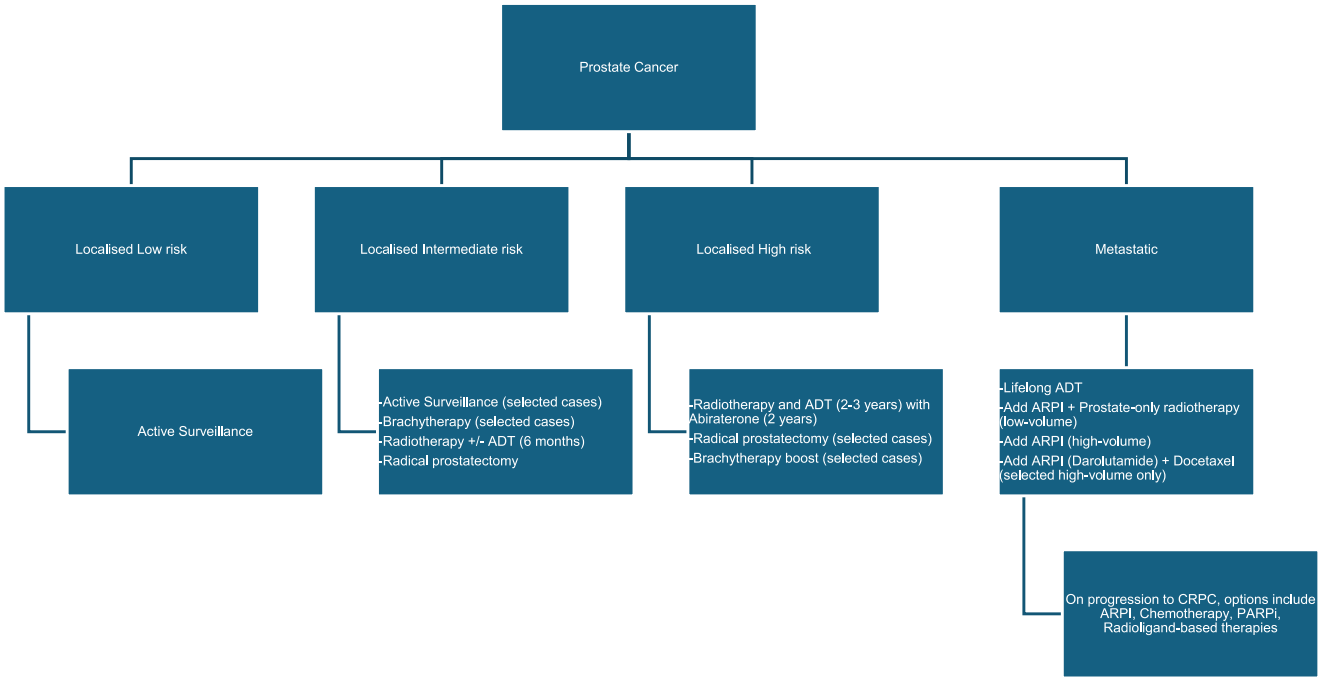

FIGURE 2 Overview of treatment options for prostate cancer. +/− indicates with or without; ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; CRPC, castrate-resistant prostate cancer; PARPi, poly(adenosine diphosphate ribose) polymerase inhibitor.

Prospective studies with predefined eligibility criteria in patients with low-grade disease, based on the studies by Epstein et al.[148] or D'Amico et al.,[114] were reported subsequently in the 2000s demonstrating the feasibility of active surveillance. The follow-up protocol included PSA testing (at three to 12-month intervals), DRE (six to 12-month intervals), a confirmatory biopsy within one year, and follow-up biopsies at intervals of one to three years.[149–155] Further evidence came from three clinical trials in the 2010s.[156–158] A meta-analysis

reported only eight prostate cancer-related deaths and five instances of metastasis during 24,981 person-years of follow-up in 7627 men from 26 active surveillance cohorts.[159]

The Scandinavian Prostate Cancer Group SPCG-4 trial randomized 695 men from Sweden, Finland, and Iceland with localized prostate cancer between 1989 and 1999 (pre-PSA era) to undergo radical prostatectomy or watchful waiting (not active surveillance). Although, at 30 years of follow-up, there was a significant relative reduction in overall mortality (26%) and prostate cancer-specific mortality (48%) in favor of surgery with a mean of 2.2 life-years gained, subset analyses of the initial analysis demonstrated very low rates of prostate cancer-specific mortality in men with low-risk disease (PSA <10 ng/mL and GS <7) and in men older than 65 years, with no significant difference noted between the two arms at 15 years.[156,160] Most men in this study had advanced disease, and few in the watchful-waiting arm ever received active treatment.[161]

The American PIVOT trial (Prostate Cancer Intervention Versus Observation Trial) randomized 731 men with localized prostate cancer to radical prostatectomy or watchful waiting between 1994 and 2002 (the era of early PSA testing). At a median follow-up of 10 years, there was no significant difference in overall survival (OS) or prostate cancer-specific mortality for men with PSA <10 ng/mL.[157] However, on extended follow-up, one life-year was gained with surgery.[162]

The ProtecT trial from the United Kingdom (International Randomized Controlled Trial Number [ISRCTN] 20141297; ClinicalTrials.gov identifier NCT02044172) randomized 1643 men with screen-detected prostate cancer to radical prostatectomy, radical radiotherapy, or active monitoring between 1999 and 2009. The proportion of men with intermediate-risk and high-risk disease according to contemporary risk stratification was 34% (D'Amico risk classification) and 29% (Cancer of the Prostate Risk Assessment [CAPRA] score, Cambridge Prognostic Group).[163] Patients in the active monitoring arm underwent PSA testing every three months in the first year and every 6–12 months thereafter without the need for protocol-defined re-biopsies; MRI was not routinely available in this era. Patients were considered for definitive treatment if their PSA levels rose by greater than 50% in one year. There was no difference in overall mortality or prostate cancer-specific mortality on follow-up at 10 and 15 years. A higher rate of metastasis in the active monitoring arm was presumed to be driven by the proportion of intermediate-risk and high-risk cancers.[158,163] Urinary and erectile functions were better in the monitoring arm.[164,165]

The approach to active surveillance is evolving, and data show that patients in GG 1[100] have a metastasis risk from <1-2% and a <1% rate of prostate cancer mortality at 10–15 years.[166–168] Modern multiparametric MRIs and targeted biopsies have improved detection rates and reduced the diagnosis of clinically insignificant cancers.[87] This approach allows routine biopsies to be avoided, which is beneficial for the patient.[169] The use of biopsy tumor volume, such as the number of positive cores or the percentage of core involvement, as an eligibility factor for surveillance is now questionable, especially as biopsy targeting strategy evolves.[170] A PSA increase alone does not justify intervention.[171–173] A PSA doubling time of <3 years has a weak link with grade progression.[174] It is uncertain whether MRI-detected cancers pose the same long-term oncologic risk as cancers of the same grade diagnosed by systematic biopsy.[175,176]

Currently, active surveillance is the preferred treatment for all individuals with low-risk prostate cancer with a life expectancy of >10 years, and for favorable intermediate-risk (either GG 1 with PSA <20 ng/mL and ≤T2, or GG 2 with PSA <10 ng/mL and ≤T2 with low tumor volume on MRI and biopsy). Safe surveillance is achieved by a combination of PSA testing every six months, multiparametric MRI every 12–24 months, consideration of biopsy at 18–24 months, and/or an MRI-directed re-biopsy on concerns of progression.[113,141,177,178] Patient or family anxiety about cancer progression is a valid reason to switch to active treatment.[179]

Surgery

Active treatment is recommended for individuals with intermediate and high grade localized prostate cancer and a life expectancy of >10 years. The SPCG-4 randomized trial has demonstrated a mortality reduction in clinically detected disease. The efficacy of surgery is less clear for those with screen-detected disease.[160,180] The usual PSA threshold for surgery is <20 ng/mL, although individuals beyond this threshold can be still considered for surgery if they have localized disease on imaging.[181,182] Most patients with high-grade prostate cancer are at a higher risk for metastases, require multimodality therapy, and merit multidisciplinary discussion. Most of those who are considering surgery are aged below 70, although occasionally very healthy individuals older than 70 years can be considered. Overall health status, including comorbidities, and not chronological age, should be taken into the decision-making process when considering an individual for treatment.[183–185] Relative contraindications are obesity or high anaesthetic risk/severe comorbidity. Oncogeriatric assessment, including comprehensive geriatric assessment and estimation of risk of death from coexisting comorbid conditions, can be useful.[186,187]

Robotic-assisted prostatectomy is the most common surgical technique, followed by radical retropubic or perineal approach. The use of multiparametric MRI combined with a validated nomogram can help predict extraprostatic extension and plan surgery.[92,188] Nerve-sparing prostatectomy can be safely undertaken in most cases, and preserving parasympathetic nerves of the pelvic plexus may spare erectile function.[189] Improved outcomes after surgery are directly correlated with the volume of procedures performed in the hospital and the experience of the surgeon.[190,191] There is some evidence to suggest that robotic prostatectomy leads to lower postoperative morbidity and margin-positive resections than laparoscopic prostatectomy, while accounting for methodological uncertainty.[192] Functional outcomes are similar between an open or a robotic approach.[193]

Surgical complications are classified as: intraoperative (i.e., blood loss, rectal injury, ureteral injury, obturator nerve injury), early (pain, lymphoceles <3%, thromboembolic events <3%) or late (urinary

incontinence, impotence).[192,194] Most patients report return of continence within 3–6 months of surgery. Incontinence rates after prostatectomy are influenced by incontinence definition, and approximately 50%–70% patients are fully continent (no pad use) at one year after surgery.[195–197] There is no difference in continence rates between robotic or open retropubic procedures.[198] Potency is reported to be 30%–75% after unilateral or 65%–75% for bilateral nerve-sparing surgeries, although the rates appear to be lower when measured by patient-reported outcomes.[196,197] Bladder neck contracture usually occurs in <5% of patients but can approach 20% in those undergoing subsequent radiotherapy.[192,194,199]

Although pelvic lymph node dissection (PLND) is frequently done for staging purposes, there are no strong data that support an OS advantage, although one trial suggests a metastasis-free survival (MFS) advantage to extended PLND (HR, 0.82; 95% CI, 0.71–0.93; $p = .003$).[200] Global surgical practice varies widely. Preoperative nomograms help predict the risk of individual lymph node involvement.[201,202] The European Association of Urology states that a risk of >7% is an indication to perform extended PLND, which improves staging but increases complications (19.8% vs. 8.2%).[27,203,204]

After surgery, individuals should have PSA checked at six to eight weeks, and the level ideally should be undetectable (<0.1 ng/mL). Up to 5% may have a detectable PSA (>0.1 ng/mL) postoperatively, which indicates a poorer prognosis.[205,206] Further PSA tests should be at 6-month intervals for the first 2–5 years and annually thereafter. A definitively rising PSA is an indication for consideration of salvage radiotherapy. A PSMA-PET scan is recommended for biochemical recurrence once PSA levels are >0.2 ng/mL.[207]

The landmark clinical trials for surgery in prostate cancer are summarized in Table 3.[156–158,160,161,163,180,208]

Radiotherapy

The use of radioisotopes to treat prostate cancer evolved in the early 1900s with the use of interstitial brachytherapy. External-beam radiotherapy gained prominence only in the second one half of the 20th century with the discovery of telecobalt and has evolved rapidly since. Radiotherapy is an essential treatment for intermediate-risk and high-risk, localized prostate cancer. Technically, conformal radiotherapy delivered using a linear accelerator reduces long-term proctitis and rectal bleeding (37% vs. 56% Radiation Therapy Oncology Group [RTOG] grade ≥1; $p = .004$; 5% vs. 15% RTOG grade ≥2; $p = .01$) compared with conventional radiotherapy without compromising local control.[209] However, an increased dose of radiotherapy (dose escalation) improves biochemical control with no benefit in survival at a cost of increased late bowel side effects.[210–216] The standard of care in terms of radiotherapy technique is intensity-modulated radiotherapy or volumetric-modulated arc therapy with image guidance.

Biologically, the behavior of prostate cancer differs from that of other cancers because of intrinsic differences in the rate of growth and repair of DNA damage and thus has higher sensitivity to an increased radiotherapy dose delivered per fraction, also known as *hypofractionation*.[217–219] Therefore, it was logical to determine whether radiotherapy schedules could be shortened to improve patient convenience and efficiency while maintaining high cure rates.

Moderate hypofractionation (between 2.4 grays [Gy] and 3.4 Gy per fraction)[220] has been studied in both superiority (Regina Elena, Fox Chase, MD Anderson, HYPRO)[221–224] and noninferiority (RTOG 0415 [ClinicalTrials.gov identifier NT00331773], ProfiT, and CHHiP [ISRCTN97182923])[225–227] randomized clinical trials compared with conventional fractionation. CHHiP was the largest randomized phase III clinical trial to test moderate hypofractionation in a population of 3216 patients from 71 centers in the United Kingdom, the Republic of Ireland, Switzerland, and New Zealand. The trial randomized individuals with T1b–T3aN0M0 prostate cancer, PSA ≤30 ng/mL, and a maximum GS of 4 + 4 to either conventional fractionation (74 Gy in 37 fractions) or one of two hypofractionated regimens (60 Gy in 20 fractions or 57 Gy in 19 fractions) using a noninferiority design. The hypofractionated regimen of 60 Gy in 20 fractions was identified as noninferior for biochemical control (HR, 0.84; 90% CI, 0.72–0.97), with similar OS and late side effects for both hypofractionated arms. For those aged 75 years and older, the regimen of 57 Gy in 19 fractions achieved similar biochemical failure rates with lower gastrointestinal toxicity.[227–229]

After it was demonstrated that moderate hypofractionation was at least as good as longer schedules, the next logical step was to test whether treatment could be further abbreviated. Ultra-hypofractionation delivers even higher doses per fraction, usually ≥5 Gy.[220] This concept was first tested in the randomized HYPO-RT-PC trial from the Nordic Cancer Union, the Swedish Cancer Society, and the Swedish Research Council (ISRCTN45905321), which compared 42 Gy in seven fractions with conventional fractionation and concluded equivalence for failure-free survival, albeit with an increase in short-term, but not long term, side effects.[230]

Stereotactic ablative radiotherapy or stereotactic body radiotherapy (SBRT) is a radiotherapy technique that can deliver ultra-hypofractionated doses to the tumor accurately while geometrically sparing normal tissues. This can be delivered on a C-arm linear accelerator, the CyberKnife system (Accuray), or an MR-linac, which combines magnetic resonance imaging with a linear accelerator. Stereotactic radiotherapy has been shown to be noninferior to longer schedules in the PACE-B phase III trial (ClinicalTrials.gov identifier NCT01584258) in terms of biochemical or clinical failure for low-risk to favorable intermediate-risk disease (GG 2; HR, 0.73; 90% CI, 0.48–1.12; $p = .004$) with a 5-year control rate of 96%.[231]

The next area of exploration is whether five-fraction treatments are safe and effective when directed at the prostate and pelvic lymph nodes. This question is currently being addressed in the PACE-NODES trial (ClinicalTrials.gov identifier NCT05613023), and data from the PRIME trial (ClinicalTrials.gov identifier NCT03561961) indicate low toxicity rates using this approach.[232,233]

MRI-guided radiotherapy allows daily online adaptation, taking into account changes in tumor and organs-at-risk position or shape,

TABLE 3 Landmark randomized phase III trials for surgery in localized prostate cancer.

Trial	Population	Intervention	Comparison	End points	Key results	Follow-up
SPCG-4 (Bill-Axelson 2011,[156] Holmberg 2024,[160] Bill-Axelson 2014[161])	695 men with localized prostate cancer, clinically detected, predominantly low risk to intermediate risk	Radical prostatectomy (RP)	Watchful waiting	OS, prostate cancer-specific mortality, metastasis	Overall mortality: 26% reduction with RP (RR, 0.74; 95% CI, 0.64–0.87) Prostate cancer-specific mortality: 48% reduction with RP (RR, 0.52; 95% CI, 0.40–0.67), Mean 2.2 life-years gained with RP (95% CI, 1.4–2.9 life-years gained) Distant metastasis: 16.7% absolute reduction at 23 years (RR, 0.54; 95% CI, 0.42–0.70; $p < .001$)	30 years
PIVOT (Wilt 2012, 2020[157,162])	731 men with localized prostate cancer, predominantly low-risk/ intermediate risk, PSA-detected, aged <75 years, PSA < 50 ng/mL, life expectancy >10 years	RP	Observation	OS, prostate cancer-specific mortality	Overall mortality: 5.7% reduction with RP (RR, 0.92; 95% CI, 0.84–1.01) Mean 1 life-year gained with RP Prostate cancer-specific mortality: 4% reduction with RP (HR, 0.63; 95% CI, 0.39–1.02; $p = .06$)	22 years; median, 18.6 years
ProtecT (Hamdy 2016, 2023[158,163])	1643 men with localized prostate cancer, predominantly low risk to intermediate risk, PSA-detected	RP, radiotherapy (RT)	Active monitoring (AM)	Prostate cancer-specific mortality, OS, metastasis, disease progression, initiation of ADT	Prostate cancer-specific mortality: 2.2% in RP, 2.9% in RT, 3.1% in AM (no significant difference across groups; $p = .53$) Metastasis: 4.7% in RP, 5.0% in RT, 9.4% in AM ($p < .001$)	Median, 15 years

Abbreviations: ADT, androgen-deprivation therapy; CI, confidence interval, OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RR, relative risk; SPGC, Scandinavian Prostate Cancer Group.

with intrafraction motion monitoring, thereby allowing a reduction in margins and potentially reducing toxicities.[234–236] MRI-guided radiotherapy also represents a potential treatment option for prostate re-irradiation for local, intraprostatic recurrences.[237] Radiotherapy has also been identified as effective in boosting the intraprostatic lesion(s), with improved cancer control and acceptable toxicities. Level 1 evidence supports its use with conventional fractionation.[238–241] A stereotactic boost regimen is well tolerated.[242] The use of proton-beam therapy for prostate cancer results in tumor control and quality of life similar to those achieved with photon-based treatment in early prostate cancer.[243]

The risk of pelvic nodal involvement in prostate cancer is clinically estimated using the Roach formula (% pelvic lymph node risk = 2/3PSA + (GS-6)10).[244] Prophylactic pelvic irradiation can address micrometastatic disease in the pelvic nodes, thereby potentially improving biochemical control and survival. The role of prophylactic pelvic radiotherapy in patients with intermediate-risk to high-risk disease who are node-negative on imaging is controversial.[245–247] Elective pelvic irradiation can improve biochemical control and disease-free survival at a risk of increasing long-term toxicities and should be discussed particularly in younger, fitter individuals with very high-risk disease.[248,249] Ongoing trial results are awaited.[250,251]

After radical radiotherapy, patients should have PSA checked at six months, then at six-month intervals for five years, and annually thereafter. Overall, biochemical control with prostate radiotherapy at five years varies by risk group but is estimated to be >90% with either moderate hypofractionation or SBRT.[227,231] Short-term side effects from radiotherapy are tiredness, urinary and/or bowel symptoms that resolve 4–8 weeks after radiotherapy completion. Moderate (grade ≥2) late urinary or bowel toxicities are noted in 10%–20% of patients at between 12 and 24 months. The risk of a serious (grade ≥3) toxicity at 2 years after SBRT is <1%.[252] Stereotactic radiotherapy slightly increases the risk of grade ≥2 urinary toxicity at 12–24 months; however, this difference was not seen in patients treated on a CyberKnife.[252] Emerging biomarkers may identify patients at higher versus lower risk of urinary toxicity after various forms of radiotherapy.[253]

Patients with intermediate-risk or high-risk, localized prostate cancer should be encouraged to make an informed choice about their decision to be treated with prostatectomy or radiotherapy. The

median life expectancy after prostate cancer treatment is 13.8 years; therefore, functional outcomes are important determinants of long-term quality of life.[254] Prostatectomy is more likely to lead to urinary incontinence or erectile dysfunction but fewer bowel symptoms compared with radiotherapy.[164,165,255] Similar outcomes were observed in a phase III clinical trial and in a larger, prospective UK multicohort study.[196,197] Individuals with preexisting poor urinary function should be treated with moderately hypofractionated radiotherapy rather than SBRT.[196,255] Radiotherapy, particularly external-beam radiotherapy, entails a small but significant risk of a second primary bladder or colorectal cancer (less than one in 250 individuals).[256,257]

