

Neoadjuvant Therapies in High-Risk Localized Prostate Cancer: Past, Present, and Future

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Abstract: Treatment for high-risk localized prostate cancer can be particularly challenging because of an elevated risk of disease recurrence. One of the proposed ways to improve the success of definitive localized treatment (such as radical prostatectomy or radiation therapy) for these patients is the addition of neoadjuvant therapy. Thus, therapeutic strategies that have demonstrated benefit in metastatic prostate cancer settings have been translated to and evaluated in the neoadjuvant setting. The therapies studied include androgen deprivation therapy, ranging from androgen receptor-specific blockade to more comprehensive androgen signaling pathway blockade; chemotherapy, especially taxane-based therapy; immunotherapy; and most recently, prostate-specific membrane antigen radioligand therapy. In this review, we provide an overview of various trials that have explored the pathologic and oncologic results of these therapies in various prostate cancer settings and discuss the emerging role of theranostics in this space.

Introduction

Prostate cancer is often diagnosed at a localized stage, but its clinical course and treatment recommendations vary widely depending on the risk stratification of the cancer. Low-risk prostate cancer is defined by the presence of all the following disease characteristics: clinical stage T1-T2a (cT1-T2a), Gleason Grade Group of 1, and a prostate-specific antigen (PSA) level of less than 10 ng/mL. Intermediate-risk prostate cancer is defined by the following: no high- or very high-risk features, cT2b-cT2c, Gleason score of 2 or 3, and/or a PSA level of 10 to 20 ng/mL.¹ High-risk prostate cancer is typically defined by one or more of the following features: Gleason score of at least 8, PSA level above 20 ng/mL, and/or clinical stage of at least T3.¹ Of note, very high-risk disease is defined by the

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presence of at least 2 high-risk features or a PSA level of at least 40 ng/mL.¹

Disease progression in patients with low-risk prostate cancer is often slow, with low rates of cancer-specific mortality on active surveillance protocols (0.1% to 3.1%).^{2,3} In contrast, high-risk localized prostate cancer is a fairly heterogeneous disease, particularly because patients can be classified as having high-risk disease on the basis of just one qualifying feature. As a result, high-risk localized prostate cancer requires unique therapeutic strategies and considerations. Patients with intermediate- or high-risk disease often undergo definitive treatment such as radical prostatectomy (RP) or radiation therapy (RT), but the literature demonstrates that patients with high-risk disease can have an elevated risk for biochemical recurrence (BCR) after these primary therapies. The risk of BCR after surgery may be as high as 50%.⁴ This elevated risk is thought to be due to the potential presence of micrometastases at the time of diagnosis,^{5,6} the increased difficulty of oncologic control during primary localized treatment, and particularly aggressive histologic subtypes.⁷ Recurrent prostate cancer carries a relatively high risk of prostate cancer–specific mortality in addition to a large logistical burden imposed by the additional treatments required.

The current American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO) guidelines (from 2022) for the treatment of high-risk localized prostate cancer endorse RP or RT plus androgen deprivation therapy (ADT).⁸ The use of RP has been increasing, driven by studies demonstrating effective local control,⁹ the ability to stage the tumor pathologically after this monotherapy, and advancements in surgical techniques. Additionally, surgery allows patients to defer or potentially avoid upfront radiation and ADT, thereby delaying exposure to their associated adverse effects, such as cardiovascular, cognitive, and hematologic toxicity.¹ These treatments can instead be reserved for salvage therapy if needed.

To maximize the success of primary RP or RT for these patients (and in turn minimize the risk of BCR), the addition of neoadjuvant therapy has been proposed. Neoadjuvant research seeks to optimize the outcomes of treatment by assisting local control—for example, by downstaging the disease before surgery or radiation and/or providing in vivo observation of a systemic response to the administered treatment.⁶ This review synthesizes the evolution of strategies for maximizing therapeutics in high-risk prostate cancer, including the discoveries of adjuvant and neoadjuvant treatments, notable trials in hormonal therapy and chemotherapy, immunotherapy, and the recently developing forefront of radioligand theranostics.

Decision-Making Tools in the Treatment of Prostate Cancer

The probability of BCR after local treatment is difficult to estimate because it is influenced by multiple tumor characteristics.¹⁰ Current literature also implicates factors such as lymph node involvement, adverse pathologic features (eg, positive surgical margins, extracapsular extension),^{10,11} tumor volume, and aggressive histologic subtypes in the development of BCR. Two pathologic variants of prostate cancer that are deemed to be particularly high-risk are cribriform pattern and intraductal carcinoma. The presence of cribriform pattern has been associated with an increased risk of BCR,⁷ as has the presence of intraductal carcinoma.¹²

Thus, the identification of these risk-associated characteristics offers important guidance for physicians when they are developing treatment strategies aimed at reducing recurrence. Biopsy tissue analysis alone may not reflect the true aggressiveness of a patient's disease, given the diversity of contributing factors to consider. For this reason, additional assessment with tissue-based genomic classifying tools, such as molecular biomarkers, has gained traction. Pretreatment tools that are used before definitive prostatectomy include the Decipher, Prolaris, and Oncotype DX genomic tests, which analyze tumor tissue from the patient's biopsy specimen. Testing options before radiation include Altera, which offers comprehensive genomic profiling by incorporating both tissue and blood samples and facilitates personalized treatment. Although currently no validated clinical trials have examined the effect of these tools, the current post hoc analyses and retrospective literature suggest that the classifier scores are of clinical utility in treatment decision making and are independently associated with risk of metastases and/or cancer-specific mortality.¹³⁻¹⁵