Androgen deprivation therapy alongside curative therapy

Androgen deprivation therapy (ADT) reduces serum testosterone, which inhibits cancer growth and reduces PSA. Earlier published clinical trials established that the addition of ADT to radiotherapy in high-risk, localized prostate cancer improves OS, with long-course ADT (≥2 years) being superior to short-course ADT (6 months).[258–262] A reduced duration of 18 months of androgen suppression was noninferior for survival with an improved quality of life, although not all men in the three-year arm received the full course.[263] A meta-analysis has demonstrated that the addition of ADT to radiotherapy improves MFS (absolute difference, 8.3%; HR, 0.85; 95% CI, 0.79–0.92) and OS (absolute difference, 7.2%; HR, 0.87; 95% CI, 0.8–0.95) at 12 years.[264,265] Dose-escalated radiotherapy combined with ADT improves biochemical recurrence-free survival but not MFS or OS.[266] Currently, the recommended duration of ADT is four to six months for intermediate-risk patients and between 18-36 months for high-risk patients. There are some data indicating that, with extremely dose-escalated radiotherapy, a duration shorter than 24 months may be sufficient.[267] When using short-duration ADT (four to six months), sequencing may be important, with one analysis suggesting improved outcomes with concurrent/adjuvant versus neoadjuvant/concurrent sequencing in the context of prostate-only radiotherapy.[268] Patients with intermediate-risk disease and Gleason 3 + 4 disease or less may be treated with radiotherapy alone.[231]

In those receiving postoperative prostate bed radiotherapy, the addition of two years of antiandrogen therapy significantly improved MFS (absolute difference; 8.5% at 12 years; $p = .005$) and OS (absolute difference, 5% at 10 years; HR, 0.77; 95% CI, 0.59–0.99; $p = .04$) compared with placebo.[269] The RADICALS-HD trial (ClinicalTrials.gov identifier NCT00541047) has established that long-course ADT (24 months) improves MFS compared with short-course ADT (six months; HR, 0.773; 95% CI, 0.612–0.975; $p = .029$).[270] No definite OS benefit was observed.[271] There is contradictory evidence regarding the use of six months of ADT, with some trials reporting a benefit in MFS or progression-free survival (PFS),[272,273] whereas others have reported none,[274] so it may be offered based on a risk–benefit discussion with the individual. The three-way comparison of the RADICALS-HD trial (none, short-course, long-course) failed to detect an MFS benefit.[275]

The time to testosterone recovery depends on the age of the individual, baseline testosterone, and duration of ADT prescribed.[276] The oral ADT relugolix achieves rapid, sustained testosterone suppression and allows for earlier testosterone recovery upon discontinuation, and it may reduce the risk of major cardiovascular adverse events.[277,278] The parenteral gonadotropin-releasing hormone (GnRH) agonist degarelix has a similar cardiac profile compared with a GnRH agonist like leuprolide.[279]

Brachytherapy

Brachytherapy using low-dose-rate permanent seeds or high-dose-rate temporary sources, either alone or in combination with external-beam radiotherapy, is an option for carefully selected patients who have intermediate-risk or high-risk disease. Contraindications for the procedure are: a large transurethral resection defect, poor lower urinary tract symptoms (peak urinary flow rate <10 cm^3 per second, and postvoid residual volume >100 cm^3), very large prostate gland, preexisting fistula, absence of a rectum, ataxia telangiectasia, or any comorbidity that precludes anesthesia. The biochemical control rate at five years is >85%, 69%–97%, and 63%–80%, respectively, for low-risk, intermediate-risk, and high-risk disease. The rate of grade 3–4 side effects is typically <5%, although some series indicate significantly higher rates of genitourinary toxicity. The rates of bowel side effects from brachytherapy alone are low.[280–282]

The addition of a brachytherapy boost after external-beam radiotherapy improves biochemical control without affecting OS, but it does increase the risk of toxicity.[283–286]

Radiotherapy after prostatectomy

Prognostic scoring and risk-stratification models can help stratify risk and outcomes after prostatectomy.[118,287] Radiotherapy could be delivered adjuvantly (routinely after prostatectomy) or as salvage (for a rising PSA). Early salvage radiotherapy has been proposed to improve all-cause mortality in individuals with high-risk factors postprostatectomy.[288–290] Although early trials of adjuvant radiotherapy suggested a benefit,[291–293] more recent trials and a meta-analysis support the use of observation and early salvage radiotherapy, given adjuvant radiotherapy has no proven benefit in terms of biochemical PFS but increased urinary and bowel toxicity.[272,294–297] Outcomes are favorable if radiotherapy is initiated at a PSA level <0.5 ng/mL, but treatment should be initiated as early as possible.[298] Early salvage radiotherapy is the standard of care, and the decision to treat can be offered at a PSA of 0.2 ng/mL or with two or three consecutive PSA rises after surgery. The addition of pelvic radiotherapy improves freedom from progression when combined with prostate bed radiotherapy and short-term ADT.[273] Radiotherapy dose escalation from 64 to 70 Gy did not improve outcomes.[299]

Focal therapy

There is insufficient evidence at this time to recommend minimally invasive focal therapy, e.g., high-intensity focused ultrasound (HIFU) or cryotherapy, for the treatment of localized prostate cancer, particularly because of the need for salvage second-line treatments and the lack of randomized clinical data, and it should be offered only within a clinical trial or a prospective registry.[76,300–302]

Systemic treatment for nonmetastatic disease

Abiraterone given for nonmetastatic, high-risk disease (defined by N1 status or at least two of T3/T4, PSA >40 ng/mL, or GS 8–10) significantly improves MFS (absolute benefit, 13% at 6 years; HR, 0.53; 95% CI, 0.44–0.64; $p < .0001$) and OS, (HR, 0.60; 95% CI. 0.48–0.73; $p < .0001$), as evidenced from a meta-analysis, and should be recommended for a duration of two years alongside three years of ADT and radiotherapy to the prostate.[303] Docetaxel chemotherapy given as neoadjuvant treatment in high-risk, localized prostate cancer can help improve relapse-free survival but does not have a benefit when given in the adjuvant setting after radical prostatectomy or radical radiotherapy.[304–310] Therefore, it is not used often, especially given the introduction of novel anti-androgens, and is not recommended in localized disease. Clinical trials with apalutamide and enzalutamide are ongoing.[311,312]

Life-prolonging treatment

Relapse after radical treatment

The PSA level that defines biochemical failure depends on the primary treatment. After radical prostatectomy, the PSA level that best predicts metastases is >0.4 ng/mL,[313] but the most widely accepted definition of biochemical relapse is PSA >0.2 ng/mL or two consecutive rises.[76] After radiotherapy, the definition of PSA failure is an increase >2 ng/mL above nadir (the lowest PSA after treatment).[314] The yield of conventional imaging is low in asymptomatic patients. The probability of a positive result on a bone scan is <5% at a PSA level <7 ng/mL.[141,315] Therefore, conventional imaging is not recommended for restaging. PSMA-PET CT has higher sensitivity, specificity, positive predictive value, and rates of detection for failures in the prostate bed, pelvic lymph nodes, and the whole body.[207,316]

A positive scan depends on the PSA level: 33% at <0.2 ng/mL, 45% at 0.2–0.49 ng/mL, 59% at 0.5–0.99 ng/mL, 75% at 1.0–1.99 ng/mL, and 95% at 2 ng/mL.[207] This can help localize the site of recurrence/metastases and lead to a change in the proposed plan of treatment.[317]

The natural history of relapsed disease is long, and life expectancy and quality of life are important parameters to consider when deciding whether to pursue local treatment.[318] Indeed, while biochemical relapse-based end points are prognostic, these are not surrogate end points for OS.[319] Local treatments include salvage prostatectomy, cryoablation, high-intensity focused ultrasound, re-irradiation with external-beam or brachytherapy, which can provide temporary biochemical control in most patients but have important morbidity considerations.[320,321] For this reason, local recurrence after radiotherapy should be confirmed by imaging (MRI and/or PET PSMA) and biopsy if imaging is suspicious for local recurrence. ADT is usually initiated on development of symptoms or metastases or with a PSA doubling time less than six months.[322] Delayed and intermittent ADT is preferred for most patients because early ADT does not improve survival.[323,324] Enzalutamide in combination with ADT improves MFS compared with ADT alone for high-risk biochemical recurrences with a PSA doubling time less than nine months, whereas enzalutamide monotherapy may be an option for those struggling with adverse effects of ADT.[325]

Radiotherapy for metastatic disease

Radiotherapy has been studied in the context of metastatic disease and has been shown to improve OS in low-volume disease when added to standard-of-care treatment, translating to an expected benefit of more than two years (HR, 0.64; 95% CI, 0.52–0.79; $p < .001$).[326–329] The benefit is even greater for those with only nonregional lymph nodes (M1a) or three or fewer bone metastases (HR for OS, 0.62; 95% CI, 0.46–0.83; HR for failure-free survival, 0.57; 95% CI, 0.47–0.70).[330] In high-volume disease, it can reduce the incidence of complications like obstructive uropathy.[331] The PEACE-1 trial (ClinicalTrials.gov identifier NCT01957436) demonstrated that adding radiotherapy to standard-of-care treatment (with abiraterone) improves radiographic PFS in men with low-volume disease, reduces serious genitourinary events, and prolongs time to castration-resistance regardless of disease volume.[332]

Oligometastatic prostate cancer is usually defined as having up to five metastatic lesions and is further subclassified on the basis of the time interval between appearance of metastases as metachronous or synchronous.[333,334] Metastasis-directed therapy can reduce the rate of biochemical recurrence, increase the time to subsequent therapy, and improve PFS[335–339]; however, an OS benefit has not yet been demonstrated in prostate cancer. The use of stereotactic radiotherapy has been shown to improve biochemical control and PFS in a randomized phase II trial of patients starting first-line therapy for castration-resistant disease.[340] Whole-pelvic nodal radiotherapy improves biochemical and regional control compared with metastasis-directed therapy for oligorecurrent pelvic nodal disease and should be considered the standard of care for pelvic nodal oligorecurrence.[341,342]

Metastatic hormone-sensitive prostate cancer

Approximately 5%–15% of all prostate cancers are metastatic (stage IV) at presentation, whereas this proportion can increase to 20%–

25% or more in countries with limited access to health care.[343–345] Reducing circulating testosterone is the backbone of metastatic prostate cancer treatment.[346,347] Metastatic disease is initially responsive to testosterone suppression (hormone-sensitive prostate cancer [HSPC]or castration-sensitive prostate cancer) but eventually progresses to a hormone-resistant phase (castration-resistance).

Androgen deprivation can be achieved by surgical (bilateral orchidectomy) or medical castration. Hormonal agents include GnRH agonists (leuprolide, goserelin, triptorelin, buserelin) or GnRH antagonists (degarelix, relugolix). Androgen receptor pathway inhibitors (ARPIs) act on the androgen receptor pathways by either competing with androgens for binding to androgen receptors or by deeply suppressing androgen production. ARPIs are classified as first-generation (flutamide, bicalutamide, nilutamide) or second-generation (apalutamide, enzalutamide, darolutamide). Second-generation ARPIs are considered more potent. Darolutamide is the only ARPI that does not cross the blood–brain barrier, thereby helping to reduce neurologic side effects.[348] Abiraterone is a potent CYP17A1 inhibitor that blocks the biosynthesis of androgens in the adrenal glands, testis, and the tumor itself.[349] Key adverse effects are summarized in Table 4.

With ADT alone, individuals with high-grade disease have a median failure-free survival of 11 months and a median OS of about 42 months.[350] Maximal androgen blockade, defined as the addition of a first-generation anti-androgen like bicalutamide to luteinizing hormone-releasing hormone (LHRH) analogues, shows a modest reduction in the risk of death with an increased risk of adverse effects.[351] The addition of docetaxel[134,306,307,352–354] or ARPIs like abiraterone,[355–359] enzalutamide,[360–363] or apalutamide,[364,365] or with ADT significantly improve OS in metastatic HSPC (mHSPC). Darolutamide in combination with ADT improves radiologic PFS; mature OS data are awaited.[366] The quantum of benefit with docetaxel in reducing the risk of death is the highest with high-volume synchronous metastasis.[367] Table 5 summarizes the results of selected landmark phase III clinical trials. These trials excluded patients with poor performance status or significant comorbidities, and the average age was younger than that seen in a real-world setting. It is known that ARPIs can increase all-grade cardiovascular events, including increases in hypertension, arrythmia, or cardiac death.[368] Patients with de novo mHSPC comprised the majority of those in the phase III trials, and caution should also be exercised when extrapolating these data for patients who relapse after primary treatment. All patients who are sufficiently fit should be offered dual therapy with ADT plus another agent; where available, we suggest this should be an ARPI rather than docetaxel. The added value of an ARPI to ADT + docetaxel was proven in two phase III trials with improved MFS and OS, whereas the added value of docetaxel to ADT + ARPI remains unknown.

Triplet or quadruplet therapeutic options have been studied in mHSPC in two important clinical trials. The PEACE-1 trial, with a 2 × 2 factorial design, randomized 1173 individuals with mHSPC to standard of care (ADT with or with intravenous docetaxel), standard of care plus radiotherapy, standard of care plus abiraterone, or standard of care plus radiotherapy plus abiraterone. At a median follow-up of 3.5 years, the combination of ADT, docetaxel, and abiraterone improved OS and radiographic PFS (rPFS) compared with ADT and docetaxel alone. The combination of standard of care with abiraterone and radiotherapy produced the best outcomes in terms of rPFS and OS.[369,370]

The ARASENS trial (ClinicalTrials.gov identifier NCT02799602) randomized 1306 individuals with mHSPC to darolutamide or placebo, both in combination with ADT and docetaxel. The addition of darolutamide significantly improved OS (HR, 0.68; 95% CI, 0.57–0.80; $p < .001$).[371] However, the *standard-of-care* arm in the ARASENS trial was ADT + docetaxel, which is no longer considered optimal. A subsequent meta-analysis demonstrated no OS benefit for triplet therapy in low-volume disease, and triplet therapy is not superior to an ARPI doublet for high-volume disease.[372] At this time, the combination of ADT, ARPI, and prostate radiotherapy remains a standard

TABLE 4 Adverse effects of androgen-deprivation therapy and androgen receptor pathway inhibitors.

Therapy	Common adverse effects	Serious or notable adverse effects	Notes
Androgen-deprivation therapy	Hot flashes, fatigue, gynecomastia, weight gain, loss of libido, muscle wasting, mood changes	Osteoporosis, cardiovascular risk, metabolic syndrome, risk of diabetes	Increases the risk of fractures because of bone density loss and may contribute to cognitive decline in long-term use.
Abiraterone	Hypertension, hypokalemia, fluid retention, liver enzyme elevation	Adrenal insufficiency, hepatotoxicity	Is co-administered with steroids to manage syndrome of secondary mineralocorticoid excess.
Enzalutamide	Fatigue, hot flashes, musculoskeletal pain, hypertension	Seizure risk, cognitive effects, cardiovascular events	Can cross the blood–brain barrier, potentially causing mild cognitive impairment and increasing fall risk, especially in older patients.
Apalutamide	Fatigue, rash (common), falls, joint pain	Fractures, cardiovascular risk, rare but severe rash, hypothyroidism	Rash is a notable side effect and generally is manageable but occasionally severe enough to warrant dose adjustment.
Darolutamide	Fatigue, pain in extremities, hypertension	Minimal blood–brain barrier penetration, few cognitive or seizure-related side effects	The structure limits central nervous system penetration.

TABLE 5 Selected trials of combination therapy for hormone-sensitive metastatic prostate cancer.

Trial	Arms (no. of patients)	Primary end point	PFS, months	OS, months	PFS	OS
GETUG AFU15 (Gravis 2013[352])	ADT + docetaxel (n = 192) vs. ADT (n = 193)	OS	22.9 vs. 12.9	62.1 vs. 48.6	HR, 0.67 ($p < .001$)	HR, 0.88 ($p = .3$)
CHAARTED (Sweeney 2015,[134] Kyriakopoulos 2018[354])	ADT + docetaxel (n = 397) vs. ADT (n = 393)	OS	20.2 vs. 11.7	57.6 vs. 47.2	HR, 0.61 ($p < .001$)	HR, 0.72 ($p = .018$)
STAMPEDE (docetaxel; James 2016,[306] Clarke 2019[353])	ADT + docetaxel (n = 724) vs. ADT (n = 362)	OS	53.4 vs. 40.7, RMST	63.1 vs. 57.1, RMST	HR, 0.69 ($p < .001$)	HR, 0.81 ($p = .003$)
LATITUDE (Fizazi 2017, 2019[355,359])	ADT + abiraterone (n = 597) vs. ADT (n = 602)	rPFS, OS	33 vs. 14.8	53.3 vs. 36.5	HR, 0.47 ($p < .001$)	HR, 0.66 ($p < .0001$)
STAMPEDE (abiraterone; James 2017, 2022[356,357])	ADT + abiraterone (n = 501) vs. ADT (n = 502)	OS	62 vs. 47, RMST	66.0 vs. 54.0, RMST	HR, 0.58 ($p < .0001$)	HR, 0.60 ($p < .0001$)
ARCHES (Armstrong 2019, 2022[360,362])	ADT + enzalutamide (n = 574) vs. ADT (n = 576)	rPFS	49.8 vs. 38.9	Not reached	HR, 0.63 ($p < .001$)	HR, 0.66 ($p < .001$)
ENZAMET (Davis 2019,[361] Sweeney 2023[363])	ADT + enzalutamide (n = 563) vs. ADT (n = 562)	OS	68 vs. 22 (PSA), 81 vs. 25 (clinical)	Not reached, 10% improvement at 5 years	HR, 0.44 (PSA); HR, 0.45 (clinical; both $p < .01$)	HR, 0.70 ($p < .0001$)
TITAN (Chi 2019, 2021[364,365])	ADT + apalutamide (n = 525) vs. ADT (n = 527)	rPFS, OS	Not reached vs. 44	Not reached vs. 52.2	HR, 0.62 ($p < .0001$)	HR, 0.65 ($p < .0001$)
ARANOTE (Saad 2024[366])	ADT + darolutamide (n = 446) vs. ADT (n = 223)	rPFS	Not reached vs. 25	Not reached, OS not mature)	HR, 0.54 ($p < .0001$)	HR, 0.81 (p = NS)

Abbreviations: ADT, androgen-deprivation therapy; HR, hazard ratio; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RMST, restricted mean survival time (proportional hazards); rPFS, radiographic progression-free survival.

of care for low-volume disease, and triplet or quadruplets with docetaxel are best reserved for de-novo, high-burden mHSPC, although optimal patient selection is still a matter of debate.[373,374] Patients should be advised that there will be a definite quality-of-life detriment when adding docetaxel chemotherapy to an ARPI doublet in mHSPC and that, if there is a benefit to having all three agents at diagnosis of metastatic disease, the magnitude of that benefit is not known.[375]

PSMA-based radioligand therapy has been shown to improve PSA control, delay progression to CRPC, and improve rPFS (HR, 0.58; 95% CI, 0.3–1.0) compared with docetaxel in high-volume mHSPC in the UpFrontPSMA phase II study (ClinicalTrials.gov NCT04343885).[376]

Castration-resistant prostate cancer

Castration-resistant prostate cancer is defined as progression of disease with serum testosterone at castrate levels (<50 ng/dl or 1.7 nmol/liter).[315] Progression can include either multiple PSA rises or radiologic progression.

Nonmetastatic castration-resistant prostate cancer

Nonmetastatic CRPC is identified by the absence of metastatic disease on conventional imaging (CT and bone scan). Nonmetastatic CRPC develops as a result of the use of early and long-term ADT in nonmetastatic prostate cancer or the initiation of early ADT in patients who have biochemical failure in whom the site of recurrence has not yet been detected.[75] The latter practice is no longer recommended, hence this scenario will become rarer in the future. Many patients previously classified with nonmetastatic CRPC would now have visible disease on modern imaging. PSMA-PET/CT is superior to conventional imaging for the detection of metastatic disease.[377] The use of PSMA-PET identified the site of disease in 98% of patients previously classified with nonmetastatic CRPC on conventional scans in a retrospective cohort on the basis of the PROMISE (Prostate Cancer Molecular Imaging Standardized Evaluation) criteria: local relapse, 24%; only pelvic disease, 44%; M1 disease, 55%, of whom

TABLE 6 Phase III trials of androgen receptor pathway inhibitors for nonmetastatic castration-resistant prostate cancer.

Trial	Arms (no. of patients)	Primary end point	MFS improvement vs. placebo, months	HR for MFS	OS analysis
PROSPER (Hussain 2018,[380] Sternberg 2020[381])	ADT + enzalutamide (n = 933) vs. ADT (n = 468)	MFS	36.6 vs. 14.7	HR, 0.29 (p < .001)	Improved: 67 vs. 56.3 months (HR, 0.73; p = .001)
SPARTAN (Smith 2018, 2021[382,383])	ADT + apalutamide (n = 806) vs. ADT (n = 401)	MFS	40.5 vs.16.2	HR, 0.28 (p < .001)	Improved: 73.9 vs. 59.9 months (HR, 0.78; p = .016)
ARAMIS (Fizazi 2019, 2020[384,385])	ADT + darolutamide (n = 955) vs. ADT (n = 554)	MFS	40.4 vs. 18.4	HR, 0.41 (p < .001)	Improved: 6% at 3 years (HR, 0.69; p = .003)

Abbreviations: ADT, androgen-deprivation therapy; HR, hazard ratio; MFS, metastasis-free survival; OS, overall survival.

about 30% had bone or visceral metastases).[378,379] The use of some novel ARPIs (Table 6) in combination with ADT helps improve MFS and OS in nonmetastatic CRPC.[380–385] Patients with luminal tumors or a high score on the genomic classifier Decipher may achieve more a sustained MFS benefit with the novel ARPI, apalutamide.[386]

Metastatic castration-resistant prostate cancer

The choice of optimal systemic therapy for metastatic CRPC (mCRPC) depends on multiple factors: age, fitness, volume of disease, previous treatment received for de-novo or metastatic hormone-sensitive disease, the presence of DNA-repair defect, and PSMA expression of the disease. ADT should be continued lifelong because androgen receptor signaling remains critical for prostate cancer cell survival and proliferation even in the castration-resistant phase.[387]

Chemotherapy in CRPC. The first approved systemic chemotherapeutic agent was mitoxantrone, which has been superseded by more effective agents like the first generation taxane, docetaxel (given with low-dose steroids),[388–390] and the second-generation, semisynthetic taxane, cabazitaxel.[391,392] Cabazitaxel and docetaxel have been compared in chemotherapy-naive patients and are equivalent for OS.[393] Cabazitaxel improves OS after docetaxel treatment compared with mitoxantrone[391] or a second-line ARPI (abiraterone)[394] and thus is an option for second-line mCRPC after docetaxel. A reduced-dose regimen is effective for OS with fewer side effects.[395] In heavily pretreated patients, carboplatin, either alone or in combination with cabazitaxel, shows modest clinical efficacy and should be reserved for cancers with an aggressive phenotype; both PFS and OS are between six and seven months.[396,397] Other chemotherapeutic agents like carboplatin/cisplatin and etoposide have shown activity, generally of short duration, for variant histologies (small cell/anaplastic), so called either because of histopathologic evidence of small cell or clinical features (visceral metastases, lytic bone metastases, low PSA).[398–402]

Non-chemotherapy treatments for CRPC. The novel anti-androgens abiraterone and enzalutamide improve OS in patients who are ARPI-naïve before or after docetaxel.[403–409] Low-dose abiraterone taken with a low-fat breakfast achieves similar blood levels to standard-dose abiraterone taken on an empty stomach because of the pharmacokinetic properties of the drug.[410] The use of Radium-223, an alpha emitter, significantly improves OS in those with progressive, bone-predominant mCRPC and can be recommended irrespective of previous docetaxel use.[411,412] Radium should be given in conjunction with bisphosphonates or denosumab for bone protection.

For individuals who are ARPI-naïve in the CRPC setting, the PEACE-3 (ClinicalTrials.gov identifier NCT02194842) results support the use of Radium-223 in combination with enzalutamide and bone-protective agents because the combination significantly improves OS compared with enzalutamide alone (HR, 0.69; 95% CI, 0.52–0.90; p = .0031).[413] For those who have been previously treated with an ARPI, a second ARPI has only modest activity and is not considered standard of care.[414] Low-dose dexamethasone can improve PSA and achieve symptomatic responses in some.[415] Key phase III clinical trials of systemic therapies for mCRPC are listed in Table 7.

Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors. DNA-repair defects are identified in up to 20%–30% of patients with mCRPC, such as germline or somatic homologous recombination repair genes (BRCA1, BRCA2) or the DNA-damage checkpoint activator ATM.[424,425] Somatic genetic testing should be offered to all patients with newly diagnosed mHSPC and is recommended for all mCRPCs. Germline testing guidelines vary, but testing should be encouraged for those with a strong family history of prostate cancer, especially at a young age, or if at least two family members on the same side of the family have been diagnosed with tumors linked to hereditary cancer-predisposition syndromes (including breast, ovarian, prostate, and pancreatic cancers).[75,113,141,426,427]

Treatment options for mCRPCs harboring homologous recombination repair gene alterations include a poly(adenosine diphosphate ribose) polymerase (PARP) inhibitor (PARPi) alone (olaparib, rucaparib) or in combination with ARPIs (abiraterone + olaparib, abiraterone + niraparib, enzalutamide + talazoparib).[416–423,428,429] Somatic genetic testing is strongly recommended before commencing a PARPi.[430] There is insufficient evidence to recommend a PARPi for patients without the mutations shown to benefit.

TABLE 7 Landmark clinical trials of systemic therapies for metastatic castrate-resistant prostate cancer.

Trial	Arms (no. of patients)	Primary end point	Median OS, months	HR for OS	PFS/rPFS
TAX 327 (Tannock 2004,[388] Berthold 2008[390])	Docetaxel three-weekly (n = 335) vs. docetaxel weekly (n = 334) vs. mitoxantrone (n = 337)	OS	19.2 vs. 17.8 vs. 16.3	HR, 0.83 both docetaxel groups (p = .04), OS improved with three-weekly (p = .009) but not weekly (p = .36) docetaxel	—
CARD (De Wit 2019[394])	Cabazitaxel (n = 129) vs. abiraterone or enzalutamide (n = 126; post-docetaxel)	ibPFS	13.6 vs. 11.0	HR, 0.64 (p = .008)	Improved (4.4 vs. 2.7 months; HR, 0.52; p < .001)
TROPIC (De Bono 2010[391,392])	Cabazitaxel (n = 378) vs. mitoxantrone (n = 377)	OS	15.1 vs. 12.7	HR, 0.70 (p < .0001)	Improved (2.8 vs. 1.4 months; HR, 0.74; p < .0001)
PROSELICA (Eisenberger 2017[395])	Cabazitaxel (20 mg/m^2; n = 598) vs. (25 mg/m^2; n = 602)	Noninferiority of OS (HR, <1.214)	13.4 vs. 14.5	HR, 1.024 (noninferior)	Similar (2.9 vs. 3.5 months; HR, 1.099)
FIRSTANA (Oudard 2017[393])	Cabazitaxel (20 mg/m^2; n = 389) vs. cabazitaxel (25 mg/m^2; n = 388) vs. docetaxel (n = 391)	OS	24.5 vs. 25.2 vs. 24.3	C20 (HR, 1.01; p = .997), C25 (HR, 0.97; p = .757)	Similar (4.4 vs. 5.1 vs. 5.3 months): C20 (HR, 1.06; p = .422), C25 (HR, 0.99; p = .804)
AFFIRM (Scher 2012[407])	Enzalutamide (n = 800) vs. placebo (n = 399)	OS	18.4 vs. 13.6	HR, 0.63 (p < .001)	Improved (8.3 vs. 2.9 months; HR, 0.40; p < .001)
PREVAIL (Beer 2014, 2017[408,409])	Enzalutamide (n = 872) vs. placebo (n = 845)	OS, rPFS	35.3 vs. 31.3	HR, 0.77 (p = .0002)	Improved (20 vs. 5.4 months; HR, 0.32; p < .0001)
COU-AA-301 (De Bono 2011,[403] Fizazi 2012[404])	Abiraterone (n = 797) vs. placebo (n = 398; post-docetaxel)	OS	15.8 vs. 11.2	HR, 0.74 (p < .0001)	Improved (5.6 vs. 3.6 months; HR, 0.66; p < .0001)
COU-AA-302 (Ryan 2013, 2015[405,406])	Abiraterone (n = 546) vs. placebo (n = 542; pre-docetaxel)	OS, rPFS	34.7 vs. 30.3	HR, 0.81 (p = .0033)	Improved (16.5 vs. 8.3 months; HR, 0.53; p < .001)
EORTC-GUCG 1333/PEACE-3 (Gillessen 2024[413])	Enzalutamide + radium-223 (n = 222) vs. enzalutamide (n = 224)	rPFS	42.3 vs. 35	HR, 0.69 (p = .0031)	Improved (19.4 vs. 16.4 months; HR, 0.69; p = .0009)
PROPEL (Clarke 2022,[416] Saad 2023[417])	Olaparib + abiraterone (n = 399) vs. placebo + abiraterone (n = 397)	ibPFS	42.1 vs. 34.7	HR, 0.81 (p = .054)	Improved (24.8 vs. 16.6 months; HR, 0.66; p < .001)
PROFOUND (De Bono 2020,[418] Hussain 2020[419])	Olaparib vs. physician's choice in HRRm patients (cohort A, BRCA1/2 vs. ATM (n = 162 vs. n = 83); cohort B, other genes (n = 94 vs. n = 48)	ibPFS in cohort A	Cohort A, 19.1 vs. 14.7; cohort B, 14.1 vs. 11.5; overall, 17.3 vs. 14	Cohort A: HR, 0.69 (p = .02); cohort B: HR, 0.96 (p = NS); overall: HR, 0.79 (p = NS)	Improved: Cohort A, 7.4 vs. 3.6 months (HR, 0.34; p < .001); overall: 5.8 vs. 3.5 months (HR, 0.49; p < .001)
TRITON3 (Fizazi 2023,[420] Bryce 2025[421])	Rucaparib (n = 270) vs. physician's choice (n = 135; patients with HRRm)	ibPFS	BRCA subgroup, 23.2 vs. 21.2; overall, 22.8 vs. 21.7	BRCA subgroup: HR, 0.91 (p = NS); overall HR, 0.99 (p = NS)	Improved: BRCA subgroup, 11.2 vs. 6.4 months (HR, 0.50; p < .001); overall: 10.2 vs. 6.4 months (HR, 0.61; p < .001)
TALAPRO2 (Agarwal 2023, 2025[422,423])	Talazoparib + enzalutamide (n = 402) vs. placebo + enzalutamide (n = 403)	rPFS	45.8 vs. 37.0	HR, 0.796 (p = .0155)	Improved: Not reached vs. 21.9 months (HR, 0.63; p < .0001)

Abbreviations: EORTC-GUCG, European Organization for Research and Treatment of Cancer Genito-Urinary Cancers Group; HR, hazard ratio; HRRm, homologous recombination repair-mutant; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Radioligand-based therapies. PSMA-based radioligands can selectively deliver radiation to PSMA-positive cells and the surrounding microenvironment. The use of Lutetium-177 (^{177}Lu)–PSMA-617 improved OS compared with the standard of care in patients who received an ARPI and one or two prior taxanes in the VISION trial (HR, 0.62; 95% CI, 0.52–0.74; $p < .001$; ClinicalTrials.gov identifier NCT03511664),[431] whereas a radiographic PFS benefit was observed in the PSMAfore trial (ClinicalTrials.gov identifier NCT04689828) in taxane-naïve individuals pretreated with an ARPI compared with a second ARPI (HR, 0.49; 95% CI, 0.39–0.61) with fewer adverse effects.[432] The SPLASH trial (ClinicalTrials.gov identifier NCT04647526) demonstrated improved rPFS with ^{177}Lu-PNT2002 compared with a change of ARPI (HR, 0.71; 95% CI, 0.55–0.92; $p = .0088$) in chemotherapy-naïve, ARPI-pretreated individuals. The crossover rate in that trial was 85%.[433]

There is no agreed consensus regarding the ideal sequencing of these agents. A suggested flowchart is represented in Figure 3. There is insufficient evidence to recommend the routine use of immunotherapy in prostate cancer treatment outside of clinical trials.

Ongoing research focuses on clinical trials of possible therapeutic targets and the identification of novel targets: Akt signaling inhibitors in PTEN loss,[434,435] PD-1 inhibitors in microsatellite instability-high tumors,[436] selective PARP1 inhibitors,[437,438] agents that target and inhibit steroid biosynthesis,[439] small molecules targeting protein degradation,[440] T-cell engagers targeting PSMA (human kallikrein 2, STEAP1),[441,442] and targeting potential markers of neuroendocrine differentiation (DLL-3, EZH2).[443,444] The natural history of prostate cancer and its clinical course is represented in Figure 4.

SURVIVORSHIP AND QUALITY OF LIFE

Over the past four decades, the five-year survival rate for patients with prostate cancer has increased from 68% to >95%, with that of localized prostate cancer approaching 100%.[445] More than one in three individuals treated for prostate cancer experience long-term decrements in their quality of life, with significant impact on their physical, mental, metabolic, and sexual health.[446,447] These include long-term toxicities from radical treatment and ongoing adverse effects of treatment for metastatic disease.

The use of lifelong ADT in combination with newer therapeutic options in metastatic prostate cancer can successfully control the disease for many years, thereby leading to a protracted natural course of the disease with features of a *chronic malignancy*. ADT itself is associated with weight gain, reduced muscle mass and bone mineral density, an increased risk of falls and fragility fractures, an increased risk of cardiovascular disease, changes to mood and cognition, depression, loss of sexual function and libido leading to reduced intimacy with their partners, and an increased risk of suicidal ideations.[448–450] Testosterone-replacement therapy can be offered

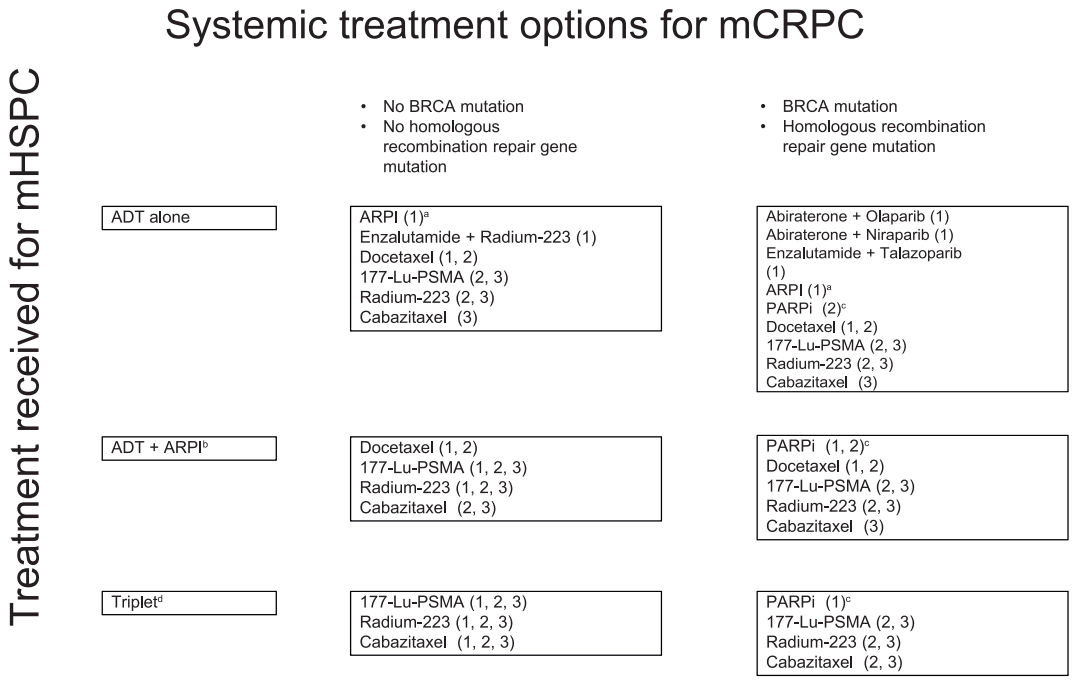

FIGURE 3 Systemic treatment options for metastatic CRPC. [a]ARPI in mCRPC, abiraterone, enzalutamide; [b]ARPI in mHSPC, apalutamide, enzalutamide, abiraterone; [c]PARPi, olaparib, rucaparib monotherapy approved after previous treatment with an ARPI; [d]triplet, ADT + docetaxel + darolutamide. The line of treatment in mCRPC is indicated in parentheses. ^{177}Lu–PSMA indicates Lutetium-177 prostate-specific membrane antigen; ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castrate-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PARPi, poly(adenosine diphosphate ribose) polymerase inhibitor.

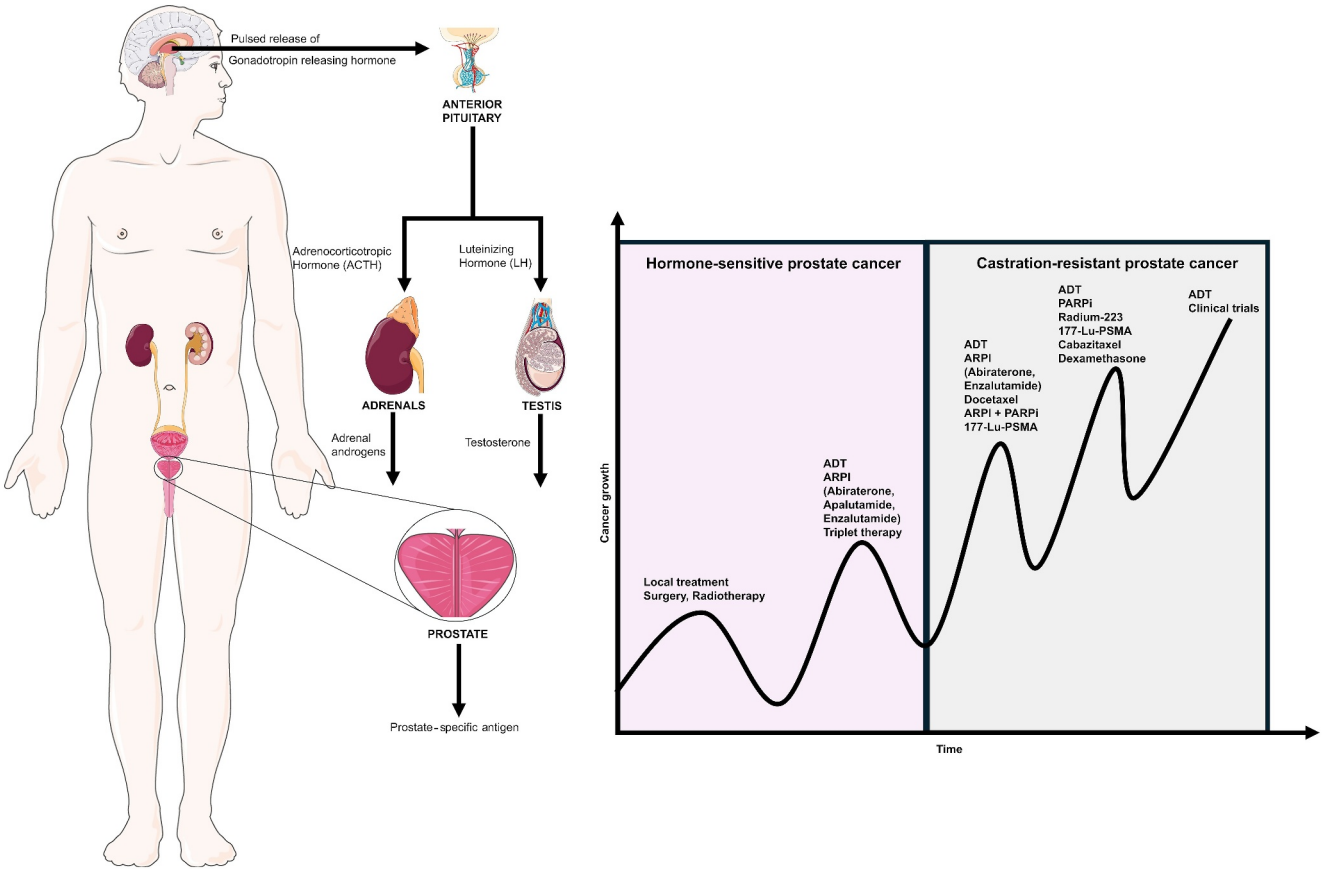

FIGURE 4 Landscape of the natural history of prostate cancer. ^{177}Lu–PSMA indicates Lutetium-177 prostate-specific membrane antigen; ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; PARPi, poly(adenosine diphosphate ribose) polymerase inhibitor. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

to individuals who have previously treated prostate cancer with a laboratory diagnosis of testosterone deficiency and a stable PSA after radiotherapy or an undetectable PSA after radical prostatectomy at least 6–12 months after primary treatment, but it should always be part of a shared decision-making process acknowledging that data are limited and the true risk or safety is unknown. Extreme caution should be exercised in those at high risk for relapse or progression. Those receiving ADT for metastatic disease, either in the hormone-sensitive or castration-resistant setting, should not be prescribed testosterone replacement.[451,452]

One in five individuals surviving five years after diagnosis report a fracture on ADT.[453] The use of additional anti-androgen therapies with ADT further increases the risk of fractures.[454] The use of a bisphosphonate reduces fracture risk in patients with M1 status, but not in those with M0 status,.[455] Zoledronic acid reduces the risk of skeletal complications and delays the time to first bone complication.[456,457] Denosumab, another bone-targeting agent, further reduces the chance of a bone complication compared with zoledronate.[458,459]

Individuals on lifelong ADT should receive calcium and Vitamin D supplementation, along with a bisphosphonate or regular dual-energy x-ray absorptiometry (DEXA) scans, with treatment as directed. Those who receive ADT for two to three years for high-risk localized disease should receive calcium/Vitamin D supplementation only. Short-term ADT for six months does not require additional supplementation. A complete dental evaluation and a completion of invasive dental procedures are recommended before initiating a bone-targeting agent. Those with a contraindication to a bisphosphonate should be monitored with dual-energy radiographic absorptiometry scans.