Therapeutic Targets in Prostate Cancer

In terms of treatment decision making and planning, options often target the androgen synthesis and signaling pathways. The androgen signaling pathway is considered the key modulator in the development and progression of prostate cancer.¹⁶ The androgen receptor (AR) plays a key role and is expressed to some degree in all prostate cancers, including both primary and metastatic lesions. Androgens (eg, testosterone and dihydrotestosterone [DHT]) bind to this receptor, activating AR transcriptional activity¹⁷ and inducing a cascade of proliferative and differentiation cellular events that are important for the controlled growth and development of epithelial and stromal prostate cells.^{18,19} For example, the AR/androgen signaling axis is thought to influence homeostasis and the

controlled growth of these specific types of prostate cells.²⁰ Such processes are essential for normal prostate physiology but can contribute to tumorigenesis when dysregulated. The AR typically plays a regulatory and suppressive role in the growth of prostatic epithelial cells, but in cancerous cells, it encourages proliferation over differentiation.²⁰

Given the central role of androgen binding and the AR in tumorigenesis, therapeutic targets stem from early observations revealing the dependence of prostate cancer on this pathway. The role of ADT was first established in 1941, when Huggins and Hodges demonstrated that blocking androgens produces clinical responses in advanced prostate cancer. Testosterone readministration reversed these effects, supporting androgen dependence. This work led to the development of pharmacologic ADT, including luteinizing hormone–releasing hormone (LHRH) agonists and antagonists as well as AR antagonists.^{21,22}

Early AR antagonists, such as flutamide, nilutamide, and bicalutamide, exert their effect by binding directly to the ligand-binding domain of ARs, thus blocking the binding of testosterone or DHT. Subsequent trials confirmed the efficacy of ADT in metastatic prostate cancer. Combined androgen blockade with goserelin (Zoladex, TerSera Therapeutics) plus flutamide delayed disease progression more effectively than orchiectomy, and the addition of flutamide to leuprolide improved progression-free survival in metastatic disease.^{23,24} Research then expanded to localized prostate cancer; multiple studies demonstrated improved disease-free and overall survival (OS) when these ADT regimens were compared with RT alone.²⁵⁻²⁷

Historically, antiandrogen agents were classified as steroidal or nonsteroidal. The early steroidal antiandrogens (cyproterone acetate, megestrol acetate) and nonsteroidal antiandrogens (flutamide, bicalutamide, nilutamide) had a similar AR-blocking function. However, the steroidal antiandrogens demonstrated progestational activity, resulting in partial LH suppression and a corresponding reduction of testosterone, likely affecting the patient's potency and libido. The steroidal antiandrogens also showed a wider range of interactions with nuclear receptors beyond the AR. In comparison, the nonsteroidal antiandrogens did not possess the same testosterone-lowering qualities or interactions beyond the AR.^{28,29} For this reason, use of these medications shifted more toward regimens that included nonsteroidal antiandrogens for maximal antiandrogen blockade with minimal off-target effects.³⁰

As noted, the binding affinity of the early AR antagonists were limited in scope.⁸ This feature, plus the common androgen withdrawal symptoms, often hindered their long-term use.⁸ On the other hand, the newer androgen receptor pathway inhibitors (ARPIs) provide a more comprehensive blockade; these medications are now considered the standard of care.⁸ ARPIs provide a

wider efficacy by exerting multiple inhibitory effects across the androgen signaling pathway. They competitively inhibit androgen binding to the AR with a higher degree of affinity than the early AR antagonists, inhibiting nuclear translocation of the hormone-AR complex and inhibiting DNA binding to the complex.³¹⁻³³ ARPIs inhibit androgens from adrenal and intratumoral sources as well; this is important, given that extratesticular androgen production has been implicated in the development of castration-resistant prostate cancer (CRPC).³⁴ These pharmacologic advantages have prompted extensive evaluation of the utility of ARPIs at various stages of prostate cancer.

Studies Exploring ARPIs as Primary Therapy in the Metastatic and Nonmetastatic Settings

ARPIs have demonstrated significant benefit to patients in the treatment of metastatic prostate cancer of various types. National Comprehensive Cancer Network guidelines endorse the incorporation of ARPIs (abiraterone, apalutamide [Erleada, Janssen], enzalutamide [Xtandi, Astellas], and darolutamide [Nubeqa, Bayer HealthCare]) for metastatic hormone-sensitive prostate cancer (mHSPC). Multiple landmark trials have helped demonstrate that the intensification of androgen-blocking agents can improve outcomes in metastatic prostate cancer (Table).

Given that metastatic cancer often has some level of androgen-independent growth, androgen-dependent pathway blockade may be useful in the nonmetastatic setting.³⁵ Several trials have been crucial in establishing the safety and efficacy of ARPIs in the management of high-risk localized prostate cancer. For example, the EMBARK trial studied the effect of enzalutamide in patients with high-risk prostate cancer after RP with recurrence of disease (defined as a PSA doubling time of ≤ 9 months and a PSA level of ≥ 2 ng/mL above the nadir after RT or of ≥ 1 ng/mL).³⁶ A combined therapy of enzalutamide and ADT was found to have a 5-year metastasis-free survival (MFS) rate of 87%, significantly higher than the rate for either enzalutamide monotherapy (80%) or ADT alone (71.4%).³⁷ Similarly, the STAMPEDE trial explored the addition of abiraterone or abiraterone plus enzalutamide (2 experimental groups) to standard ADT (control group) as a first-line therapy for patients with nonmetastatic prostate cancer. Intermediate-term results demonstrated longer MFS in the combination groups than in the control group. The hazard ratio (HR) for MFS was 0.54 (95% CI, 0.43-0.68) for abiraterone and 0.53 (95% CI, 0.39-0.71) for abiraterone plus enzalutamide, and the HR for OS was 0.63 (95% CI, 0.48-0.82) for abiraterone and 0.54 (95% CI, 0.39-0.76) for abiraterone plus enzalutamide.³⁷

Table. Notable Trials With Associated Progression-Free Survival and Overall Survival Rates