Individuals should be counseled to maintain a healthy weight for their height, avoid high-calorific food, avoid smoking, and limit alcohol consumption. They should engage in physical activity and weight-bearing exercises. A structured exercise program leads to improved muscular strength, cardiorespiratory fitness, and functional task performance; reduces fatigue; and helps to improve biomarkers for carbohydrate metabolism, thereby leading to weight loss.[460,461] Individuals should have access to mental health services and should be offered psychotherapy and pharmacotherapy, as appropriate. Couples should be encouraged to discuss sexual intimacy and should be offered counseling and support services, as needed. Screening for cardiovascular and metabolic diseases should follow usual recommendations (monitoring of blood pressure, lipids, and glucose).[462] The addition of metformin to ADT significantly improves metabolic parameters like hemoglobin A1c, fasting glucose, total and low-density-lipoprotein cholesterol and reduces weight gain and metabolic syndrome.[463]

FRAIL PATIENTS

Frailty is a multidimensional, complex state of diminished physical reserve resulting in decreased resilience and increased vulnerability to stressors. It is an important consideration in treating elderly patients with prostate cancer.[464] Estimating life expectancy, differentiating between chronologic and biologic age, and comprehensive geriatric and frailty assessments are recommended to screen and manage patients older than 70 years or those who have >5% weight loss because of chronic illness.[464–469] Management of prostate cancer in such patients should be tailored to their overall health status and personal preferences, with individuals deemed physically fit offered the same treatment options as their chronologically younger counterparts.[184] A key component in decision making to offer radical-intent treatment is a life expectancy >10 years; in most developed nations, this is reached at an age between 75 and 80 years in the absence of chronic comorbidities.[185,470]

Tailored treatment decisions with modifications in the usual standards of care are recommended, such as reducing the duration of ADT in those with competing comorbidities. Curative-intent radiotherapy can be offered to a dose of 57 Gy in 19 fractions in those aged 75 years and older, with biochemical control in >85% but with reduced long-term late bowel side effects.[229] Another option is weekly hypofractionated radiotherapy to a dose of 36 Gy in six fractions, extrapolated from the metastatic setting, to treat localized disease, with a five-year PFS rate >80%.[471]

ARPIs like abiraterone and enzalutamide can also be prescribed safely in older adults and dose-reduced where needed.[472,473] The use of Radium-223 is generally safe for frailer patients, with only minor differences for fracture risk observed beyond second-line treatment in CRPC compared with other treatment options.[474]

CONCLUSIONS

Prostate cancer encompasses a wide spectrum of clinical scenarios, ranging from low-risk disease, in which treatment can only harm and not extend life, to a fatal disease, which still claims too many lives globally. Appropriate risk stratification and individualized treatment are keys to good management. Emerging data and new therapies will continue to refine therapeutic paradigms and improve outcomes for individuals with prostate cancer.

ACKNOWLEDGMENTS

Alison Tree is supported by the Cancer Research UK Radiation Research Center of Excellence at the Institute of Cancer Research and The Royal Marsden National Health Service (NHS) Foundation Trust (Grants A28724 and RRCOER-Jun24/100006) and by a Cancer Research UK Program grant (Grant C33589/A28284). The Royal Marsden NHS Foundation Trust/Institute of Cancer Research receives research funding from Elekta as part of the Magnetic Resonance Linac Consortium. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

Aidan Adkins reports personal/consulting fees from Novartis; and support for other professional activities from Europa Uomo, Movember Foundation, Prostate Cancer Research, Prostate Cancer UK, and Tackle Prostate Cancer outside the submitted work. Amar Kishan reports grants/contracts from Janssen Biotech Inc. and Point Biopharma; personal/consulting fees from Boston Scientific Corporation, Janssen Biotech, Lantheus, and Varian Medical Systems Inc.; and stock ownership in Viewray Technologies Inc. outside the submitted work. Chris Parker reports personal/consulting fees from Blue Earth Therapeutics, Janssen Pharmaceuticals, and Novartis; and service on a Data and Safety Monitoring board for Telix outside the submitted work. Angela Pathmanathan reports grants/contracts and support for professional activities from Cancer Research UK; and support for other professional activities from Elekta, the Institute of Cancer Research, Janssen Pharmaceuticals, and Prostate Cancer UK outside the submitted work. Alison Reid reports personal/consulting fees/honoraria or travel assistance from Astellas Pharma, AstraZeneca UK Ltd., and Janssen Pharmaceuticals outside the submitted work. Oliver Sartor reports personal/consulting fees from Advanced Accelerator Applications, Amgen, ARTbio, Astellas Pharma, AstraZeneca AB, AstraZeneca Pharmaceuticals LP, Bavarian-Nordic, Bayer, Clarity Pharmaceuticals, Clovis Oncology Inc., Constellation Pharmaceuticals, Convergent Therapeutics Inc., Blue Earth Diagnostics Ltd., Bristol Myers Squibb, Daiichi Sankyo, Dendreon Pharmaceuticals LLC, EMD Serono, Endocyte, Exelixis, Fusion Pharmaceuticals, Genzyme Corporation, Hengrui Therapeutics AG, Invitae, Isotopen Technologien Meunchen, Janssen Biotech Inc., Janssen Scientific Affairs LLC, Merck, Morphimmune, Moyvant, Myriad Genetic Laboratories Inc., Noria Therapeutics, NorthStar, Novartis, Noxopharm, Pfizer, Point Biopharma, Progenics/Lantheus Medical, Progenics Pharmaceuticals Inc., Sanofi and Genzyme US Companies, Taiho Pharmaceutical, Telix Pharmaceuticals, Tempus, TeneBio, Tessa Therapeutics, and Theranostics outside the submitted work. Nicholas Van As reports grants/contracts, personal/consulting fees, and support for other professional activities from Accuray Inc. and Varian outside the submitted work. Jochen Walz reports grants/contracts from Exact Imaging; and personal/consulting and/or advisory fees/honoraria from A3P, AAA/Novartis, ANNA/C-TRUS, Astellas Pharma Europe, AstraZeneca, Bayer, Blue Earth Diagnostics, BXTA, Curium US LLC, Intuitive Surgical, Ipsen, Janssen Cilag EAME, Lightpoint Medical, Lucida, Telix, and Veracyte Inc. outside the submitted work. Alison Tree reports grants/contracts from Accuray Inc., Elekta, and Varian; honoraria or travel assistance from Accuray Inc., Bayer, and Janssen Cilag; a gift from Bayer; and travel support from Elekta outside the submitted work. The remaining authors disclosed no conflicts of interest.

ORCID

Deep Chakrabarti https://orcid.org/0000-0002-9511-6844
Alison Reid https://orcid.org/0000-0001-8567-4941
Jochen Walz https://orcid.org/0000-0002-1379-7608

REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263. doi:10.3322/caac.21834
2. Bray F, Colombet M, Aitken JF, et al., eds. *Cancer Incidence in Five Continents* Vol. XII (IARC CancerBase No. 19). International Agency for Research on Cancer; 2023. Accessed December 4, 2024, https://ci5.iarc.who.int/
3. Chen R, Ren S, Yiu MK, et al. Prostate cancer in Asia: a collaborative report. *Asian J Urol*. 2014;1:15-29. doi:10.1016/j.ajur.2014.08.007
4. Kimura T, Egawa S. Epidemiology of prostate cancer in Asian countries. *Int J Urol*. 2018;25(6):524-531. doi:10.1111/iju.13593
5. James ND, Tannock I, N'Dow J, et al. The Lancet Commission on prostate cancer: planning for the surge in cases. *Lancet*. 2024;403(10437):1683-1722. doi:10.1016/s0140-6736(24)00651-2
6. Crawford ED. Epidemiology of prostate cancer. *Urology*. 2003;62(6 suppl):3-12. doi:10.1016/j.urology.2003.10.013
7. Rebello RJ, Oing C, Knudsen KE, et al. Prostate cancer. *Nat Rev Dis Primers*. 2021;7(1):9. doi:10.1038/s41572-020-00243-0
8. World Cancer Research Fund. *Prostate cancer*. World Cancer Research Fund; 2024. Accessed December 4, 2024. https://www.wcrf.org/diet-activity-and-cancer/cancer-types/prostate-cancer/
9. Huncharek M, Haddock KS, Reid R, Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health*. 2010;100(4):693-701. doi:10.2105/ajph.2008.150508
10. Salem S, Salahi M, Mohseni M, et al. Major dietary factors and prostate cancer risk: a prospective multicenter case-control study. *Nutr Cancer*. 2010;63(1):21-27. doi:10.1080/01635581.2010.516875
11. Hurst R, Hooper L, Norat T, et al. Selenium and prostate cancer: systematic review and meta-analysis. *Am J Clin Nutr*. 2012;96(1):111-122. doi:10.3945/ajcn.111.033373
12. Aune D, Navarro Rosenblatt DA, Chan DS, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. *Am J Clin Nutr*. 2015;101(1):87-117. doi:10.3945/ajcn.113.067157
13. Lachance G, Robitaille K, Laaraj J, et al. The gut microbiome-prostate cancer crosstalk is modulated by dietary polyunsaturated long-chain fatty acids. *Nat Commun*. 2024;15(1):3431. doi:10.1038/s41467-024-45332-w
14. Fujita K, Matsushita M, De Velasco MA, et al. The gut-prostate axis: a new perspective of prostate cancer biology through the gut microbiome. *Cancers (Basel)*. 2023;15(5):1375. doi:10.3390/cancers15051375
15. Colldén H, Landin A, Wallenius V, et al. The gut microbiota is a major regulator of androgen metabolism in intestinal contents. *Am J Physiol Endocrinol Metab*. 2019;317(6):E1182-E1192. doi:10.1152/ajpendo.00338.2019
16. Pernigoni N, Zagato E, Calcinotto A, et al. Commensal bacteria promote endocrine resistance in prostate cancer through androgen biosynthesis. *Science*. 2021;374(6564):216-224. doi:10.1126/science.abf8403
17. Rebbeck TR, Devesa SS, Chang BL, et al. Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of African descent. *Prostate Cancer*. 2013;2013:560857. doi:10.1155/2013/560857
18. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. *Eur Urol*. 2020;77(1):38-52. doi:10.1016/j.eururo.2019.08.005
19. Watts EL, Appleby PN, Perez-Cornago A, et al. Low free testosterone and prostate cancer risk: a collaborative analysis of 20 prospective studies. *Eur Urol*. 2018;74(5):585-594. doi:10.1016/j.eururo.2018.07.024
20. Haider A, Zitzmann M, Doros G, Isbarn H, Hammerer P, Yassin A. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. *J Urol*. 2015;193(1):80-86. doi:10.1016/j.juro.2014.06.071
21. Rider JR, Wilson KM, Sinnott JA, Kelly RS, Mucci LA, Giovannucci EL. Ejaculation frequency and risk of prostate cancer: updated results with an additional decade of follow-up. *Eur Urol*. 2016;70(6):974-982. doi:10.1016/j.eururo.2016.03.027
22. Hemminki K. Familial risk and familial survival in prostate cancer. *World J Urol*. 2012;30(2):143-148. doi:10.1007/s00345-011-0801-1
23. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA*. 2016;315(1):68. doi:10.1001/jama.2015.17703
24. Tan DSW, Mok TSK, Rebbeck TR. Cancer genomics: diversity and disparity across ethnicity and geography. *J Clin Oncol*. 2016;34(1):91-101. doi:10.1200/jco.2015.62.0096
25. Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk. *BJU Int*. 2003;91(9):789-794. doi:10.1046/j.1464-410x.2003.04232.x
26. Stewart RW, Lizama S, Peairs K, Sateia HF, Choi Y. Screening for prostate cancer. *Semin Oncol*. 2017;44(1):47-56. doi:10.1053/j.seminoncol.2017.02.001
27. Mottet N, vanden Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2021;79(2):243-262. doi:10.1016/j.eururo.2020.09.042
28. Verze P, Cai T, Lorenzetti S. The role of the prostate in male fertility, health and disease. *Nat Rev Urol*. 2016;13(7):379-386. doi:10.1038/nrurol.2016.89
29. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443-453. doi:10.1056/nejmoa1603144
30. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol*. 2019;5(4):523-528. doi:10.1001/jamaoncol.2018.6760
31. Pritchard CC, Offit K, Nelson PS. DNA-repair gene mutations in metastatic prostate cancer. *N Engl J Med*. 2016;375(18):1802-1805. doi:10.1056/nejmc1611147
32. Ewing CM, Ray AM, Lange EM, et al. Germline mutations in *HOXB13* and prostate-cancer risk. *N Engl J Med*. 2012;366(2):141-149. doi:10.1056/nejmoa1110000
33. Karlsson R, Aly M, Clements M, et al. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. *Eur Urol*. 2014;65(1):169-176. doi:10.1016/j.eururo.2012.07.027
34. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, et al. Prevalence of theHOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. *Ann Oncol*. 2015;26(4):756-761. doi:10.1093/annonc/mdv004
35. Lynch HT, Kosoko-Lasaki O, Leslie SW, et al. Screening for familial and hereditary prostate cancer. *Int J Cancer*. 2016;138(11):2579-2591. doi:10.1002/ijc.29949
36. Ni Raghallaigh H, Eeles R. Genetic predisposition to prostate cancer: an update. *Fam Cancer*. 2022;21(1):101-114. doi:10.1007/s10689-021-00227-3

37. David MK, Leslie SW. *Prostate-Specific Antigen*. StatPearls Publishing; 2024.
38. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Urology Group. *Cochrane Database Syst Rev*. 2013;2013(1):CD004720. doi:10.1002/14651858.cd004720.pub3
39. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med*. 1987;317(15):909-916. doi:10.1056/nejm198710083171501
40. Martin RM, Donovan JL, Turner EL, et al. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. *JAMA*. 2018;319(9):883. doi:10.1001/jama.2018.0154
41. Martin RM, Turner EL, Young GJ, et al. Prostate-specific antigen screening and 15-year prostate cancer mortality: a secondary analysis of the CAP randomized clinical trial. *JAMA*. 2024;331(17):1460. doi:10.1001/jama.2024.4011
42. Andriole GL, Crawford ED, Grubb RL, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360(13):1310-1319. doi:10.1056/nejmoa0810696
43. Andriole GL, Crawford ED, Grubb RL, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104(2):125-132. doi:10.1093/jnci/djr500
44. Kovac E, Carlsson SV, Lilja H, et al. Association of baseline prostate-specific antigen level with long-term diagnosis of clinically significant prostate cancer among patients aged 55 to 60 years: a secondary analysis of a cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *JAMA Netw Open*. 2020;3(1):e1919284. doi:10.1001/jamanetworkopen.2019.19284
45. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360(13):1320-1328. doi:10.1056/nejmoa0810084
46. Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med*. 2012;366:981-990. doi:10.1056/nejmoa1113135
47. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384(9959):2027-2035. doi:10.1016/s0140-6736(14)60525-0
48. Hugosson J, Roobol MJ, Månsson M, et al. A 16-yr follow-up of the European Randomized Study of Screening for Prostate Cancer. *Eur Urol*. 2019;76(1):43-51. doi:10.1016/j.eururo.2019.02.009
49. Auvinen A, Moss SM, Tammela TLJ, et al. Absolute effect of prostate cancer screening: balance of benefits and harms by center within the European Randomized Study of Prostate Cancer Screening. *Clin Cancer Res*. 2016;22(1):243-249. doi:10.1158/1078-0432.ccr-15-0941
50. Frånlund M, Månsson M, Godtman RA, et al. Results from 22 years of follow-up in the Goteborg randomized population-based prostate cancer screening trial. *J Urol*. 2022;208(2):292-300. doi:10.1097/ju.0000000000002696
51. Macefield RC, Macefield RC, Metcalfe C, et al. Impact of prostate cancer testing: an evaluation of the emotional consequences of a negative biopsy result. *Br J Cancer*. 2010;102(9):1335-1340. doi:10.1038/sj.bjc.6605648
52. Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. *JAMA*. 2014;311(11):1143. doi:10.1001/jama.2014.2085
53. 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
54. Eklund M, Nordström T, Aly M, et al. The Stockholm-3 (STHLM3) model can improve prostate cancer diagnostics in men aged 50–69 yr compared with current prostate cancer testing. *Eur Urol Focus*. 2018;4(5):707-710. doi:10.1016/j.euf.2016.10.009
55. Eldred-Evans D, Burak P, Connor MJ, et al. Population-based prostate cancer screening with magnetic resonance imaging or ultrasonography: the IP1-PROSTAGRAM study. *JAMA Oncol*. 2021;7(3):395-402. doi:10.1001/jamaoncol.2020.7456
56. Hugosson J, Månsson M, Wallström J, et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. *N Engl J Med*. 2022;387(23):2126-2137. doi:10.1056/nejmoa2209454
57. Hugosson J, Godtman RA, Wallstrom J, et al. Results after four years of screening for prostate cancer with PSA and MRI. *N Engl J Med*. 2024;391(12):1083-1095. doi:10.1056/nejmoa2406050
58. European Council. *Council updates its recommendation to screen for cancer [press release]*. European Council; December 9, 2022.
59. European Association of Urology (EAU). *PRAISE-U. Smart Early Detection of Prostate Cancer*. EAU; 2024. Accessed December 4, 2024. https://uroweb.org/praise-u
60. Bratt O, Godtman RA, Jiborn T, et al. Population-based organised prostate cancer testing: results from the first invitation of 50-year-old men. *Eur Urol*. 2024;85(3):207-214. doi:10.1016/j.eururo.2023.11.013
61. Beebe-Dimmer JL, Kapron AL, Fraser AM, Smith KR, Cooney KA. Risk of prostate cancer associated with familial and hereditary cancer syndromes. *J Clin Oncol*. 2020;38(16):1807-1813. doi:10.1200/jco.19.02808
62. Nyberg T, Frost D, Barrowdale D, et al. Prostate cancer risks for male BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Eur Urol*. 2020;77(1):24-35. doi:10.1016/j.eururo.2019.08.025
63. Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. *Eur Urol*. 2019;76(6):831-842. doi:10.1016/j.eururo.2019.08.019
64. Bancroft EK, Page EC, Brook MN, et al. A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. *Lancet Oncol*. 2021;22(11):1618-1631. doi:10.1016/s1470-2045(21)00522-2
65. Benafif S, Ni Raghallaigh H, McGrowder E, et al. The BARCODE1 pilot: a feasibility study of using germline single nucleotide polymorphisms to target prostate cancer screening. *BJU Int*. 2022;129(3):325-336. doi:10.1111/bju.15535
66. Eeles RA, Bancroft EK, McHugh JK, et al. Effect of polygenic risk score for clinically significant prostate cancer in a screening program: the BARCODE 1 study results [abstract]. *J Clin Oncol*. 2024;42(16 suppl):10500. doi:10.1200/jco.2024.42.16_suppl.10500
67. Moghul M, Tran A, Croft F, et al. The Man Van: a pilot study of using mobile targeted case-finding to address health inequalities in prostate cancer. *Int J Cancer*. 2024;155(12):2246-2252. doi:10.1002/ijc.35169
68. Burki T. Prostate Cancer UK launches the TRANSFORM trial. *Lancet*. 2024;403(10438):1738. doi:10.1016/s0140-6736(24)00912-7
69. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2019;69(3):184-210. doi:10.3322/caac.21557
70. Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin*. 2010;60(2):70-98. doi:10.3322/caac.20066
71. American Cancer Society (ACS). *American Cancer Society Recommendations for Prostate Cancer Early Detection*. ACS; 2023. Accessed

December 4, 2024. https://www.cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/acs-recommendations.html
72. Wei JT, Barocas D, Carlsson S, et al. Early detection of prostate cancer: AUA/SUO guideline part I: prostate cancer screening. *J Urol*. 2023;210(1):46-53. doi:10.1097/ju.0000000000003491
73. Tikkinen KAO, Dahm P, Lytvyn L, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ*. 2018;362:k3581. doi:10.1136/bmj.k3581
74. Grossman DC, Grossman DC, Curry SJ, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901. doi:10.1001/jama.2018.3710
75. Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(9):1119-1134. doi:10.1016/j.annonc.2020.06.011
76. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer—2024 update. Part I: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2024;86(2):148-163. doi:10.1016/j.eururo.2024.03.027
77. Denijs FB, Van Harten MJ, Meenderink JJL, et al. Risk calculators for the detection of prostate cancer: a systematic review. *Prostate Cancer Prostatic Dis*. 2024;27(3):544-557. doi:10.1038/s41391-024-00852-w
78. Anger CM, Stallworth JL, Rais-Bahrami S. Integrating risk calculators into routine clinical workflow for the detection of prostate cancer: next steps to achieve widespread adoption. *Prostate Cancer Prostatic Dis*. 2024;27(3):365-366. doi:10.1038/s41391-024-00859-3
79. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. *Genes Dev*. 2018;32(17-18):1105-1140. doi:10.1101/gad.315739.118
80. Parnham A, Serefoglu EC. Retrograde ejaculation, painful ejaculation and hematospermia. *Transl Androl Urol*. 2016;5(4):592-601. doi:10.21037/tau.2016.06.05
81. Suzman DL, Boikos SA, Carducci MA. Bone-targeting agents in prostate cancer. *Cancer Metastasis Rev*. 2014;33(2-3):619-628. doi:10.1007/s10555-013-9480-2
82. Nam RK, Toi A, Klotz LH, et al. Assessing individual risk for prostate cancer. *J Clin Oncol*. 2007;25(24):3582-3588. doi:10.1200/jco.2007.10.6450
83. Kirby M, Merriel SW, Olajide O, et al. Is the digital rectal exam any good as a prostate cancer screening test? *Br J Gen Pract*. 2024;74(740):137-139. doi:10.3399/bjgp24x736677
84. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med*. 2018;378(19):1767-1777. doi:10.1056/nejmoa1801993
85. Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol*. 2019;20(1):100-109. doi:10.1016/s1470-2045(18)30569-2
86. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 2017;389(10071):815-822. doi:10.1016/s0140-6736(16)32401-1
87. Drost FJH, Osses D, Nieboer D, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. *Eur Urol*. 2020;77(1):78-94. doi:10.1016/j.eururo.2019.06.023
88. van Der Leest M, Cornel E, Israël B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naive men with elevated prostate-specific antigen: a large prospective multicenter clinical study. *Eur Urol*. 2019;75:570-578. doi:10.1016/eururo.2018.11.023
89. Faria R, Soares MO, Spackman E, et al. Optimising the diagnosis of prostate cancer in the era of multiparametric magnetic resonance imaging: a cost-effectiveness analysis based on the Prostate MR Imaging Study (PROMIS). *Eur Urol*. 2018;73(1):23-30. doi:10.1016/j.eururo.2017.08.018
90. Marenco J, Orczyk C, Collins T, Moore C, Emberton M. Role of MRI in planning radical prostatectomy: what is the added value? *World J Urol*. 2019;37(7):1289-1292. doi:10.1007/s00345-019-02762-2
91. Baack Kukreja J, Bathala TK, Reichard CA, et al. Impact of preoperative prostate magnetic resonance imaging on the surgical management of high-risk prostate cancer. *Prostate Cancer Prostatic Dis*. 2020;23(1):172-178. doi:10.1038/s41391-019-0171-0
92. De Rooij M, Hamoen EHJ, Witjes JA, Barentsz JO, Rovers MM. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. *Eur Urol*. 2016;70(2):233-245. doi:10.1016/j.eururo.2015.07.029
93. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours. *Eur Urol*. 2016;70(1):106-119. doi:10.1016/j.eururo.2016.02.028
94. Van Leenders GJLH, Van Der Kwast TH, Grignon DJ, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2020;44(8):e87-e99. doi:10.1097/pas.0000000000001497
95. Smith SC, Gandhi JS, Moch H, et al. Similarities and differences in the 2019 ISUP and GUPS recommendations on prostate cancer grading: a guide for practicing pathologists. *Adv Anat Pathol*. 2021;28:1-7. doi:10.1097/pap.0000000000000287
96. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Rep*. 1996;50:125-128.
97. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int*. 2013;111(5):753-760. doi:10.1111/j.1464-410x.2012.11611.x
98. Gordetsky J, Epstein J. Grading of prostatic adenocarcinoma: current state and prognostic implications. *Diagn Pathol*. 2016;11(1):25. doi:10.1186/s13000-016-0478-2
99. Short E, Warren AY, Varma M. Gleason grading of prostate cancer: a pragmatic approach. *Diagn Histopathol*. 2019;25(10):371-378. doi:10.1016/j.mpdhp.2019.07.001
100. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol*. 2016;40(2):244-252. doi:10.1097/pas.0000000000000530
101. Basourakos SP, Tzeng M, Lewicki PJ, et al. Tissue-based biomarkers for the risk stratification of men with clinically localized prostate cancer. *Front Oncol*. 2021;11:676716. doi:10.3389/fonc.2021.676716
102. Murray TBJ. The pathogenesis of prostate cancer. In: Bott SRJ, Ng KL, eds. *Prostate Cancer*. Exon Publications; 2021:29-42.
103. Humphrey PA. Histological variants of prostatic carcinoma and their significance. *Histopathology*. 2012;60(1):59-74. doi:10.1111/j.1365-2559.2011.04039.x
104. Epstein JI, Woodruff JM. Adenocarcinoma of the prostate with endometrioid features. A light microscopic and immunohistochemical study of ten cases. *Cancer*. 1986;57(1):111-119. doi:10.1002/1097-0142(19860101)57:1<111::aid-cncr2820570123>3.0.co;2-n
105. Shehabeldin AN, Ro JY. Neuroendocrine tumors of genitourinary tract: recent advances. *Ann Diagn Pathol*. 2019;42:48-58. doi:10.1016/j.anndiagpath.2019.06.009

106. Mishra S, Goel H, Awasthi N, Puri A, Mahapatra R, Pal DK. Primary adenosquamous carcinoma of the prostate: a rare aggressive tumor. *Clin Genitourin Cancer*. 2014;12(1):e29-e31. doi:10.1016/j.clgc.2013.08.006
107. Ellis CL, Epstein JI. Metastatic prostate adenocarcinoma to the penis: a series of 29 cases with predilection for ductal adenocarcinoma. *Am J Surg Pathol*. 2015;39(1):67-74. doi:10.1097/pas.0000000000000289
108. Accetta PA, Gardner WA. Adenosquamous carcinoma of prostate. *Urology*. 1983;22(1):73-75. doi:10.1016/0090-4295(83)90355-2
109. Wang J, Wang FW, LaGrange CA, Hemstreet GP. Clinical features and outcomes of 25 patients with primary adenosquamous cell carcinoma of the prostate. *Rare Tumors*. 2010;2(3):130-134. doi:10.4081/rt.2010.e47
110. Al-Qassim Z, Mohammed A, Payne D, Stocks PJ, Khan Z. Squamous cell carcinoma of the prostate following treatment with an LHRH-agonist: a rare case of transformation of adenocarcinoma of the prostate. *Cent European J Urol*. 2014;67(1):26-28. doi:10.5173/ceju.2014.01.art5
111. Alanee S, Moore A, Nutt M, et al. Contemporary incidence and mortality rates of neuroendocrine prostate cancer. *Anticancer Res*. 2015;35:4145-4150.
112. Wang HT, Yao YH, Li BG, Tang Y, Chang JW, Zhang J. Neuroendocrine prostate cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from NEPC diagnosis—a systematic review and pooled analysis. *J Clin Oncol*. 2014;32(30):3383-3390. doi:10.1200/jco.2013.54.3553
113. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.1*. 2024. Accessed December 4, 2024. https://www.nccn.org/
114. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280(11):969. doi:10.1001/jama.280.11.969
115. Tward JD, Huang HC, Esteva A, et al. Prostate cancer risk stratification in NRG Oncology phase III randomized trials using multimodal deep learning with digital histopathology. *JCO Precis Oncol*. 2024(8):e2400145. doi:10.1200/po.24.00145
116. Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment Score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J Urol*. 2005;173(6):1938-1942. doi:10.1097/01.ju.0000158155.33890.e7
117. Healthcare Quality Improvement Partnership (HQIP). Using the Cambridge Prognostic Groups for risk stratification of prostate cancer in the National Prostate Cancer Audit: how could it impact our estimates of potential 'over-treatment. HQIP; 2021. Accessed December 4, 2024. https://www.npca.org.uk/wp-content/uploads/2021/02/NPCA-Short-Report-2021_Using-the-CPG-in-the-NPCA_Final-11.02.21.pdf
118. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: a straightforward tool for improved prediction of outcomes after radical prostatectomy. *Cancer*. 2011;117(22):5039-5046. doi:10.1002/cncr.26169
119. McKay RR, Feng FY, Wang AY, Wallis CJD, Moses KA. Recent advances in the management of high-risk localized prostate cancer: local therapy, systemic therapy, and biomarkers to guide treatment decisions. *Am Soc Clin Oncol Educ Book*. 2020;40:e241-e252. doi:10.1200/EDBK_279459
120. Kattan MW, Eastham JA, Stapleton AMF, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst*. 1998;90(10):766-771. doi:10.1093/jnci/90.10.766
121. Van den Broeck T, Moris L, Gevaert T, et al. Validation of the Decipher test for predicting distant metastatic recurrence in men with high-risk nonmetastatic prostate cancer 10 years after surgery. *Eur Urol Oncol*. 2019;2(5):589-596. doi:10.1016/j.euo.2018.12.007
122. Parry MG, Cowling TE, Sujenthiran A, et al. Risk stratification for prostate cancer management: value of the Cambridge Prognostic Group classification for assessing treatment allocation. *BMC Med*. 2020;18(1):114. doi:10.1186/s12916-020-01588-9
123. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA–PET in prostate cancer management. *Nat Rev Urol*. 2016;13(4):226-235. doi:10.1038/nrurol.2016.26
124. Williams S. Molecular imaging of newly diagnosed prostate cancer. *Cancer J*. 2020;26(1):43-47. doi:10.1097/ppo.0000000000000427
125. Eiber M, Fendler WP, Rowe SP, et al. Prostate-specific membrane antigen ligands for imaging and therapy. *J Nucl Med*. 2017;58(suppl 2):67S-76S. doi:10.2967/jnumed.116.186767
126. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet*. 2020;395(10231):1208-1216. doi:10.1016/s0140-6736(20)30314-7
127. Corfield J, Perera M, Bolton D, Lawrentschuk N. 68Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. *World J Urol*. 2018;36(4):519-527. doi:10.1007/s00345-018-2182-1
128. Von Eyben FE, Kairemo K. Meta-analysis of 11C-choline and 18F-choline PET/CT for management of patients with prostate cancer. *Nucl Med Commun*. 2014;35(3):221-230. doi:10.1097/mnm.0000000000000040
129. Hofman MS, Kasivisvanathan V, Link E, et al. Baseline nodal status on 68Ga-PSMA-11 positron emission tomography/computed tomography in men with intermediate- to high-risk prostate cancer is prognostic for treatment failure: follow-up of the proPSMA trial. *Eur Urol Oncol*. Published online November 28, 2024. doi:10.1016/j.euo.2024.11.006
130. Nakanishi K, Tanaka J, Nakaya Y, et al. Whole-body MRI: detecting bone metastases from prostate cancer. *Jpn J Radiol*. 2022;40(3):229-244. doi:10.1007/s11604-021-01205-6
131. Winfield JM, Blackledge MD, Tunariu N, Koh DM, Messiou C. Whole-body MRI: a practical guide for imaging patients with malignant bone disease. *Clin Radiol*. 2021;76(10):715-727. doi:10.1016/j.crad.2021.04.001
132. De Feria CRE, Hofman MS, Segard T, et al. Is prostate-specific membrane antigen positron emission tomography/computed tomography imaging cost-effective in prostate cancer: an analysis informed by the proPSMA trial. *Eur Urol*. 2021;79(3):413-418. doi:10.1016/j.eururo.2020.11.043
133. Vapiwala N, Hofman MS, Murphy DG, Williams S, Sweeney C. Strategies for evaluation of novel imaging in prostate cancer: putting the horse back before the cart. *J Clin Oncol*. 2019;37(10):765-769. doi:10.1200/jco.18.01927
134. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746. doi:10.1056/nejmoa1503747
135. Barbato F, Fendler WP, Rauscher I, et al. PSMA PET for the assessment of metastatic hormone-sensitive prostate cancer volume of disease. *J Nucl Med*. 2021;62(12):1747-1750. doi:10.2967/jnumed.121.262120
136. Weiner AB, Agrawal R, Valle LF, et al. Impact of PSMA PET on prostate cancer management. *Curr Treat Options Oncol*. 2024;25(2):191-205. doi:10.1007/s11864-024-01181-9

137. Chow KM, So WZ, Lee HJ, et al. Head-to-head comparison of the diagnostic accuracy of prostate-specific membrane antigen positron emission tomography and conventional imaging modalities for initial staging of intermediate- to high-risk prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2023;84(1):36-48. doi:10.1016/j.eururo.2023.03.001
138. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99. doi:10.3322/caac.21388
139. Buyyounouski MK, Choyke PL, McKenney JK, et al. Prostate cancer—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(3):245-253. doi:10.3322/caac.21391
140. Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, part I: introduction, risk assessment, staging, and risk-based management. *J Urol*. 2022;208(1):10-18. doi:10.1097/ju.0000000000002757
141. European Association of Urology (EAU). *EAU Guidelines on Prostate Cancer*. EAU; 2024. Accessed December 4, 2024. https://uroweb.org/guidelines/prostate-cancer
142. Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol*. 2004;5(2):101-106. doi:10.1016/s1470-2045(04)01384-1
143. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med*. 1994;330(4):242-248. doi:10.1056/nejm199401273300403
144. Johansson JE. Expectant management of early stage prostatic cancer: Swedish experience. *J Urol*. 1994;152(5 pt 2):1753-1756. doi:10.1016/s0022-5347(17)32378-9
145. Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet*. 1997;349(9056):906-910. doi:10.1016/s0140-6736(96)09380-4
146. Adolfsson J, Steineck G, Hedlund PO. Deferred treatment of clinically localized low-grade prostate cancer: actual 10-year and projected 15-year follow-up of the Karolinska series. *Urology*. 1997;50(5):722-726. doi:10.1016/s0090-4295(97)00320-8
147. Albertsen PC, Hanley AJ, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA*. 1998;280(11):975-980. doi:10.1001/jama.280.11.975
148. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA*. 1994;271(5):368-374. doi:10.1001/jama.1994.03510290050036
149. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol*. 2002;167(4):1664-1669. doi:10.1016/s0022-5347(05)65174-9
150. Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. *J Urol*. 2002;167(3):1231-1234. doi:10.1016/s0022-5347(05)65271-8
151. Patel MI, DeConcini DT, Lopez-Corona E, Ohori M, Wheeler T, Scardino PT. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. *J Urol*. 2004;171(4):1520-1524. doi:10.1097/01.ju.0000118224.54949.78
152. van den Bergh RCN, Roemeling S, Roobol MJ, Roobol W, Schröder FH, Bangma CH. Prospective validation of active surveillance in prostate cancer: the PRIAS study. *Eur Urol*. 2007;52(6):1560-1563. doi:10.1016/j.eururo.2007.05.011
153. Van As NJ, Parker CC. Active surveillance with selective radical treatment for localized prostate cancer. *Cancer J*. 2007;13(5):289-294. doi:10.1097/ppo.0b013e318156ff65
154. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer*. 2008;112(12):2664-2670. doi:10.1002/cncr.23502
155. Newcomb LF, Brooks JD, Carroll PR, et al. Canary prostate active surveillance study: design of a multi-institutional active surveillance cohort and biorepository. *Urology*. 2010;75(2):407-413. doi:10.1016/j.urology.2009.05.050
156. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011;364(18):1708-1717. doi:10.1056/nejmoa1011967
157. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012;367(3):203-213. doi:10.1056/nejmoa1113162
158. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424. doi:10.1056/nejmoa1606220
159. Simpkin AJ, Tilling K, Martin RM, et al. Systematic review and meta-analysis of factors determining change to radical treatment in active surveillance for localized prostate cancer. *Eur Urol*. 2015;67(6):993-1005. doi:10.1016/j.eururo.2015.01.004
160. Holmberg L, Garmo H, Andersson SO, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*. 2024;391(14):1362-1364. doi:10.1056/nejmc2406108
161. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*. 2014;370(10):932-942. doi:10.1056/nejmoa1311593
162. Wilt TJ, Vo TN, Langsetmo L, et al. Radical prostatectomy or observation for clinically localized prostate cancer: extended follow-up of the Prostate Cancer Intervention Versus Observation Trial (PIVOT). *Eur Urol*. 2020;77(6):713-724. doi:10.1016/j.eururo.2020.02.009
163. Hamdy FC, Donovan JL, Lane JA, et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med*. 2023;388(17):1547-1558. doi:10.1056/nejmoa2214122
164. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med*. 2016;375(15):1425-1437. doi:10.1056/nejmoa1606221
165. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes 12 years after localized prostate cancer treatment. *NEJM Evid*. 2023;2(4):EVIDoa2300018. doi:10.1056/evidoa2300018
166. Tosoian JJ, Mamawala M, Epstein JI, et al. Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort. *Eur Urol*. 2020;77(6):675-682. doi:10.1016/j.eururo.2019.12.017
167. Newcomb LF, Schenk JM, Zheng Y, et al. Long-term outcomes in patients using protocol-directed active surveillance for prostate cancer. *JAMA*. 2024;331(24):2084. doi:10.1001/jama.2024.6695
168. Tanne JH. Low risk prostate cancer: active surveillance does not increase unfavourable outcomes, study finds. *BMJ*. 2024;385:q1213. doi:10.1136/bmj.q1213
169. Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging-based active surveillance for prostate cancer: a large cohort study. *Eur Urol*. 2020;78(3):443-451. doi:10.1016/j.eururo.2020.03.035
170. Loeb S, Bruinsma SM, Nicholson J, et al. Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. *Eur Urol*. 2015;67(4):619-626. doi:10.1016/j.eururo.2014.10.010
171. Ng MK, Van As N, Thomas K, et al. Prostate-specific antigen (PSA) kinetics in untreated, localized prostate cancer: PSA velocity vs PSA doubling time. *BJU Int*. 2009;103(7):872-876. doi:10.1111/j.1464-410x.2008.08116.x
172. Iremashvili V, Manoharan M, Lokeshwar SD, Rosenberg DL, Pan D, Soloway MS. Comprehensive analysis of post-diagnostic prostate-