Trial (y)	Therapy (EXP vs SOC)	Risk group	PFS/rPFS/MFS, HR (EXP vs SOC)	OS/PCSS, HR (EXP vs SOC)
ARNEO (2023)	Neoadjuvant degarelix + apalutamide vs neoadjuvant degarelix + placebo	High-risk localized	N/A	N/A
GETUG-12 (2018)	Docetaxel + ADT vs ADT alone	High-risk localized	12-y MFS: 0.81 (95% CI, 0.6-1.09) 12-y RFS: 0.71 (95% CI, 0.55-0.93)	12-y PCSS: 0.7 (95% CI, 0.4-1.22)
EMBARK (2023)	Enzalutamide + ADT vs placebo + ADT	High-risk biochemical recurrence	PFS: 0.42 (95% CI, 0.3-0.61)	0.59* (95% CI, 0.38-0.91)
STAMPEDE (2017)	Abiraterone + ADT vs ADT	Locally advanced or metastatic	3-y PFS: 0.40 (95% CI, 0.34-0.47)	OS: 0.63 (95% CI, 0.52-0.76)
PROTEUS (ongoing)	Apalutamide (before and after RP) + ADT vs placebo + ADT	Localized high-risk or locally advanced	Ongoing	Ongoing
LATITUDE (2019)	Abiraterone + ADT vs placebo + ADT	mHSPC	rPFS: 0.47 (95% CI, 0.39-0.55)	OS: 0.66 (95% CI, 0.56-0.78)
ARANOTE (2024)	Darolutamide + ADT vs ADT	mHSPC	rPFS: 0.54 (95% CI, 0.41-0.71)	OS: 0.81 (95% CI, 0.59-1.12)
CHAARTED (2015)	Docetaxel + ADT vs ADT alone	mHSPC	PFS: 0.61 (95% CI, 0.51-0.72)	OS: 0.61 (95% CI, 0.47-0.80)
LUNAR (2023)	¹⁷⁷ Lu-PNT2002 + SBRT vs SBRT	Oligorecurrent mHSPC	PFS: 0.37 (95% CI, 0.22-0.61)	Not given
AFFIRM (2014)	Enzalutamide vs placebo	mCRPC	rPFS: <75 y: 0.45 (95% CI, 0.38-0.53) rPFS ≥75 y: 0.27 (95% CI, 0.20-0.37)	OS, <75 y: 0.63 (95% CI, 0.52-0.78) OS, ≥75 y: 0.61 (95% CI, 0.43-0.86)
VISION (2021)	¹⁷⁷ Lu-PSMA-617 + SOC vs SOC	PSMA-positive mCRPC	rPFS: 0.4 (99.2% CI, 0.29-0.57)	OS: 0.62 (95% CI, 0.52-0.74)
PSMAfore (2024)	¹⁷⁷ Lu-PSMA-617 vs change in ARPI	PSMA-positive mCRPC, previously failed ARPI	rPFS: 0.49 (95% CI, 0.39-0.61)	OS: 0.98 (95% CI, 0.75-1.28)

*Reported as MFS/OS by study.

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; EXP, experimental treatment; HR, hazard ratio; ¹⁷⁷Lu, lutetium 177; MFS, metastasis-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; N/A, not available; OS, overall survival; PCSS, prostate cancer-specific survival; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; RFS, relapse-free survival; RP, radical prostatectomy; rPFS, radiographic PFS; SOC, standard-of-care treatment; SBRT, stereotactic body radiotherapy; y, year(s).

Hormone Therapy in the Neoadjuvant Setting

Given the demonstrated efficacy of ADT and ARPIs in the primary treatment of prostate cancer, research efforts have aimed to extend these therapeutic benefits to the neoadjuvant setting. One goal of neoadjuvant hormonal therapy is to reduce the disease burden before surgery to maximize the chance of achieving complete tumor removal and negative surgical margins. These are thought to be helpful for patients with an elevated risk of recurrence—that is, patients with high-risk or very

high-risk prostate cancer.

The results of neoadjuvant hormonal therapy before surgery date back to the 1990s, when Labrie and colleagues found decreased rates of positive surgical margins in patients with cT2-cT3 disease who received neoadjuvant flutamide and an LHRH agonist before RP (neoadjuvant therapy + RP: 7.8%, RP alone: 33.8%).³⁸ Intermediate-term results of studies that explored the use of goserelin, leuprolide, and/or flutamide before RP often showed decreased rates of positive surgical margins and other pathologic results, but these results did not

translate into meaningful oncologic improvements, such as increased OS or BCR-free rates.^{39,40}

Multiple systematic reviews have summarized the literature about neoadjuvant AR antagonists, explaining that although the results show improved pathologic findings, the literature is still lacking proven long-term oncologic outcomes, especially in the setting of high-risk localized disease.⁷ Given the documented benefits of ARPIs in patients with metastatic and nonmetastatic disease, further emphasis was placed on testing the effects of neoadjuvant ARPIs.³⁴

The ARNEO trial evaluated the addition of neoadjuvant apalutamide to a regimen of degarelix (Firmagon, Ferring) before RP. All patients were followed after surgery until PSA relapse, and no median follow-up time was reported. This study found improved rates of measurable residual disease (MRD; 38% vs 9.1%; $P=.002$) and tumor downstaging (40% vs 30%; $P=0.3$); however, changes in the BCR rates were not significant (control group, 96% BCR-free; apalutamide group: 93% BCR-free).⁴¹ As noted by the study, longer-term trials are required for a better evaluation of oncologic outcomes.