specific antigen kinetics as predictor of a prostate cancer progression in active surveillance patients. *BJU Int*. 2013;111(3):396-403. doi:10.1111/j.1464-410x.2012.11295.x
173. Whitson JM, Porten SP, Hilton JF, et al. The relationship between prostate specific antigen change and biopsy progression in patients on active surveillance for prostate cancer. *J Urol*. 2011;185(5):1656-1660. doi:10.1016/j.juro.2010.12.042
174. Thomsen FB, Brasso K, Berg KD, et al. Association between PSA kinetics and cancer-specific mortality in patients with localised prostate cancer: analysis of the placebo arm of the SPCG-6 study. *Ann Oncol*. 2016;27(3):460-466. doi:10.1093/annonc/mdv607
175. Kovac E, Vertosick EA, Sjoberg DD, Vickers AJ, Stephenson AJ. Effects of pathological upstaging or upgrading on metastasis and cancer-specific mortality in men with clinical low-risk prostate cancer. *BJU Int*. 2018;122(6):1003-1009. doi:10.1111/bju.14418
176. Gaffney CD, Tin AL, Fainberg J, et al. The oncologic risk of magnetic resonance imaging-targeted and systematic cores in patients treated with radical prostatectomy. *Cancer*. 2023;129(23):3790-3796. doi:10.1002/cncr.34981
177. Eastham JA, Boorjian SA, Kirkby E. Clinically localized prostate cancer: AUA/ASTRO guideline. *J Urol*. 2022;208(1):10-18. doi:10.1097/JU.0000000000002854
178. National Institute for Health and Care Excellence (NICE). *Prostate cancer: diagnosis and management*. NICE; 2021. Accessed December 4, 2024. https://www.nice.org.uk/guidance/ng131
179. Lam TBL, MacLennan S, Willemse PPM, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (DETECTIVE study). *Eur Urol*. 2019;76(6):790-813. doi:10.1016/j.eururo.2019.09.020
180. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. *N Engl J Med*. 2018;379(24):2319-2329. doi:10.1056/nejmoa1807801
181. Walz J, Joniau S, Chun FK, et al. Pathological results and rates of treatment failure in high-risk prostate cancer patients after radical prostatectomy. *BJU Int*. 2011;107(5):765-770. doi:10.1111/j.1464-410x.2010.09594.x
182. Spahn M, Joniau S, Gontero P, et al. Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. *Eur Urol*. 2010;58:1-7. doi:10.1016/j.eururo.2010.03.001
183. Boyle HJ, Alibhai S, Decoster L, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. *Eur J Cancer*. 2019;116:116-136. doi:10.1016/j.ejca.2019.04.031
184. Droz JP, Albrand G, Gillessen S, et al. Management of prostate cancer in elderly patients: recommendations of a task force of the International Society of Geriatric Oncology. *Eur Urol*. 2017;72(4):521-531. doi:10.1016/j.eururo.2016.12.025
185. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol*. 2011;29(10):1335-1341. doi:10.1200/jco.2010.31.2330
186. Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. *BMJ*. 2011;343:d6553. doi:10.1136/bmj.d6553
187. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8
188. Steuber T, Graefen M, Haese A, et al. Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. *J Urol*. 2006;175(3):939-944. doi:10.1016/s0022-5347(05)00342-3
189. Walz J, Epstein JI, Ganzer R, et al. A critical analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: an update. *Eur Urol*. 2016;70(2):301-311. doi:10.1016/j.eururo.2016.01.026
190. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. *N Engl J Med*. 2002;346(15):1138-1144. doi:10.1056/nejmsa011788
191. Gershman B, Meier SK, Jeffery MM, et al. Redefining and contextualizing the hospital volume-outcome relationship for robot-assisted radical prostatectomy: implications for centralization of care. *J Urol*. 2017;198(1):92-99. doi:10.1016/j.juro.2017.01.067
192. Ramsay C, Pickard R, Robertson C, et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. *Health Technol Assess*. 2012;16(41):1-313. doi:10.3310/hta16410
193. Coughlin GD, Yaxley JW, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. *Lancet Oncol*. 2018;19(8):1051-1060. doi:10.1016/s1470-2045(18)30357-7
194. Schraudenbach P, Bermejo CE. Management of the complications of radical prostatectomy. *Curr Urol Rep*. 2007;8(3):197-202. doi:10.1007/s11934-007-0006-8
195. Haglind E, Carlsson S, Stranne J, et al. Urinary incontinence and erectile dysfunction after robotic versus open radical prostatectomy: a prospective, controlled, nonrandomised trial. *Eur Urol*. 2015;68(2):216-225. doi:10.1016/j.eururo.2015.02.029
196. van As N, Yasar B, Griffin C, et al. Radical prostatectomy versus stereotactic radiotherapy for clinically localised prostate cancer: results of the PACE-A randomised trial. *Eur Urol*. 2024;86(6):566-576. doi:10.1016/j.eururo.2024.08.030
197. Bridge J, Labban M, Cole AP, et al. Urinary and sexual impact of robotic radical prostatectomy: reporting of patient-reported outcome measures in the first year after radical prostatectomy in a contemporary multicentre cohort in the United Kingdom. *Eur Urol Open Sci*. 2024;64:11-21. doi:10.1016/j.euros.2024.05.003
198. Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. *Eur Urol*. 2012;62(3):405-417. doi:10.1016/j.eururo.2012.05.045
199. Weldon VE, Tavel FR, Neuwirth H. Continence, potency and morbidity after radical perineal prostatectomy. *J Urol*. 1997;158(4):1470-1475. doi:10.1016/s0022-5347(01)64245-9
200. Touijer KA, Vertosick EA, Sjoberg DD, et al. Pelvic lymph node dissection in prostate cancer: update from a randomized clinical trial of limited versus extended dissection. *Eur Urol*. 2024;87(2):253-260. doi:10.1016/j.eururo.2024.10.006
201. Briganti A, Larcher A, Abdollah F, et al. Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol*. 2012;61(3):480-487. doi:10.1016/j.eururo.2011.10.044
202. Gandaglia G, Ploussard G, Valerio M, et al. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. *Eur Urol*. 2019;75(3):506-514. doi:10.1016/j.eururo.2018.10.012
203. Briganti A, Chun FKH, Salonia A, et al. Complications and other surgical outcomes associated with extended pelvic

lymphadenectomy in men with localized prostate cancer. *Eur Urol*. 2006;50(5):1006-1013. doi:10.1016/j.eururo.2006.08.015
204. Fossati N, Willemse PPM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. *Eur Urol*. 2017;72(1):84-109. doi:10.1016/j.eururo.2016.12.003
205. Ploussard G, Staerman F, Pierrevelcin J, et al. Predictive factors of oncologic outcomes in patients who do not achieve undetectable prostate specific antigen after radical prostatectomy. *J Urol*. 2013;190(5):1750-1756. doi:10.1016/j.juro.2013.04.073
206. Wiegel T, Bartkowiak D, Bottke D, et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96-02 trial. *Int J Radiat Oncol Biol Phys*. 2015;91(2):288-294. doi:10.1016/j.ijrobp.2014.09.039
207. Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur Urol*. 2020;77(4):403-417. doi:10.1016/j.eururo.2019.01.049
208. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med*. 2017;377(2):132-142. doi:10.1056/nejmoa1615869
209. Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet*. 1999;353(9149):267-272. doi:10.1016/s0140-6736(98)05180-0
210. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2007;8(6):475-487. doi:10.1016/s1470-2045(07)70143-2
211. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2014;15(4):464-473. doi:10.1016/s1470-2045(14)70040-3
212. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(1):67-74. doi:10.1016/j.ijrobp.2007.06.054
213. Beckendorf V, Guerif S, Le Prisé E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys*. 2011;80(4):1056-1063. doi:10.1016/j.ijrobp.2010.03.049
214. Al-Mamgani A, Van Putten WLJ, Heemsbergen WD, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;72(4):980-988. doi:10.1016/j.ijrobp.2008.02.073
215. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol*. 2010;28(7):1106-1111. doi:10.1200/jco.2009.25.8475
216. Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: the NRG Oncology RTOG 0126 randomized clinical trial. *JAMA Oncol*. 2018;4(6):e180039. doi:10.1001/jamaoncol.2018.0039
217. Fowler JF. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. *Acta Oncol*. 2005;44(3):265-276. doi:10.1080/02841860410002824
218. Wang JZ, Guerrero M, Li XA. How low is the α/β ratio for prostate cancer? *Int J Radiat Oncol Biol Phys*. 2003;55(1):194-203. doi:10.1016/s0360-3016(02)03828-2
219. Khoo VS, Dearnaley DP. Question of dose, fractionation and technique: ingredients for testing hypofractionation in prostate cancer—the CHHiP trial. *Clin Oncol (R Coll Radiol)*. 2008;20(1):12-14. doi:10.1016/j.clon.2007.10.008
220. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: an ASTRO, ASCO, and AUA evidence-based guideline. *J Clin Oncol*. 2018;36(34):3411-3430. doi:10.1200/jco.18.01097
221. Arcangeli G, Saracino B, Arcangeli S, et al. Moderate hypofractionation in high-risk, organ-confined prostate cancer: final results of a phase III randomized trial. *J Clin Oncol*. 2017;35(17):1891-1897. doi:10.1200/jco.2016.70.4189
222. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol*. 2013;31:3860-3868. doi:10.1200/jco.2013.51.1972
223. Hoffman KE, Voong KR, Levy LB, et al. Randomized trial of hypofractionated, dose-escalated, intensity-modulated radiation therapy (IMRT) versus conventionally fractionated IMRT for localized prostate cancer. *J Clin Oncol*. 2018;36(29):2943-2949. doi:10.1200/jco.2018.77.9868
224. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(8):1061-1069. doi:10.1016/s1470-2045(16)30070-5
225. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol*. 2016;34(20):2325-2332. doi:10.1200/jco.2016.67.0448
226. Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol*. 2017;35(17):1884-1890. doi:10.1200/jco.2016.71.7397
227. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;17(8):1047-1060. doi:10.1016/s1470-2045(16)30102-4
228. Syndikus I, Griffin C, Philipps L, et al. 10-year efficacy and comorbidity outcomes of a phase III randomised trial of conventional vs. hypofractionated high dose intensity modulated radiotherapy for prostate cancer (CHHiP; CRUK/06/016) [abstract]. *J Clin Oncol*. 2023;41(6 suppl):304. doi:10.1200/jco.2023.41.6_suppl.304
229. Wilson JM, Dearnaley DP, Syndikus I, et al. The efficacy and safety of conventional and hypofractionated high-dose radiation therapy for prostate cancer in an elderly population: a subgroup analysis of the CHHiP trial. *Int J Radiat Oncol Biol Phys*. 2018;100(5):1179-1189. doi:10.1016/j.ijrobp.2018.01.016
230. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet*. 2019;394(10196):385-395. doi:10.1016/s0140-6736(19)31131-6
231. van As N, Griffin C, Tree A, et al. Phase 3 trial of stereotactic body radiotherapy in localized prostate cancer. *N Engl J Med*. 2024;391(15):1413-1425. doi:10.1056/nejmoa2403365
232. The Institute of Cancer Research. PACE-NODES. *A phase III randomised trial of 5 fraction prostate SBRT versus 5 fraction prostate and pelvic nodal SBRT*. Health Research Authority; 2024. Accessed December 4, 2024. https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/pace-nodes/
233. Murthy V, Maitre P, Arunsingh M, et al. OC-0924 Prostate RT In high risk or N+ moderate vs extreme hypofractionation (PRIME):

an interim analysis. *Radiother Oncol*. 2023;182:S770-S771. doi:10.1016/s0167-8140(23)08750-9

234. 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
235. Westley RL, Biscombe K, Dunlop A, et al. Interim toxicity analysis from the randomized HERMES trial of 2- and 5-fraction magnetic resonance imaging–guided adaptive prostate radiation therapy. *Int J Radiat Oncol Biol Phys*. 2024;118(3):682-687. doi:10.1016/j.ijrobp.2023.09.032
236. Kishan AU, Lamb JM, Wilhalme H, et al. Magnetic resonance imaging versus computed tomography guidance for stereotactic body radiotherapy in prostate cancer: 2-year outcomes from the MIRAGE randomized clinical trial. *Eur Urol*. 2024;12:S0302-2838(24)02688-5. doi:10.1016/j.eururo.2024.10.026
237. Boldrini L, Romano A, Chiloiro G, et al. Magnetic resonance guided SBRT reirradiation in locally recurrent prostate cancer: a multicentric retrospective analysis. *Radiat Oncol*. 2023;18(1):84. doi:10.1186/s13014-023-02271-y
238. Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the FLAME randomized phase III trial. *J Clin Oncol*. 2021;39(7):787-796. doi:10.1200/jco.20.02873
239. Draulans C, Haustermans K, Pos FJ, et al. Stereotactic body radiotherapy with a focal boost to the intraprostatic tumor for intermediate and high risk prostate cancer: 5-year efficacy and toxicity in the hypo-FLAME trial. *Radiother Oncol*. 2024;201:110568. doi:10.1016/j.radonc.2024.110568
240. De Cock L, Draulans C, Pos FJ, et al. From once-weekly to semi-weekly whole prostate gland stereotactic radiotherapy with focal boosting: primary endpoint analysis of the multicenter phase II hypo-FLAME 2.0 trial. *Radiother Oncol*. 2023;185:109713. doi:10.1016/j.radonc.2023.109713
241. Tree AC, Satchwell L, Alexander E, et al. Standard and hypofractionated dose escalation to intraprostatic tumor nodules in localized prostate cancer: 5-year efficacy and toxicity in the DELINEATE trial. *Int J Radiat Oncol Biol Phys*. 2023;115(2):305-316. doi:10.1016/j.ijrobp.2022.09.058
242. Yasar B, Suh YE, Chapman E, et al. Simultaneous focal boost with stereotactic radiation therapy for localized intermediate- to high-risk prostate cancer: primary outcomes of the SPARC phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2024;120(1):49-58. doi:10.1016/j.ijrobp.2024.03.009
243. Efstathiou JA, Yeap BY, Michalski JM, et al. Prostate advanced radiation technologies investigating quality of life (PARTIQoL): phase III randomized clinical trial of proton therapy vs. IMRT for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2024;120(2 suppl):S1. doi:10.1016/j.ijrobp.2024.08.012
244. Roach M, Marquez C, Yuo HS, et al. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 1994;28(1):33-37. doi:10.1016/0360-3016(94)90138-4
245. Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(11):1504-1515. doi:10.1016/s1470-2045(18)30528-x
246. Blanchard P, Faivre L, Lesaunier F, et al. Outcome according to elective pelvic radiation therapy in patients with high-risk localized prostate cancer: a secondary analysis of the GETUG 12 phase 3 randomized trial. *Int J Radiat Oncol Biol Phys*. 2016;94(1):85-92. doi:10.1016/j.ijrobp.2015.09.020
247. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. *Int J Radiat Oncol Biol Phys*. 2016;96(4):759-769. doi:10.1016/j.ijrobp.2016.06.2455
248. Murthy V, Maitre P, Bhatia J, et al. Late toxicity and quality of life with prostate only or whole pelvic radiation therapy in high risk prostate cancer (POP-RT): a randomised trial. *Radiother Oncol*. 2020;145:71-80. doi:10.1016/j.radonc.2019.12.006
249. Murthy V, Maitre P, Kannan S, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. *J Clin Oncol*. 2021;39(11):1234-1242. doi:10.1200/jco.20.03282
250. Syndikus I, Cruickshank C, Staffurth J, et al. PIVOTALboost: a phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost (CRUK/16/018). *Clin Transl Radiat Oncol*. 2020;25:22-28. doi:10.1016/j.ctro.2020.08.003
251. NRG Oncology. Radiation Therapy Oncology Group (RTOG) Study 0924: Androgen Deprivation Therapy and High Dose Radiotherapy With or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial. NRG Oncology; 2024. Accessed December 4, 2024. https://www.nrgoncology.org/Clinical-Trials/Protocol/rtog-0924?filter=rtog-0924
252. Tree AC, Ostler P, Van Der Voet H, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2022;23(10):1308-1320. doi:10.1016/s1470-2045(22)00517-4
253. Kishan AU, Marco N, Schulz-Jaavall MB, et al. Germline variants disrupting microRNAs predict long-term genitourinary toxicity after prostate cancer radiation. *Radiother Oncol*. 2022;167:226-232. doi:10.1016/j.radonc.2021.12.040
254. Walz J, Gallina A, Saad F, et al. A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. *J Clin Oncol*. 2007;25(24):3576-3581. doi:10.1200/jco.2006.10.3820
255. Resnick MJ, Koyama T, Fan K-H, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med*. 2013;368(5):436-445. doi:10.1056/nejmoa1209978
256. Wallis CJD, Mahar AL, Choo R, et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BMJ*. 2016;352:i851. doi:10.1136/bmj.i851
257. Murray L, Henry A, Hoskin P, Siebert FA, Venselaar J. Second primary cancers after radiation for prostate cancer: a systematic review of the clinical data and impact of treatment technique. *Radiother Oncol*. 2014;110(2):213-228. doi:10.1016/j.radonc.2013.12.012
258. Bolla M, De Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009;360(24):2516-2527. doi:10.1056/nejmoa0810095
259. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002;360(9327):103-108. doi:10.1016/s0140-6736(02)09408-4
260. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group protocol

92–02. *J Clin Oncol*. 2003;21:3972-3978. doi:10.1200/jco.2003.11.023
261. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet*. 2009;373(9660):301-308. doi:10.1016/s0140-6736(08)61815-2
262. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*. 2011;378(9809):2104-2111. doi:10.1016/s0140-6736(11)61095-7
263. Nabid A, Carrier N, Martin AG, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. *Eur Urol*. 2018;74(4):432-441. doi:10.1016/j.eururo.2018.06.018
264. Kishan AU, Sun Y, Hartman H, et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. *Lancet Oncol*. 2022;23(2):304-316. doi:10.1016/s1470-2045(21)00705-1
265. Kishan AU, Sun Y, Pisansky TM, et al. Individual patient data Meta-Analysis of Randomized Trials in Cancer of the Prostate (MARCAP) Consortium: impact of androgen deprivation therapy use and duration with definitive radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2021;111(3):S5-S6. doi:10.1016/j.ijrobp.2021.07.046
266. Kishan AU, Wang X, Sun Y, et al. High-dose radiotherapy or androgen deprivation therapy (HEAT) as treatment intensification for localized prostate cancer: an individual patient–data network meta-analysis from the MARCAP Consortium. *Eur Urol*. 2022;82(1):106-114. doi:10.1016/j.eururo.2022.04.003
267. Kishan AU, Steigler A, Denham JW, et al. Interplay between duration of androgen deprivation therapy and external beam radiotherapy with or without a brachytherapy boost for optimal treatment of high-risk prostate cancer: a patient-level data analysis of 3 cohorts. *JAMA Oncol*. 2022;8:e216871. doi:10.1001/jamaoncol.2021.6871
268. Ma TM, Sun Y, Malone S, et al. Sequencing of androgen-deprivation therapy of short duration with radiotherapy for nonmetastatic prostate cancer (SANDSTORM): a pooled analysis of 12 randomized trials. *J Clin Oncol*. 2023;41(4):881-892. doi:10.1200/jco.22.00970
269. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Engl J Med*. 2017;376(5):417-428. doi:10.1056/nejmoa1607529
270. Parker CC, Kynaston H, Cook AD, et al. Duration of androgen deprivation therapy with postoperative radiotherapy for prostate cancer: a comparison of long-course versus short-course androgen deprivation therapy in the RADICALS-HD randomised trial. *Lancet*. 2024;403(10442):2416-2425. doi:10.1016/s0140-6736(24)00549-x
271. Burdett S, Fisher D, Parker CC, et al. LBA64 Duration of androgen suppression with post-operative radiotherapy (DADSPORT): a collaborative meta-analysis of aggregate data [abstract]. *Ann Oncol*. 2022;33(suppl 7):S1428-S1429. doi:10.1016/j.annonc.2022.08.067
272. Carrie C, Magné N, Burban-Provost P, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. *Lancet Oncol*. 2019;20(12):1740-1749. doi:10.1016/s1470-2045(19)30486-3
273. Pollack A, Karrison TG, Balogh AG, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. *Lancet*. 2022;399(10338):1886-1901. doi:10.1016/s0140-6736(21)01790-6
274. Parker CC, Clarke NW, Cook AD, et al. Adding 6 months of androgen deprivation therapy to postoperative radiotherapy for prostate cancer: a comparison of short-course versus no androgen deprivation therapy in the RADICALS-HD randomised controlled trial. *Lancet*. 2024;403(10442):2405-2415. doi:10.1016/s0140-6736(24)00548-8
275. Parker CC, Clarke NW, Cook AD, et al. Randomised trial of no, short-term, or long-term androgen deprivation therapy with postoperative radiotherapy after radical prostatectomy: results from the three-way comparison of RADICALS-HD (NCT00541047). *Eur Urol*. 2024;86(5):422-430. doi:10.1016/j.eururo.2024.07.026
276. Ong WL, Romero T, Roy S, et al. Testosterone recovery following androgen suppression and prostate radiotherapy (TRANSPORT): a pooled analysis of five randomized trials from the Meta-Analysis of Randomized Trials in Cancer of the Prostate (MARCAP) Consortium. *Eur Urol*. 2025;87(1):49-57. doi:10.1016/j.eururo.2024.09.009
277. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020;382(23):2187-2196. doi:10.1056/nejmoa2004325
278. Tutrone R, Saad F, George DJ, et al. Testosterone recovery for relugolix versus leuprolide in men with advanced prostate cancer: results from the phase 3 HERO study. *Eur Urol Oncol*. 2024;7(4):906-913. doi:10.1016/j.euo.2023.11.024
279. Lopes RD, Higano CS, Slovin SF, et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial. *Circulation*. 2021;144(16):1295-1307. doi:10.1161/circulationaha.121.056810
280. Zaorsky NG, Davis BJ, Nguyen PL, et al. The evolution of brachytherapy for prostate cancer. *Nat Rev Urol*. 2017;14(7):415-439. doi:10.1038/nrurol.2017.76
281. Ghadjar P, Oesch SL, Rentsch CA, et al. Late toxicity and five year outcomes after high-dose-rate brachytherapy as a monotherapy for localized prostate cancer. *Radiat Oncol*. 2014;9(1):122. doi:10.1186/1748-717x-9-122
282. Uribe-Lewis S, Uribe J, Bourke V, et al. Long-term survival after low-dose-rate brachytherapy for prostate cancer: the Royal Surrey experience. *BJU Int*. 2022;129(6):723-730. doi:10.1111/bju.15585
283. Oh J, Tyldesley S, Pai H, et al. An updated analysis of the survival endpoints of ASCENDE-RT. *Int J Radiat Oncol Biol Phys*. 2023;115(5):1061-1070. doi:10.1016/j.ijrobp.2022.11.005
284. Rodda S, Tyldesley S, Morris WJ, et al. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;98(2):286-295. doi:10.1016/j.ijrobp.2017.01.008
285. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol*. 2012;103(2):217-222. doi:10.1016/j.radonc.2012.01.007
286. Hoskin PJ, Rojas AM, Ostler PJ, Bryant L, Lowe GJ. Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: mature 12-year results. *Radiother Oncol*. 2021;154:214-219. doi:10.1016/j.radonc.2020.09.047
287. Tilki D, Preisser F, Graefen M, Huland H, Pompe RS. External validation of the European Association of Urology biochemical recurrence risk groups to predict metastasis and mortality after radical prostatectomy in a European cohort. *Eur Urol*. 2019;75(6):896-900. doi:10.1016/j.eururo.2019.03.016
288. Stish BJ, Pisansky TM, Harmsen WS, et al. Improved metastasis-free and survival outcomes with early salvage radiotherapy in

men with detectable prostate-specific antigen after prostatectomy for prostate cancer. *J Clin Oncol*. 2016;34(32):3864-3871. doi:10.1200/jco.2016.68.3425

289. Tilki D, Chen MH, Wu J, et al. Prostate-specific antigen level at the time of salvage therapy after radical prostatectomy for prostate cancer and the risk of death. *J Clin Oncol*. 2023;41(13):2428-2435. doi:10.1200/jco.22.02489
290. Tilki D, Chen MH, Wu J, et al. Adjuvant versus early salvage radiation therapy for men at high risk for recurrence following radical prostatectomy for prostate cancer and the risk of death. *J Clin Oncol*. 2021;39(20):2284-2293. doi:10.1200/jco.20.03714
291. Bolla M, Van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet*. 2005;366(9485):572-578. doi:10.1016/s0140-6736(05)67101-2
292. Swanson GP, Thompson IM, Tangen C, et al. Phase III randomized study of adjuvant radiation therapy versus observation in patients with pathologic T3 prostate cancer (SWOG 8794) [abstract]. *Int J Radiat Oncol Biol Phys*. 2005;63(suppl 1):S1. doi:10.1016/j.ijrobp.2005.07.007
293. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol*. 2009;27(18):2924-2930. doi:10.1200/jco.2008.18.9563
294. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet*. 2020;396(10260):1413-1421. doi:10.1016/s0140-6736(20)31553-1
295. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol*. 2020;21(10):1331-1340. doi:10.1016/s1470-2045(20)30456-3
296. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol*. 2020;21(10):1341-1352. doi:10.1016/s1470-2045(20)30454-x
297. Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet*. 2020;396(10260):1422-1431. doi:10.1016/s0140-6736(20)31952-8
298. Van den Broeck T, van den Bergh RCN, Arfi N, et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. *Eur Urol*. 2019;75(6):967-987. doi:10.1016/j.eururo.2018.10.011
299. Ghadjar P, Hayoz S, Bernhard J, et al. Dose-intensified versus conventional-dose salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy: the SAKK 09/10 randomized phase 3 trial. *Eur Urol*. 2021;80:306-315. doi:10.1016/j.eururo.2021.05.033
300. Guang ZLP, Kristensen G, Røder A, Brasso K. Oncological and functional outcomes of whole-gland HIFU as the primary treatment for localized prostate cancer: a systematic review. *Clin Genitourin Cancer*. 2024;22(4):102101. doi:10.1016/j.clgc.2024.102101
301. Ehdaie B, Tempany CM, Holland F, et al. MRI-guided focused ultrasound focal therapy for patients with intermediate-risk prostate cancer: a phase 2b, multicentre study. *Lancet Oncol*. 2022;23(7):910-918. doi:10.1016/s1470-2045(22)00251-0
302. Parry MG, Sujenthiran A, Nossiter J, et al. Prostate cancer outcomes following whole-gland and focal high-intensity focused ultrasound. *BJU Int*. 2023;132(5):568-574. doi:10.1111/bju.16122
303. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet*. 2022;399(10323):447-460. doi:10.1016/s0140-6736(21)02437-5
304. Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. *Lancet Oncol*. 2015;16(7):787-794. doi:10.1016/s1470-2045(15)00011-x
305. Rosenthal SA, Hu C, Sartor O, et al. Effect of chemotherapy with docetaxel with androgen suppression and radiotherapy for localized high-risk prostate cancer: the randomized phase III NRG Oncology RTOG 0521 trial. *J Clin Oncol*. 2019;37(14):1159-1168. doi:10.1200/jco.18.02158
306. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163-1177. doi:10.1016/s0140-6736(15)01037-5
307. Vale CL, Burdett S, Rydzewska LHM, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol*. 2016;17(2):243-256. doi:10.1016/s1470-2045(15)00489-1
308. Ahlgren GM, Flodgren P, Tammela TLJ, et al. Docetaxel versus surveillance after radical prostatectomy for high-risk prostate cancer: results from the prospective randomised, open-label phase 3 Scandinavian Prostate Cancer Group 12 trial. *Eur Urol*. 2018;73(6):870-876. doi:10.1016/j.eururo.2018.01.012
309. Kellokumpu-Lehtinen PL, Hjälm-Eriksson M, Thellenberg-Karlsson C, et al. Docetaxel versus surveillance after radical radiotherapy for intermediate- or high-risk prostate cancer—results from the prospective, randomised, open-label phase III SPCG-13 trial. *Eur Urol*. 2019;76(6):823-830. doi:10.1016/j.eururo.2019.08.010
310. Lin DW, Shih MC, Aronson W, et al. Veterans Affairs Cooperative Studies Program Study #553: chemotherapy after prostatectomy for high-risk prostate carcinoma: a phase III randomized study. *Eur Urol*. 2020;77(5):563-572. doi:10.1016/j.eururo.2019.12.020
311. Sandler HM, McKenzie MR, Tombal BF, et al. ATLAS: a randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide (ARN-509) in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy [abstract]. *J Clin Oncol*. 2016;34(15 suppl):TPS5087. doi:10.1200/jco.2016.34.15_suppl.tps5087
312. Williams S, Davis ID, Sweeney C, et al. Randomised phase 3 trial of enzalutamide in androgen deprivation therapy (ADT) with radiation therapy for high risk, clinically localized prostate cancer: ENZARAD (ANZUP 1303) [abstract]. *J Clin Oncol*. 2018;36(6 suppl):TPS156. doi:10.1200/jco.2018.36.6_suppl.tps156
313. Toussi A, Stewart-Merrill SB, Boorjian SA, et al. Standardizing the definition of biochemical recurrence after radical prostatectomy—what prostate specific antigen cut point best predicts a durable increase and subsequent systemic progression? *J Urol*. 2016;195(6):1754-1759. doi:10.1016/j.juro.2015.12.075
314. Abramowitz MC, Li T, Buyyounouski MK, et al. The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *Cancer*. 2008;112(1):55-60. doi:10.1002/cncr.23139

315. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II—2020 update: treatment of relapsing and metastatic prostate cancer. *Eur Urol*. 2021;79(2):263-282. doi:10.1016/j.eururo.2020.09.046
316. Pienta KJ, Gorin MA, Rowe SP, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with ^{18}F-DCFPyL in prostate cancer patients (OSPREY). *J Urol*. 2021;206(1):52-61. doi:10.1097/ju.0000000000001698
317. Morris MJ, Rowe SP, Gorin MA, et al. Diagnostic performance of 18F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR phase III, multicenter study. *Clin Cancer Res*. 2021;27(13):3674-3682. doi:10.1158/1078-0432.ccr-20-4573
318. Zumsteg ZS, Spratt DE, Romesser PB, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. *Eur Urol*. 2015;67(6):1009-1016. doi:10.1016/j.eururo.2014.09.028
319. Roy S, Romero T, Michalski JM, et al. Biochemical recurrence surrogacy for clinical outcomes after radiotherapy for adenocarcinoma of the prostate. *J Clin Oncol*. 2023;41(32):5005-5014. doi:10.1200/JCO.23.00617
320. Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative oncologic and toxicity outcomes of salvage radical prostatectomy versus nonsurgical therapies for radiorecurrent prostate cancer: a meta–regression analysis. *Eur Urol Focus*. 2016;2:158-171. doi:10.1016/j.euf.2015.09.004
321. Valle LF, Lehrer EJ, Markovic D, et al. A systematic review and meta-analysis of local salvage therapies after radiotherapy for prostate cancer (MASTER). *Eur Urol*. 2021;80(3):280-292. doi:10.1016/j.eururo.2020.11.010
322. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol*. 2005;23(9):2028-2037. doi:10.1200/jco.2005.00.067
323. Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol*. 2016;17(6):727-737. doi:10.1016/s1470-2045(16)00107-8
324. Loblaw A, Bassett J, D'Este C, et al. Timing of androgen deprivation therapy for prostate cancer patients after radiation: planned combined analysis of two randomized phase 3 trials [abstract]. *J Clin Oncol*. 2018;36(15 suppl):5018. doi:10.1200/jco.2018.36.15_suppl.5018
325. Freedland SJ, De Almeida Luz M, De Giorgi U, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. *N Engl J Med*. 2023;389(16):1453-1465. doi:10.1056/nejmoa2303974
326. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018;392(10162):2353-2366. doi:10.1016/s0140-6736(18)32486-3
327. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: long-term results from the STAMPEDE randomised controlled trial. *PLoS Med*. 2022;19(6):e1003998. doi:10.1371/journal.pmed.1003998
328. Boevé LMS, Hulshof MCCM, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol*. 2019;75(3):410-418. doi:10.1016/j.eururo.2018.09.008
329. Burdett S, Boevé LM, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. *Eur Urol*. 2019;76(1):115-124. doi:10.1016/j.eururo.2019.02.003
330. Ali A, Hoyle A, Haran ÁM, et al. Association of bone metastatic burden with survival benefit from prostate radiotherapy in patients with newly diagnosed metastatic prostate cancer: a secondary analysis of a randomized clinical trial. *JAMA Oncol*. 2021;7(4):555-563. doi:10.1001/jamaoncol.2020.7857
331. Jones C, Dutey-Magn P, Murphy L, et al. 1782P Prostate radiotherapy reduces long-term risk of obstructive uropathy in metastatic hormone sensitive prostate cancer (mHSPC): results from the STAMPEDE M1|RT comparison [abstract]. *Ann Oncol*. 2023;34(suppl 2):S963. doi:10.1016/j.annonc.2023.09.2732
332. Bossi A, Foulon S, Maldonado X, et al. Efficacy and safety of prostate radiotherapy in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet*. 2024;404(10467):2065-2076. doi:10.1016/s0140-6736(24)01865-8
333. Battaglia A, De Meerleer G, Tosco L, et al. Novel insights into the management of oligometastatic prostate cancer: a comprehensive review. *Eur Urol Oncol*. 2019;2:174-188. doi:10.1016/j.euo.2018.09.005
334. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21(1):e18-e28. doi:10.1016/s1470-2045(19)30718-1
335. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36(5):446-453. doi:10.1200/jco.2017.75.4853
336. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6(5):650-659. doi:10.1001/jamaoncol.2020.0147
337. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019;393(10185):2051-2058. doi:10.1016/s0140-6736(18)32487-5
338. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol*. 2020;38(25):2830-2838. doi:10.1200/jco.20.00818
339. Tang C, Sherry AD, Haymaker C, et al. Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: the EXTEND phase 2 randomized clinical trial. *JAMA Oncol*. 2023;9(6):825-834. doi:10.1001/jamaoncol.2023.0161
340. Francolini G, Allegra AG, Detti B, et al. Stereotactic body radiation therapy and abiraterone acetate for patients affected by oligometastatic castrate-resistant prostate cancer: a randomized phase II trial (ARTO). *J Clin Oncol*. 2023;41(36):5561-5568. doi:10.1200/jco.23.00985
341. Ost P, Siva S, Braband S, et al. Salvage treatment of oligorecurrent nodal prostate cancer metastases (STORM). *Radiother Oncol*. 2024;194:S2485-S2487. doi:10.1016/s0167-8140(24)02299-0

342. Ost P, Siva S, Brabrand S, et al. Salvage metastasis-directed therapy versus elective nodal radiotherapy for oligorecurrent nodal prostate cancer metastases (PEACE V–STORM): a phase 2, open-label, randomised controlled trial. *Lancet Oncol*. Published online May 2, 2025. doi:10.1016/s1470-2045(25)00197-4
343. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. *Cancer Stat Facts: Prostate Cancer*. National Cancer Institute; 2024. Accessed December 4, 2024. https://seer.cancer.gov/statfacts/html/prost.html
344. American Cancer Society. *Cancer Facts & Figures 2024*. American Cancer Society; 2024. Accessed December 4, 2024. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2024-cancer-facts-figures.html
345. Miller DC, Hafez KS, Stewart A, Montie JE, Wei JT. Prostate carcinoma presentation, diagnosis, and staging: an update from the National Cancer Data Base. *Cancer*. 2003;98(6):1169-1178. doi:10.1002/cncr.11635
346. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2007 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol*. 2007;25(12):1596-1605. doi:10.1200/jco.2006.10.1949
347. Massie CE, Lynch A, Ramos-Montoya A, et al. The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis: AR coordinates anabolic program in prostate cancer. *EMBO J*. 2011;30(13):2719-2733. doi:10.1038/emboj.2011.158
348. Rice MA, Malhotra SV, Stoyanova T. Second-generation antiandrogens: from discovery to standard of care in castration resistant prostate cancer. *Front Oncol*. 2019;9:801. doi:10.3389/fonc.2019.00801
349. Rehman Y, Rosenberg JE. Abiraterone acetate: oral androgen biosynthesis inhibitor for treatment of castration-resistant prostate cancer. *Drug Des Devel Ther*. 2012;13:13-18. doi:10.2147/dddt.s15850
350. James ND, Spears MR, Clarke NW, et al. Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). *Eur Urol*. 2015;67(6):1028-1038. doi:10.1016/j.eururo.2014.09.032
351. Chodak G, Gomella L, Phung DH. Combined androgen blockade in advanced prostate cancer: looking back to move forward. *Clin Genitourin Cancer*. 2007;5(6):371-378. doi:10.3816/cgc.2007.n.019
352. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(2):149-158. doi:10.1016/s1470-2045(12)70560-0
353. Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol*. 2019;30(12):1992-2003. doi:10.1093/annonc/mdz396
354. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol*. 2018;36(11):1080-1087. doi:10.1200/jco.2017.75.3657
355. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360. doi:10.1056/nejmoa1704174
356. James ND, De Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338-351. doi:10.1056/nejmoa1702900
357. James ND, Clarke NW, Cook A, et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). *Int J Cancer*. 2022;151(3):422-434. doi:10.1002/ijc.34018
358. Rydzewska LHM, Burdett S, Vale CL, et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2017;84:88-101. doi:10.1016/j.ejca.2017.07.003
359. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2019;20(5):686-700. doi:10.1016/s1470-2045(19)30082-8
360. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37(32):2974-2986. doi:10.1200/jco.19.00799
361. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381(2):121-131. doi:10.1056/nejmoa1903835
362. Armstrong AJ, Azad AA, Iguchi T, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2022;40(15):1616-1622. doi:10.1200/jco.22.00193
363. Sweeney CJ, Martin AJ, Stockler MR, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2023;24(4):323-334. doi:10.1016/s1470-2045(23)00063-3
364. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24. doi:10.1056/nejmoa1903307
365. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol*. 2021;39(20):2294-2303. doi:10.1200/jco.20.03488
366. Saad F, Vjaters E, Shore N, et al. Darolutamide in combination with androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase III ARANOTE trial. *J Clin Oncol*. 2024;42(36):4271-4281. doi:10.1200/jco-24-01798
367. Vale CL, Fisher D, Godolphin P, et al. Defining more precisely the effects of docetaxel plus ADT for men with mHSPC: meta-analysis of individual participant data from randomized trials [abstract]. *J Clin Oncol*. 2022;40(16 suppl):5070. doi:10.1200/jco.2022.40.16_suppl.5070
368. El-Taji O, Taktak S, Jones C, Brown M, Clarke N, Sachdeva A. Cardiovascular events and androgen receptor signaling inhibitors in advanced prostate cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2024;10(7):874-884. doi:10.1001/jamaoncol.2024.1549
369. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet*. 2022;399(10336):1695-1707. doi:10.1016/s0140-6736(22)00367-1
370. Bossi A, Foulon S, Maldonado X, et al. Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): results of PEACE-1, a phase 3 randomized trial with a 2 × 2 design [abstract]. *J Clin Oncol*. 2023;41(17 suppl):LBA5000. doi:10.1200/jco.2023.41.17_suppl.lba5000
371. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132-1142. doi:10.1056/nejmoa2119115