A recent phase 2 study from China explored the addition of darolutamide, another ARPI, to a neoadjuvant regimen of ADT before RP in patients with high-risk or very high-risk prostate cancer.⁴² At 12-month follow-up, the progression-free survival (PFS) rate was 90%. The relatively short follow-up limits the evaluation of oncologic outcomes, but at present, no other studies with long-term oncologic outcomes are available for comparison. Millan and colleagues also recently conducted an analysis of an open-label trial and described the long-term outcomes (median follow-up, 7.3 years) of patients with intermediate-, high-, or very high-risk localized or regional prostate cancer who had received a regimen of neoadjuvant ADT and enzalutamide before RP. This study found a 5-year BCR-free rate of 64.15% and a cancer-specific survival rate of 94.3% for this group. Although the study was limited by the lack of a control group, it concluded that the use of neoadjuvant enzalutamide and ADT is associated with favorable long-term outcomes and supported continued investigation into this therapy for patients with localized prostate cancer.⁴³

Devos and colleagues performed a systematic review of the role of neoadjuvant hormonal therapy in localized prostate cancer (unfavorable intermediate-risk or high-risk disease). This review discussed the documented decreases in positive surgical margins and residual cancer burden observed when patients in the ARPI arms were compared with those who received classic ADT, but the authors noted that long-term and oncologic outcomes data are still scarce.³⁴

Results from the currently active PROTEUS study

will also contribute meaningfully. PROTEUS is a randomized, double-blind, placebo-controlled phase 3 trial evaluating the addition of neoadjuvant apalutamide to ADT for localized high-risk prostate cancer or locally advanced prostate cancer.⁴⁴ Primary outcomes will examine pathologic complete response (pCR) and MFS, with secondary endpoints including PSA-free survival and PFS; the estimated study completion is in 2028.

The Role of Chemotherapy

Other systemic treatments, such as chemotherapy, also have been explored for these patient populations. Early trials explored the use of nontaxane treatment regimens that ultimately failed to show significant clinical benefit; for example, SWOG S9921 tested mitoxantrone, and RTOG 9902 tested paclitaxel, estramustine (Emcyt, Pfizer), and oral etoposide.^{45,46} However, later trials using taxane-based regimens yielded results with more favorable efficacy and tolerability, as described in the Table. One of the most commonly used taxane-based chemotherapeutic agents is docetaxel; literature offers multiple potential mechanisms of action for these agents, including binding to and interfering with microtubule function, thereby leading to cell cycle arrest and the subsequent suppression of cell viability, or micronucleation and subsequent membrane rupture.⁴⁷ Long-term results of the STAMPEDE trial demonstrated longer OS in patients with metastatic hormone-naïve prostate cancer who were treated with docetaxel plus ADT than in those treated with ADT alone⁴⁸; however, results of another trial arm that evaluated the use of docetaxel with hormonal therapy in patients with nonmetastatic disease did not demonstrate long-term benefit.⁴⁹

The application of docetaxel was then translated to the neoadjuvant setting. One open-label, nonrandomized, single-center phase 2 trial assigned patients with locally advanced prostate cancer to 6 weeks of neoadjuvant docetaxel therapy before RP. Final pathology demonstrated residual cancer in all specimens, but at 2-year follow-up, 71% of the patients were clinically and biochemically free of disease.⁵⁰ A 10-year follow-up of this same cohort found a promising OS rate of 79.7% and a prostate cancer-specific survival rate of 92.2%.⁵¹

Results from phase 3 trials were congruent. The phase 3 GETUG-12 trial randomized patients with intermediate- or high-risk disease to RT and ADT alone or to RT and ADT with neoadjuvant/adjunct docetaxel and estramustine. At a median follow-up of 12 years, addition of the chemotherapy regimen was associated with an increased 12-year relapse-free survival rate (49.4%; 95% CI, 42.5-56.3) in comparison with ADT (36.3%; 95% CI, 29.7-43.5; HR, 0.71; 95% CI, 0.55-0.93; $P=.01$).

The data showed no significant increase in secondary cancer rates in the chemotherapy arm.⁵² The CALGB 90203 trial tested the addition of neoadjuvant docetaxel plus ADT before RP vs RP alone in patients with clinically localized high-risk prostate cancer. Although some secondary endpoints demonstrated improvement (overall biochemical PFS, OS, MFS), the primary endpoint (improved biochemical PFS at 3 years) was not met, and the study noted that further follow-up is needed to clarify the potential benefits seen.⁵³ Studies have continued to explore this treatment, with some finding significant improvements in oncologic outcomes such as biochemical PFS⁵⁶ and others finding no significant differences.⁵⁴

Overall, these trials helped clarify the utility of specific chemotherapies in the management of high-risk localized prostate cancer. Although such neoadjuvant approaches have shown potential for improving pathologic and oncologic outcomes, their use is limited by systemic toxicity and the risk of secondary malignancy, prompting the exploration of more precise cytotoxic strategies such as immunotherapy and radiopharmaceuticals.

Exploring the Use of Immunotherapy

Emerging research has explored immunotherapy as a more “personalized” strategy in the treatment of prostate cancer, leveraging approaches that target tumor-specific immune mechanisms and, ideally, better protect normal cells. One of the most studied is the programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck). Given that the expression of PD-1 by T cells allows cancer cells expressing the complementary programmed death–ligand 1 (PD-L1) protein to evade recognition by host immune cells, the blockade of PD-1 is an important anticancer strategy and is also used in numerous other malignancies.⁵⁵ Pembrolizumab has been evaluated in the locally advanced and metastatic prostate cancer settings with some promise,^{56,57} but long-term results are pending.

Poly(ADP-ribose) polymerase (PARP) inhibitors offer another strategy for precisely targeting the offensive immune mechanisms of cancers. These medications are especially important in the treatment of cancers that lack homologous recombination repair (HRR) genes (a specific type of DNA repair), as this lack causes overreliance on a PARP-mediated repair mechanism. Blocking the alternative repair pathway in cancer cells can lead to an accumulation of DNA damage and cell death, so that blockage is an attractive therapeutic target.⁵⁸ Several US Food and Drug Administration (FDA)–approved medications of this class include olaparib (Lynparza, AstraZeneca), rucaparib (Rubraca, Clovis Oncology), and talazoparib (Talzenna, Pfizer; approved for administration with enzalutamide),⁵⁹ which showed benefit in patients

with mCRPC who had HRR gene mutations.^{60–62}

Research on the neoadjuvant application of PARP inhibitors is growing. The phase 2 NCT04030559 and NePtune trials are testing the utility of niraparib (Zejula, GlaxoSmithKline) and olaparib, respectively, in patients with unfavorable intermediate- to high-risk prostate cancer and HRR gene deficiencies.⁵⁸ A phase 2 trial is evaluating the addition of pembrolizumab plus olaparib vs the addition of single-agent pembrolizumab to standard ADT with RT for patients with high-risk localized prostate cancer (NCT05568550). Primary outcomes will assess PSA nadir after RT, and secondary outcomes will assess BCR and MFS at 3 years.

Radiopharmaceuticals

Like immunotherapy, radioligand therapy is a new class of precise therapies utilized for several cancer treatments. Radioligand therapies consist of a radiation-emitting component (radionuclide chelator and isotope) complexed to a targeting agent (a small molecule that targets a specific antibody or antigen).⁶³ Radioligand therapy provides the unique advantage of delivering targeted radiation-emitting isotopes to cells expressing tumor-specific characteristics, ideally sparing normal tissue and effectively targeting cancer-specific cells. The first FDA-approved radiopharmaceutical was radium 223, and current clinical trials are evaluating additional radioisotopes for therapeutic use.⁶³

Lutetium 177 (¹⁷⁷Lu) PSMA-617 is a new radionuclide being explored for patients with high-risk localized prostate cancer. This is a theranostic therapy based on preoperative imaging with prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT). PSMA PET/CT tags and highlights the membrane-bound glycoprotein PSMA, which is highly expressed on prostate cancer-specific cells.⁶⁴ Thus, through the targeting of prostate cancer cells via PSMA recognition and the cytotoxic action induced by the beta-emitting radioligand ¹⁷⁷Lu, this therapy is thought to provide more precise “on-target” therapeutics while minimizing “off-target” side effects.^{63,65}

First, phase 1 trials demonstrated the safety and feasibility of this therapy.⁶⁵ Research then moved into phase 2 studies to evaluate its efficacy in metastatic disease. The UpFrontPSMA study is a multi-institutional, open-label, randomized trial that included patients with high-volume mHSPC.⁶⁶ Patients were randomized to receive either ¹⁷⁷Lu-PSMA-617 plus docetaxel (experimental) or docetaxel alone (standard of care), and all patients also received ADT. A total of 41% of patients in the experimental group had undetectable PSA level at 48 weeks, which was the primary endpoint of the study, vs 16% in

the standard-of-care group.⁶⁶

The VISION trial demonstrated the efficacy of ¹⁷⁷Lu-PSMA-617 in the mCRPC population.⁶⁷ This international open-label trial included patients who previously had received at least one course of ADT and 1 to 2 cycles of chemotherapy, as well as a positive PSMA scan result. The ¹⁷⁷Lu-PSMA-617 group demonstrated improved image-based PFS (median, 8.7 vs 3.4 months; HR for progression or death, 0.4; 99.2% CI, 0.29-0.57; $P<.001$) and OS (median, 15.3 vs 11.3 months; HR for death, 0.62; 95% CI, 0.52-0.74; $P<.001$). The phase 3 PSMAfore trial also studied efficacy in patients with mCRPC. This open-label, randomized study delivered either ¹⁷⁷Lu-PSMA-617 or “change of ARPI” to abiraterone or enzalutamide (all patients had experienced disease progression once on a previous ARPI). In the primary analysis, the study found that the experimental ¹⁷⁷Lu-PSMA-617 group demonstrated longer radiographic PFS (experimental, 11.6 months vs ARPI, 5.59 months; HR, 0.49; 95% CI, 0.39-0.61).⁶⁸ Taken together, these trials support the growing role of ¹⁷⁷Lu-PSMA-617 in the treatment of metastatic prostate cancer.

The results have also prompted investigation into the earlier application of these therapies. The LUNAR trial is an open-label, randomized, 2-arm, single-center phase 2 trial that seeks to compare the efficacy of neoadjuvant Lu-177-PNT2002 with that of traditional stereotactic body radiotherapy in patients with oligorecurrence.⁶⁹ Current regimens offer metastasis-directed therapy as stereotactic body radiation or surgery, but progression to distant metastatic disease often requires additional therapy.⁶⁹ In recently reported results, at a median follow-up of 22 months, the Lu-177-PNT2002 group had significantly better PFS (the primary endpoint), at 17.6 vs 7.4 months (HR, 0.37; 95% CI, 0.22-0.61; $P<.0001$).

Clinical trials are now exploring the role of radioligand therapy in localized high-risk prostate cancer. The first trial to explore this was the LuTectomy trial, a phase 1 trial that tested the safety and feasibility of neoadjuvant ¹⁷⁷Lu-PSMA in this category of patients.⁷⁰ Adverse events were well tolerated, with no Clavien-Dindo grade 3 or higher complications found. Taking this further, the prospective, nonrandomized, single-arm, interventional phase 2 PRELUDE trial will evaluate the outcomes of neoadjuvant ¹⁷⁷Lu-PSMA-617 before RP in patients with high-risk, PSMA-defined prostate-only disease. Primary outcomes will focus on the downstaging of prostate cancer following RP. The trial is currently open and accruing patients (NCT06798558).