372. Riaz IB, Naqvi SAA, He H, et al. First-line systemic treatment options for metastatic castration-sensitive prostate cancer: a living systematic review and network meta-analysis. *JAMA Oncol*. 2023;9(5):635-645. doi:10.1001/jamaoncol.2022.7762
373. Roy S, Fervaha G, Spratt DE, et al. Prostate radiotherapy in low-volume metastatic hormone-sensitive prostate cancer: a network meta-analysis. *Eur Urol*. 2024;86(1):10-17. doi:10.1016/j.eururo.2024.03.018
374. Chakrabarti D, Parker CC. Metastatic hormone-sensitive prostate cancer: patient selection for prostate radiotherapy. *Eur Urol*. 2024;86(1):18-19. doi:10.1016/j.eururo.2024.04.011
375. Rush HL, Murphy L, Morgans AK, et al. Quality of life in men with prostate cancer randomly allocated to receive docetaxel or abiraterone in the STAMPEDE trial. *J Clin Oncol*. 2022;40(8):825-836. doi:10.1200/jco.21.00728
376. Azad AA, Bressel M, Tan H, et al. LBA66 UpFrontPSMA: a randomised phase II study of sequential 177Lu-PSMA-617 and docetaxel (D) versus docetaxel in metastatic hormone-sensitive prostate cancer (mHSPC) [abstract]. *Ann Oncol*. 2024;35(suppl 2):S1255-S1256. doi:10.1016/j.annonc.2024.08.2309
377. Holzgreve A, Armstrong WR, Clark KJ, et al. PSMA-PET/CT findings in patients with high-risk biochemically recurrent prostate cancer with no metastatic disease by conventional imaging. *JAMA Netw Open*. 2025;8(1):e2452971. doi:10.1001/jamanetworkopen.2024.52971
378. Fendler WP, Weber M, Iravani A, et al. Prostate-specific membrane antigen ligand positron emission tomography in men with nonmetastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2019;25(24):7448-7454. doi:10.1158/1078-0432.ccr-19-1050
379. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. *J Nucl Med*. 2018;59(3):469-478. doi:10.2967/jnumed.117.198119
380. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-2474. doi:10.1056/nejmoa1800536
381. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2020;382(23):2197-2206. doi:10.1056/nejmoa2003892
382. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418. doi:10.1056/nejmoa1715546
383. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. *Eur Urol*. 2021;79(1):150-158. doi:10.1016/j.eururo.2020.08.011
384. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-1246. doi:10.1056/nejmoa1815671
385. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383(11):1040-1049. doi:10.1056/nejmoa2001342
386. Feng FY, Thomas S, Saad F, et al. Association of molecular subtypes with differential outcome to apalutamide treatment in nonmetastatic castration-resistant prostate cancer. *JAMA Oncol*. 2021;7:1005-1014. doi:10.1001/jamaoncol.2021.1463
387. Massard C, Fizazi K. Targeting continued androgen receptor signaling in prostate cancer. *Clin Cancer Res*. 2011;17(12):3876-3883. doi:10.1158/1078-0432.ccr-10-2815
388. Tannock IF, De Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512. doi:10.1056/nejmoa040720
389. Petrylak DP, Tangen CM, Hussain MHA, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351(15):1513-1520. doi:10.1056/nejmoa041318
390. Berthold DR, Pond GR, Soban F, De Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol*. 2008;26(2):242-245. doi:10.1200/jco.2007.12.4008
391. De Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154. doi:10.1016/s0140-6736(10)61389-x
392. De Bono JS, Oudard S, Ozguroglu M, et al. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational phase III trial (TROPIC) [abstract]. *J Clin Oncol*. 2010;28(15 suppl):4508. doi:10.1200/jco.2010.28.15_suppl.4508
393. Oudard S, Fizazi K, Sengeløv L, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III trial—FIRSTANA. *J Clin Oncol*. 2017;35(28):3189-3197. doi:10.1200/jco.2016.72.1068
394. De Wit R, De Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381(26):2506-2518. doi:10.1056/nejmoa1911206
395. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in postdocetaxel patients with metastatic castration-resistant prostate cancer—PROSELICA. *J Clin Oncol*. 2017;35(28):3198-3206. doi:10.1200/jco.2016.72.1076
396. Corn PG, Heath EI, Zurita A, et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial. *Lancet Oncol*. 2019;20(10):1432-1443. doi:10.1016/s1470-2045(19)30408-5
397. Pemberton L, Allen C, Handel E, et al. Carboplatin in metastatic castrate resistant prostate cancer: a retrospective study of heavily pretreated patients (COMPACT). *Clin Genitourin Cancer*. 2024;22(2):580-585. doi:10.1016/j.clgc.2024.01.013
398. Fléchon A, Pouessel D, Ferlay C, et al. Phase II study of carboplatin and etoposide in patients with anaplastic progressive metastatic castration-resistant prostate cancer (mCRPC) with or without neuroendocrine differentiation: results of the French Genito-Urinary Tumor Group (GETUG) P01 trial. *Ann Oncol*. 2011;22(11):2476-2481. doi:10.1093/annonc/mdr004
399. Loriot Y, Massard C, Gross-Goupil M, et al. Combining carboplatin and etoposide in docetaxel-pretreated patients with castration-resistant prostate cancer: a prospective study evaluating also neuroendocrine features. *Ann Oncol*. 2009;20(4):703-708. doi:10.1093/annonc/mdn694
400. Amato RJ, Logothetis CJ, Hallinan R, Ro JY, Sella A, Dexeus FH. Chemotherapy for small cell carcinoma of prostatic origin. *J Urol*. 1992;147(3 pt 2):935-937. doi:10.1016/s0022-5347(17)37427-x
401. Papandreou CN, Daliani DD, Thall PF, et al. Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate. *J Clin Oncol*. 2002;20(14):3072-3080. doi:10.1200/jco.2002.12.065
402. Aparicio AM, Harzstark AL, Corn PG, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. *Clin Cancer Res*. 2013;19(13):3621-3630. doi:10.1158/1078-0432.ccr-12-3791
403. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005. doi:10.1056/nejmoa1014618
404. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-

blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992. doi:10.1016/s1470-2045(12)70379-0
405. Ryan CJ, Smith MR, De Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148. doi:10.1056/nejmoa1209096
406. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160. doi:10.1016/s1470-2045(14)71205-7
407. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197. doi:10.1056/nejmoa1207506
408. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433. doi:10.1056/nejmoa1405095
409. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. *Eur Urol*. 2017;71(2):151-154. doi:10.1016/j.eururo.2016.07.032
410. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol*. 2018;36(14):1389-1395. doi:10.1200/jco.2017.76.4381
411. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter Radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223. doi:10.1056/nejmoa1213755
412. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of Radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol*. 2014;15(12):1397-1406. doi:10.1016/s1470-2045(14)70474-7
413. Gillessen S, Choudhury A, Saad F, et al. LBA1 A randomized multicenter open label phase III trial comparing enzalutamide vs a combination of Radium-223 (Ra223) and enzalutamide in asymptomatic or mildly symptomatic patients with bone metastatic castration-resistant prostate cancer (mCRPC): first results of EORTC-GUCG 1333/PEACE-3 [abstract]. *Ann Oncol*. 2024;35(suppl 2):S1254. doi:10.1016/j.annonc.2024.08.2307
414. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol*. 2019;20(12):1730-1739. doi:10.1016/s1470-2045(19)30688-6
415. Venkitaraman R, Lorente D, Murthy V, et al. A randomised phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. *Eur Urol*. 2015;67(4):673-679. doi:10.1016/j.eururo.2014.10.004
416. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid*. 2022;1(9):EVIDoa2200043. doi:10.1056/evidoa2200043
417. Saad F, Clarke NW, Oya M, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24(10):1094-1108. doi:10.1016/s1470-2045(23)00382-0
418. De Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102. doi:10.1056/nejmoa1911440
419. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;383(24):2345-2357. doi:10.1056/nejmoa2022485
420. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or physician's choice in metastatic prostate cancer. *N Engl J Med*. 2023;388(8):719-732. doi:10.1056/nejmoa2214676
421. Bryce AH, McDermott RS, Piulats JM, et al. Rucaparib vs docetaxel (DTX) or second-generation androgen pathway inhibitor (ARPI) therapy for metastatic castration-resistant prostate cancer (mCRPC): TRITON3 final overall survival (OS) and safety [abstract]. *J Clin Oncol*. 2025;43(5 suppl):155. doi:10.1200/jco.2025.43.5_suppl.155
422. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10398):291-303. doi:10.1016/s0140-6736(23)01055-3
423. Agarwal N, Azad A, Carles J, et al. Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial [abstract]. *J Clin Oncol*. 2025;43(5 suppl):LBA18. doi:10.1200/jco.2025.43.5_suppl.lba18
424. Shui IM, Burcu M, Shao C, et al. Real-world prevalence of homologous recombination repair mutations in advanced prostate cancer: an analysis of two clinico-genomic databases. *Prostate Cancer Prostatic Dis*. 2023;27(4):728-735. doi:10.1038/s41391-023-00764-1
425. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell*. 2015;161(5):1215-1228. doi:10.1016/j.cell.2015.05.001
426. Lowrance W, Dreicer R, Jarrard DF, et al. Updates to advanced prostate cancer: AUA/SUO guideline (2023). *J Urol*. 2023;209(6):1082-1090. doi:10.1097/ju.0000000000003452
427. Giri VN, Knudsen KE, Kelly WK, et al. Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. *J Clin Oncol*. 2018;36(4):414-424. doi:10.1200/jco.2017.74.1173
428. Chi KN, Rathkopf D, Smith MR, et al.; MAGNITUDE Principal Investigators. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2023;41(18):3339-3351. doi:10.1200/jco.22.01649
429. Fizazi K, Azad AA, Matsubara N, et al. First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial. *Nat Med*. 2024;30(1):257-264. doi:10.1038/s41591-023-02704-x
430. Gillessen S, Turco F, Davis ID, et al. Management of patients with advanced prostate cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC). *Eur Urol*. 2025;87(2):157-216. doi:10.1016/j.eururo.2024.09.017
431. Sartor O, De Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385(12):1091-1103. doi:10.1056/nejmoa2107322
432. Morris MJ, Castellano D, Herrmann K, et al. 177Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. *Lancet*. 2024;404(10459):1227-1239. doi:10.1016/s0140-6736(24)01653-2
433. Sartor O, Jiang DM, Smoragiewicz M, et al. LBA65 Efficacy of 177Lu-PNT2002 in PSMA-positive mCRPC following progression on an androgen-receptor pathway inhibitor (ARPI) (SPLASH) [abstract]. *Ann Oncol*. 2024;35(suppl 2):S1254-S1255. doi:10.1016/j.annonc.2024.08.2308
434. De Bono JS, De Giorgi U, Rodrigues DN, et al. Randomized phase II study evaluating Akt blockade with ipatasertib, in combination with abiraterone, in patients with metastatic prostate cancer with and without PTEN loss. *Clin Cancer Res*. 2019;25(3):928-936. doi:10.1158/1078-0432.ccr-18-0981

435. Sweeney C, Bracarda S, Sternberg CN, et al. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*. 2021;398(10295):131-142. doi:10.1016/s0140-6736(21)00580-8
436. Abida W, Cheng ML, Armenia J, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. *JAMA Oncol*. 2019;5(4):471-478. doi:10.1001/jamaoncol.2018.5801
437. Ronson GE, Piberger AL, Higgs MR, et al. PARP1 and PARP2 stabilise replication forks at base excision repair intermediates through Fbh1-dependent Rad51 regulation. *Nat Commun*. 2018;9(1):746. doi:10.1038/s41467-018-03159-2
438. Azad A, Voskoboynik M, Palma Dos Reis AF, et al. Phase 1/2a study of AZD5305, a novel poly(adenosine diphosphate ribose) polymerase (PARP) 1-selective inhibitor in combination with new hormonal agents (NHAs) in patients (pts) with metastatic prostate cancer (mPC) [abstract]. *J Clin Oncol*. 2023;41(6 suppl):TPS296. doi:10.1200/jco.2023.41.6_suppl.tps296
439. Bernard-Tessier A, Utriainen T, Cook N, et al. Impact of activating androgen receptor (AR) mutations on AR sensitivity to alternative ligands and response to ODM-208, a selective, first-in-class CYP11A1 inhibitor, in patients with advanced metastatic castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol*. 2022;40(16 suppl):5057. doi:10.1200/jco.2022.40.16_suppl.5057
440. Gao X, Burris III HA, Vuky J, et al. Phase 1/2 study of ARV-110, an androgen receptor (AR) PROTAC degrader, in metastatic castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol*. 2022;40(6 suppl):017. doi:10.1200/jco.2022.40.6_suppl.017
441. Shen F, Kelly WK, Pandit-Taskar N, et al. Preclinical characterization of human kallikrein 2 (hK2) as a novel target for the treatment of prostate cancer [abstract]. *J Clin Oncol*. 2024;42(4 suppl):202. doi:10.1200/jco.2024.42.4_suppl.202
442. Bhatia V, Kamat NV, Pariva TE, et al. Targeting advanced prostate cancer with STEAP1 chimeric antigen receptor T cell and tumor-localized IL-12 immunotherapy. *Nat Commun*. 2023;14(1):2041. doi:10.1038/s41467-023-37874-2
443. Puca L, Gavyert K, Sailer V, et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. *Sci Transl Med*. 2019;11(484):eaav0891. doi:10.1126/scitranslmed.aav0891
444. Schade AE, Kuzmickas R, Rodriguez CL, et al. Combating castration-resistant prostate cancer by co-targeting the epigenetic regulators EZH2 and HDAC. *PLoS Biol*. 2023;21(4):e3002038. doi:10.1371/journal.pbio.3002038
445. Noone AM, Howlader N, Krapcho M, et al., eds. *SEER Cancer Statistics Review, 1975–2015*. National Cancer Institute; 2018. Accessed December 4, 2024. https://seer.cancer.gov/archive/csr/1975_2015/index.html
446. Chipperfield K, Fletcher J, Millar J, et al. Predictors of depression, anxiety and quality of life in patients with prostate cancer receiving androgen deprivation therapy. *Psychooncology*. 2013;22(10):2169-2176. doi:10.1002/pon.3269
447. Ralph N, Ng SK, Zajdlewicz L, et al. Ten-year quality of life outcomes in men with prostate cancer. *Psychooncology*. 2020;29(2):444-449. doi:10.1002/pon.5255
448. Rhee H, Gunter JH, Heathcote P, et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int*. 2015;115(suppl 5):3-13. doi:10.1111/bju.12964
449. Donovan KA, Walker LM, Wassersug RJ, Thompson LMA, Robinson JW. Psychological effects of androgen-deprivation therapy on men with prostate cancer and their partners. *Cancer*. 2015;121(24):4286-4299. doi:10.1002/cncr.29672
450. Edmunds K, Tuffaha H, Galvão DA, Scuffham P, Newton RU. Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review. *Support Care Cancer*. 2020;28(5):2079-2093. doi:10.1007/s00520-019-05255-5
451. Kaplan AL, Hu JC, Morgentaler A, Mulhall JP, Schulman CC, Montorsi F. Testosterone therapy in men with prostate cancer. *Eur Urol*. 2016;69(5):894-903. doi:10.1016/j.eururo.2015.12.005
452. Michaud JE, Billups KL, Partin AW. Testosterone and prostate cancer: an evidence-based review of pathogenesis and oncologic risk. *Ther Adv Urol*. 2015;7(6):378-387. doi:10.1177/1756287215597633
453. Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005;352(2):154-164. doi:10.1056/nejmoa041943
454. Smith M, Parker C, Saad F, et al. Addition of Radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:408-419. doi:10.1016/s1470-2045(18)30860-x
455. Jones C, Sachdeva A, Murphy L, et al. MP11-13 Clinical fracture incidence in metastatic hormone-sensitive prostate cancer (mHSPC) and risk-reduction following addition of zoledronic acid to androgen deprivation therapy (ADT) with or without docetaxel (DOC): long-term results from 2 phase 3 trials from the STAMPEDE platform protocol [abstract]. *J Urol*. 2023;209(suppl 4):e129. doi:10.1097/ju.0000000000003226.13
456. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458-1468. doi:10.1093/jnci/94.19.1458
457. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96(11):879-882. doi:10.1093/jnci/djh141
458. D'Oronzo S, Coleman R, Brown J, Silvestris F. Metastatic bone disease: pathogenesis and therapeutic options: up-date on bone metastasis management. *J Bone Oncol*. 2019;15:004. doi:10.1016/j.jbo.2018.10.004
459. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813-822. doi:10.1016/s0140-6736(10)62344-6
460. Wright JL, Schenk JM, Gulati R, et al. The Prostate Cancer Active Lifestyle Study (PALS): a randomized controlled trial of diet and exercise in overweight and obese men on active surveillance. *Cancer*. 2024;130(12):2108-2119. doi:10.1002/cncr.35241
461. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. *J Clin Oncol*. 2014;32(4):335-346. doi:10.1200/jco.2013.49.5523
462. Resnick MJ, Lacchetti C, Penson DF; American Society of Clinical Oncology. Prostate cancer survivorship care guidelines: American Society of Clinical Oncology practice guideline endorsement. *J Oncol Pract*. 2015;11(3):e445-e449. doi:10.1200/jop.2015.004606
463. Gillessen S, Murphy LR, James ND, et al. LBA70 Adding metformin to androgen deprivation therapy (ADT) for patients (pts) with metastatic hormone sensitive prostate cancer (mHSPC): overall survival (OS) results from the multi-arm, multi-stage randomised platform trial STAMPEDE [abstract]. *Ann Oncol*. 2024;35(suppl 2):S1258-S1259. doi:10.1016/j.annonc.2024.08.2313

464. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J Clin*. 2017;67(5):362-377. doi:10.3322/caac.21406
465. van Kan GA, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. *J Am Med Dir Assoc*. 2008;9(2):71-72. doi:10.1016/j.jamda.2007.11.005
466. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc*. 2001;49(12):1691-1699. doi:10.1046/j.1532-5415.2001.49281.x
467. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32(24):2595-2603. doi:10.1200/jco.2013.54.8347
468. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489-495. doi:10.1503/cmaj.050051
469. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. *Cancer*. 2005;104(9):1998-2005. doi:10.1002/cncr.21422
470. University of California, Berkeley; Max Planck Institute for Demographic Research. Human Mortality Database. Accessed December 4, 2024. https://www.mortality.org
471. Sundahl N, Brand D, Parker C, et al. Weekly ultra-hypofractionated radiotherapy in localised prostate cancer. *Clin Transl Radiat Oncol*. 2024;47:100800. doi:10.1016/j.ctro.2024.100800
472. Smith MR, Rathkopf DE, Mulders PFA, et al. Efficacy and safety of abiraterone acetate in elderly (75 years or older) chemotherapy naive patients with metastatic castration resistant prostate cancer. *J Urol*. 2015;194(5):1277-1284. doi:10.1016/j.juro.2015.07.004
473. Graff JN, Baciarello G, Armstrong AJ, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol*. 2016;27(2):286-294. doi:10.1093/annonc/mdv542
474. Stattin P, Westerberg M, Lissbrant IF, et al. Real world outcomes in patients with metastatic, castration-resistant prostate cancer treated with Radium-223 in routine clinical practice in Sweden. *Clin Genitourin Cancer*. 2023;21(1):107.e1-107.e9. doi:10.1016/j.clgc.2022.09.002

How to cite this article: Chakrabarti D, Albertsen P, Adkins A, et al. The contemporary management of prostate cancer. *CA Cancer J Clin*. 2025;75(6):552-586. doi:10.3322/caac.70020