Despite these advances, radioligand therapy remains limited by the challenge of optimizing the radiation dose to maximize efficacy while minimizing renal toxicity.⁷¹ Thus,

the concept of radiohybrid PSMA ligands (rhPSMA) is being increasingly studied; this therapy maximizes the theranostic opportunity of radioligands via labeling with diagnostic and therapeutic radiometals (fluorine 18).⁷² Preclinical studies have identified rhPSMA-10.1 and rhPSMA-10.2 as promising theranostic candidates, with high rates of tumor uptake and fast clearance from the kidneys.⁷³ The phase 1/2 Nautilus trial will explore the safety and efficacy of neoadjuvant ¹⁷⁷Lu-rhPSMA-10.1 in patients with high-risk, localized prostate cancer before primary RP. The 2 study arms will include patients with either neoadjuvant ¹⁷⁷Lu-rhPSMA-10.1 alone or neoadjuvant ¹⁷⁷Lu-rhPSMA-10.1 plus degarelix. Study completion is planned for 2027 (NCT06066437).

As research on lutetium-based radioligand therapy has progressed, other radioisotope candidates have also emerged. Whereas lutetium 177 is a beta-emitting particle, actinium 225 is an alpha-emitting particle, thought to deliver more energy than the former and thus induce more cellular damage with fewer radiation events.⁷⁴ However, research comparing the efficacy of these treatments is early and ongoing.⁷⁴ Notably, the phase 1 LUTACT study will compare safety, pathologic response, tumor-absorbed dose, and more in neoadjuvant ¹⁷⁷Lu-PSMA-617, neoadjuvant ²²⁵Ac-PSMA-617, and control arms (no neoadjuvant therapy before RP) in patients with high-risk localized prostate cancer (NCT07054346). Together, these efforts highlight a broader shift toward optimizing radionuclide selection to enhance therapeutic efficacy while balancing toxicity in radioligand therapy.

Conclusions

The treatment of high-risk localized prostate cancer poses unique challenges owing to the elevated risk of recurrence. The literature has explored multiple methods of decreasing this risk with adjuvant and neoadjuvant hormonal therapy, chemotherapy, immunotherapy, and radioligand therapy. Radioligand therapy offers particular advantages in comparison with the traditional approaches of hormonal therapy and chemotherapy, with improved ability to target prostate cancer cells and use a theranostic approach. Studies so far show potential, and ongoing trials will continue to contribute meaningfully to decision making guidance in the treatment of prostate cancer.

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References

- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Prostate cancer. Version 5.2026. January 23, 2026. Accessed April 20, 2026. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
- 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):2084-2093.
- Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med*. 2013;368(17):1547-1558.
- Hamada R, Nakashima J, Ohori M, et al. Preoperative predictive factors and further risk stratification of biochemical recurrence in clinically localized high-risk prostate cancer. *Int J Clin Oncol*. 2016;21(3):595-600.
- Devos G, Vansevenant B, De Meerleer G. Neoadjuvant treatment with androgen receptor signaling inhibitors prior to radical prostatectomy: a systematic review. *World J Urol*. 2021;39(9):3177-3185.
- McKay RR, Choueiri TK, Taplin ME. Rationale for and review of neoadjuvant therapy prior to radical prostatectomy for patients with high-risk prostate cancer. *Drugs*. 2013;73(13):1417-1430.
- Russo GI, Soeterik T, Puche-Sanz I, et al; European Association of Urology Young Academic Urologists. Oncological outcomes of cribriform histology pattern in prostate cancer patients: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*. 2023;26(4):646-654.
- 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.
- Chierigo F, Wenzel M, Würrschimmel C, et al. Survival after radical prostatectomy versus radiation therapy in high-risk and very high-risk prostate cancer. *J Urol*. 2022;207(2):375-384.
- Liu H, Zhou H, Yan L, et al. Prognostic significance of six clinicopathological features for biochemical recurrence after radical prostatectomy: a systematic review and meta-analysis. *Oncotarget*. 2017;9(63):32238-32249.
- Ball MW, Partin AW, Epstein JI. Extent of extraprostatic extension independently influences biochemical recurrence-free survival: evidence for further pT3 subclassification. *Urology*. 2015;85(1):161-164.
- Miura N, Mori K, Mostafaei H, et al. The prognostic impact of intraductal carcinoma of the prostate: a systematic review and meta-analysis. *J Urol*. 2020;204(5):909-917.
- Nguyen PL, Huang HR, Spratt DE, et al. Analysis of a biopsy-based genomic classifier in high-risk prostate cancer: meta-analysis of the NRG Oncology/Radiation Therapy Oncology Group 9202, 9413, and 9902 phase 3 randomized trials. *Int J Radiat Oncol Biol Phys*. 2023;116(3):521-529.
- Spratt DE, Yousefi K, Dehesi S, et al. Individual patient-level meta-analysis of the performance of the Decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. *J Clin Oncol*. 2017;35(18):1991-1998.
- Jairath NK, Dal Pra A, Vince R Jr, et al. A systematic review of the evidence for the Decipher genomic classifier in prostate cancer. *Eur Urol*. 2021;79(3):374-383.
- Li C, Cheng D, Li P. Androgen receptor dynamics in prostate cancer: from disease progression to treatment resistance. *Front Oncol*. 2025;15:1542811.
- Lonergan PE, Tindall DJ. Androgen receptor signaling in prostate cancer development and progression. *J Carcinog*. 2011;10:20.
- Nantermet PV, Xu J, Yu Y, et al. Identification of genetic pathways activated by the androgen receptor during the induction of proliferation in the ventral prostate gland. *J Biol Chem*. 2004;279(2):1310-1322.
- Culig Z, Klocker H, Bartsch G, Steiner H, Hobisch A. Androgen receptors in prostate cancer. *J Urol*. 2003;170(4 Pt 1):1363-1369.
- Zhou Y, Bolton EC, Jones JO. Androgens and androgen receptor signaling in prostate tumorigenesis. *J Mol Endocrinol*. 2015;54(1):R15-R29.
- Huggins C, Stevens RE, Hodges CV. The effects of castration on advanced carcinoma of the prostate gland. *Arch Surg*. 1941;43(2):209-223.
- The Nobel Prize in Physiology or Medicine 1966. NobelPrize.org. Accessed May 5, 2026. <https://www.nobelprize.org/prizes/medicine/1966/summary/>
- Keuppens F, Whelan P, Carneiro de Moura JL, et al. Orchiectomy versus goserelin plus flutamide in patients with metastatic prostate cancer (EORTC 30853). European Organization for Research and Treatment of Cancer—genitourinary Group. *Cancer*. 1993;72(12)(suppl):3863-3869.
- Benson RC Jr, Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Dorr FA. National Cancer Institute study of luteinizing hormone-releasing hormone plus flutamide versus luteinizing hormone-releasing hormone plus placebo. *Semin Oncol*. 1991;18(5)(suppl 6):9-12.
- 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):103-106.
- Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010;11(11):1066-1073.
- Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of Radiation Therapy Oncology Group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol*. 2008;26(15):2497-2504.
- McLeod DG. Antiandrogenic drugs. *Cancer*. 1993;71(3)(suppl):1046-1049.
- Chen Y, Clegg NJ, Scher HI. Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target. *Lancet Oncol*. 2009;10(10):981-991.
- Chen L, Wolff DW, Xie Y, Lin MF, Tu Y. Cyproterone acetate enhances TRAIL-induced androgen-independent prostate cancer cell apoptosis via up-regulation of death receptor 5. *BMC Cancer*. 2017;17(1):179.
- Schalken J and Fitzpatrick JM. Enzalutamide: targeting the androgen signalling pathway in metastatic castration-resistant prostate cancer. *BJU Int*. 2016;117(2):215-225.
- Fizazi K, Smith MR, Tombal B. Clinical development of darolutamide: a novel androgen receptor antagonist for the treatment of prostate cancer. *Clin Genitourin Cancer*. 2018;16(5):332-340.
- Boukova M, Spetsieris N, Efsthathiou E. An evaluation of apalutamide for the treatment of prostate cancer. *Expert Opin Pharmacother*. 2020;21(13):1537-1546.
- Devos G, Devlies W, De Meerleer G, et al. Neoadjuvant hormonal therapy before radical prostatectomy in high-risk prostate cancer. *Nat Rev Urol*. 2021;18(12):739-762.
- Jacob A, Raj R, Allison DB, Myint ZW. Androgen receptor signaling in prostate cancer and therapeutic strategies. *Cancers (Basel)*. 2021;13(21):5417.
- Freedland SJ, de Almeida Luz M, De Giorgi U, et al; EMBARK Study. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. *N Engl J Med*. 2023;389(16):1453-1465.
- Attard G, Murphy L, Clarke NW, et al; Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. 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.
- Labrie F, Cusan L, Gomez JL, et al. Downstaging by combination therapy with flutamide and an LHRH agonist before radical prostatectomy. *Cancer Surv*. 1995;23:149-156.
- Schulman CC, Debruyne FM, Forster G, Selvaggi FP, Lizza AR, Witjes WP; European Study Group on Neoadjuvant Treatment of Prostate Cancer. 4-Year follow-up results of a European prospective randomized study on neoadjuvant hormonal therapy prior to radical prostatectomy in T2-3N0M0 prostate cancer. *Eur Urol*. 2000;38(6):706-713.
- Soloway MS, Pareek K, Sharifi R, et al; Lupron Depot Neoadjuvant Prostate Cancer Study Group. Neoadjuvant androgen ablation before radical prostatectomy in cT2bN0M0 prostate cancer: 5-year results. *J Urol*. 2002;167(1):112-116.
- Devos G, Tosco L, Baldewijns M, et al. ARNEO: a randomized phase II trial of neoadjuvant degarelix with or without apalutamide prior to radical prostatectomy for high-risk prostate cancer. *Eur Urol*. 2023;83(6):508-518.
- Zhang X, Zhou F, Lu T, et al. Neoadjuvant darolutamide plus androgen deprivation therapy for high-risk and locally advanced prostate cancer: a multicenter, open-label, single-arm, phase II trial. *World J Urol*. 2025;43(1):58.
- Millan B, Pramod N, Blachman-Braun R, et al. Long-term follow-up of neoadjuvant enzalutamide plus androgen deprivation therapy in localized prostate cancer: a secondary analysis of a neoadjuvant feasibility trial. *Prostate*. 2026;86(3):365-371.
- Taplin M, Gleave M, Evans CP, et al. PROTEUS: a randomized, double-blind, placebo (PBO)-controlled, phase 3 trial of apalutamide (APA) plus androgen deprivation therapy (ADT) versus PBO plus ADT prior to radical prostatectomy (RP) in patients with localized high-risk or locally advanced prostate cancer (PC) [ASCO abstract TPS5100]. *J Clin Oncol*. 2019;37(15)(suppl).
- Hussain M, Tangen CM, Thompson IM Jr, et al. Phase III intergroup trial of adjuvant androgen deprivation with or without mitoxantrone plus prednisone in

patients with high-risk prostate cancer after radical prostatectomy: SWOG S9921. *J Clin Oncol*. 2018;36(15):1498-1504.

46. Rosenthal SA, Hunt D, Sartor AO, et al. A phase 3 trial of 2 years of androgen suppression and radiation therapy with or without adjuvant chemotherapy for high-risk prostate cancer: final results of Radiation Therapy Oncology Group phase 3 randomized trial NRG Oncology RTOG 9902. *Int J Radiat Oncol Biol Phys*. 2015;93(2):294-302.

47. Xu AP, Xu LB, Smith ER, Fleishman JS, Chen ZS, Xu XX. Cell death in cancer chemotherapy using taxanes. *Front Pharmacol*. 2024;14:1338633.

48. 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.

49. James ND, Ingleby FC, Clarke NW, et al. Docetaxel for nonmetastatic prostate cancer: long-term survival outcomes in the STAMPEDE randomized controlled trial. *JNCI Cancer Spectr*. 2022;6(4):pkac043.

50. Dreicer R, Magi-Galluzzi C, Zhou M, et al. Phase II trial of neoadjuvant docetaxel before radical prostatectomy for locally advanced prostate cancer. *Urology*. 2004;63(6):1138-1142.

51. Zhao B, Yerram NK, Gao T, Dreicer R, Klein EA. Long-term survival of patients with locally advanced prostate cancer managed with neoadjuvant docetaxel and radical prostatectomy. *Urol Oncol*. 2015;33(4):164.e19-164.e23.

52. Fizazi K, Carmel A, Joly F, et al. Updated results of GETUG-12, a phase III trial of docetaxel-based chemotherapy in high-risk localized prostate cancer, with a 12-year follow-up [ESMO abstract 791O]. *Ann Oncol*. 2018;29(8)(suppl).

53. Eastham JA, Heller G, Halabi S, et al; Cancer and Leukemia Group B 90203 (Alliance). Radical prostatectomy with or without neoadjuvant chemohormonal therapy in localized, high-risk prostate cancer. *J Clin Oncol*. 2020;38(26):3042-3050.

54. Qian H, Chi C, Tricard T, et al. A prospective randomized trial of neoadjuvant chemohormonal therapy vs hormonal therapy in locally advanced prostate cancer treated by radical prostatectomy. *J Urol*. 2024;211(5):648-655.

55. Kwok G, Yau TCC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). *Hum Vaccin Immunother*. 2016;12(11):2777-2789.

56. Hansen AR, Massard C, Ott PA, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. *Ann Oncol*. 2018;29(8):1807-1813.

57. Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. *J Clin Oncol*. 2020;38(5):395-405.

58. Habaka M, Daly GR, Shinyanbola D, et al. PARP inhibitors in the neoadjuvant setting: a comprehensive overview of the rationale for their use, past and ongoing clinical trials. *Curr Oncol Rep*. 2025;27(5):533-551.

59. Antonarakis ES, Gomella LG, Petrylak DP. When and how to use PARP inhibitors in prostate cancer: a systematic review of the literature with an update on on-going trials. *Eur Urol Oncol*. 2020;3(5):594-611.

60. Fallah J, Xu J, Weinstock C, et al. FDA approval summary: olaparib in combination with abiraterone for treatment of patients with *BRCA*-mutated metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2024;42(5):605-613.

61. Anscher MS, Chang E, Gao X, et al. FDA approval summary: rucaparib for the treatment of patients with deleterious *BRCA*-mutated metastatic castrate-resistant prostate cancer. *Oncologist*. 2021;26(2):139-146.

62. Heiss BL, Chang E, Gao X, et al. US Food and Drug Administration approval summary: talazoparib in combination with enzalutamide for treatment of patients with homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2024;42(15):1851-1860.

63. Bent EH, Morris MJ. Prostate cancer radioligand therapy: PSMA and beyond, current landscape and future directions. *Curr Oncol Rep*. 2025;27(10):1170-1184.

64. Kuppermann D, Calais J, Marks LS. Imaging prostate cancer: clinical utility of prostate-specific membrane antigen. *J Urol*. 2022;207(4):769-778.

65. Golan S, Frumer M, Zohar Y, et al. Neoadjuvant ¹⁷⁷Lu-PSMA-I&T radionuclide treatment in patients with high-risk prostate cancer before radical prostatectomy: a single-arm phase 1 trial. *Eur Urol Oncol*. 2023;6(2):151-159.

66. Azad AA, Bressel M, Tan H, et al; UpFrontPSMA Study Team. Sequential [¹⁷⁷Lu]Lu-PSMA-617 and docetaxel versus docetaxel in patients with metastatic hormone-sensitive prostate cancer (UpFrontPSMA): a multicentre, open-label, randomised, phase 2 study. *Lancet Oncol*. 2024;25(10):1267-1276.

67. Sartor O, de Bono J, Chi KN, et al; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385(12):1091-1103.

68. Morris MJ, Castellano D, Herrmann K, et al; PSMAfore Investigators. ¹⁷⁷Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naïve patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. *Lancet*. 2024;404(10459):1227-1239.

69. Ma TM, Czernin J, Felix C, et al. LUNAR: a randomized phase 2 study of ¹⁷⁷lutetium-PSMA neoadjuvant to ablative radiotherapy for oligorecurrent prostate cancer (clinical trial protocol). *BJU Int*. 2023;132(1):65-74.

70. Eapen RS, Buteau JB, Jackson P, et al. Administering [¹⁷⁷Lu]Lu-PSMA-617 prior to radical prostatectomy in men with high-risk localised prostate cancer (LuTectomy): a single-centre, single-arm, phase 1/2 study. *Eur Urol*. 2024;85(3):217-226.

71. Foxton C, Waldron B, Veggerby Grönlund R, et al. Preclinical evaluation of ¹⁷⁷Lu-rhPSMA-10.1, a radiopharmaceutical for prostate cancer: biodistribution and therapeutic efficacy. *J Nucl Med*. 2025;66(4):599-604.

72. Yusufi N, Wurzer A, Herz M, et al. Comparative preclinical biodistribution, dosimetry, and endoradiotherapy in metastatic castration-resistant prostate cancer using ^{19F}/¹⁷⁷Lu-rhPSMA-7.3 and ¹⁷⁷Lu-PSMA I&T. *J Nucl Med*. 2021;62(8):1106-1111.

73. Wurzer A, De Rose F, Fischer S, et al. Preclinical comparison of [¹⁷⁷Lu]Lu-rhPSMA-10.1 and [¹⁷⁷Lu]Lu-rhPSMA-10.2 for endoradiotherapy of prostate cancer: biodistribution and dosimetry studies. *EJNMMI Radiopharm Chem*. 2024;9(1):18.

74. Ninatti G, Scilipoti P, Pini C, et al. Time for action: actinium-225 PSMA-targeted alpha therapy for metastatic prostate cancer - a systematic review and meta-analysis. *Theranostics*. 2025;15(8):3386-3399.