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AUA Guideline Article

Clinically Localized Prostate Cancer: AUA/ASTRO Guideline Amendment (2026)

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Purpose: Following completion of the 2025 Update Literature Review (ULR), the American Urological Association (AUA) incorporated new evidence generated since the 2022 publication of this Guideline via the AUA Amendment process. The resulting 2026 Guideline Amendment addresses updated recommendations to provide a clinical framework for the evaluation and management of clinically localized prostate cancer.

Materials and Methods: In 2025, this Guideline was reviewed via the AUA ULR process, which identified 29 studies for full-text review that were published between July 1, 2021 and December 5, 2024. An additional 8 studies were identified reviewing artificial intelligence (AI) as it relates to disease management. Relevant studies were incorporated into the Guideline evidence base, and Guideline statements were updated as appropriate.

Results: The Panel developed evidence- and consensus-based statements based on an updated review to provide guidance on evaluation and management of clinically localized prostate cancer. These updates are detailed herein.

Conclusions: This Amendment provides several new insights, including revised guidance on imaging, updated information on shared decision-making (SDM), and new direction regarding radiation treatment and disease management. This Guideline will require further review as the diagnostic and treatment options in this space continue to evolve.

Key Words: cancer, clinical, evidence, prostate, prostate cancer, therapy

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BACKGROUND

Prostate cancer remains the most common non-cutaneous cancer among US men.[1] As the vast majority of newly-diagnosed prostate cancer patients have clinically localized disease, evidence-based guideline statements to support clinical decision-making represent important tools to facilitate the delivery of high-quality care.

An important component of the updated Guideline is the continued utilization of a risk stratification classification for patients with newly diagnosed clinically localized disease. The Panel believes that risk stratification facilitates patient counseling, should be used in SDM for treatment recommendations, and facilitates clinical trial enrollment. Recognizing that

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various risk classifications have been described, the Panel elected to maintain a risk group model (Table 1). The Panel understands that risk assessment may be refined as new information becomes available.

The intention of the risk groups is to provide a framework to discuss management options. The importance of SDM between patient and clinician is emphasized in the statements and supporting text. In addition to detailing the components of risk stratification, the Guideline is also addresses indications for staging in the newly diagnosed patient, provides risk-based treatment approaches to be reviewed by the clinician with the patient, and offers recommendations for post-treatment follow-up.

Further, information is outlined regarding specifics of care delivery for various therapeutic modalities, such as pelvic lymph node management during radical prostatectomy, radiation dosage and fields, and androgen deprivation therapy (ADT), as well as principles of active surveillance. Further, the Panel identified several areas of ongoing study that are likely to be of significant relevance in the future for the care of patients with clinically localized disease, including genomic tumor tissue testing and advanced imaging.

GUIDELINE STATEMENTS

Staging

Clinicians may use magnetic resonance imaging (MRI) of the prostate in any risk category to determine extent and location of disease in the prostate, guide surveillance biopsies, or plan treatment. (Conditional Recommendation; Evidence Level: Grade B)

Table 1. *Risk Group Classification for Clinically Localized Prostate Cancer*

Low-risk	PSA $<$ 10 ng/mL and grade group 1 and clinical stage T1-T2a
Intermediate-risk	PSA 10-$<$ 20 ng/mL OR grade group 2-3 OR clinical stage T2b-c
	Favorable: Grade group 1 with PSA 10-$<$ 20 ng/mL or clinical stage T2b-c and $<$ 50%[a] biopsy cores positive OR grade group 2 with PSA$<$ 10 ng/mL and clinical stage T1-2a and $<$ 50% biopsy cores positive
	Unfavorable: Grade group 1 with PSA 10-$<$ 20 ng/mL and clinical stage T2b-c OR grade group 2 with PSA 10-$<$ 20 ng/mL and/or clinical stage T2b-c and/or $\geq$ 50%[a] biopsy cores positive OR grade group 3 with PSA $<$ 20 ng/mL
High-risk	PSA $\geq$ 20 ng/mL OR grade group 4-5 OR clinical stage T3

[a] Percent biopsy cores positive is the total number of cores containing cancer divided by total number of cores obtained $\times$ 100.[15]
This is not the percentage of cancer within a positive core. Regarding assessment of the percent biopsy cores positive for risk stratification, the Panel acknowledges that with the increasing use of pre-biopsy magnetic resonance imaging (MRI) and subsequent targeted biopsies, multiple cores may be obtained from a targeted lesion. Multiple cores from the same lesion should be considered as a single core (ie, for the calculation of percentage cores positive in risk assessment). If all cores are negative, that is considered a single negative core. If one or more cores from the same lesion is positive, that is considered a single positive core, with the higher Gleason score used for risk stratification.[16]

Although imaging results are not considered in assigning local (T) stage, multi-parametric MRI (mpMRI) of the prostate can provide important information about the extent and location of disease within the prostate, as well as anatomic information, which can influence management decisions.

MRI can localize the index lesion with moderate sensitivity and high specificity, with a large-scale meta-analysis showing a sensitivity of 57 to 61% and specificity of 88 to 96% for extraprostatic extension and seminal vesicle involvement.[2] MRI has been compared with digital rectal exam (DRE) for staging in single-institution studies. In one such study including 506 men who underwent clinical staging by DRE alone and then with MRI followed by surgery, MRI had a sensitivity of 51% for $\geq$ T3a disease as compared with 12% for DRE ($P < .01$).[3] However, specificity was somewhat lower for MRI as compared with DRE (82% vs 97%, $P < .01$). Nonetheless, while there are several systems for determining the likelihood of extraprostatic extension based on MRI findings, consensus on such a definition is lacking.[4-6] Most systems incorporate tumor-capsule contact length and morphologic features, such as capsular bulge.

Use of higher field strength (ie, stronger magnet, such as 3T instead of 1.5T) improves sensitivity of MRI, as does the addition of functional sequences, including diffusion-weighted imaging (DWI), dynamic contrast enhanced imaging (DCE), and magnetic resonance spectroscopic imaging (MRSI) to standard T2-weighted imaging. However, biparametric MRI, limited to T2 and diffusion-weighted phases is non-inferior to mpMRI, which adds the dynamic contrast-enhanced phase for detection of grade group 2 or higher prostate cancer. Thus, biparametric MRI is a reasonable substitute for mpMRI.[7]

In men choosing active surveillance, MRI should be used for targeted biopsy if available but should not replace surveillance biopsies. Additionally, MRI and targeted biopsy should be used for patient selection in focal therapy and for follow-up after treatment; however, it should be used as a complementary study and should not replace tissue sampling.

In radiotherapy, the FLAME trial demonstrated improved 5-year biochemical disease-free survival in intermediate- and high-risk patients who received a radiation 'boost' to MRI-visible targets in addition to whole-gland radiation compared to whole-gland treatment alone (92% vs 85%; HR: 0.45, $P < .01$).[8,9] Follow-up showed a lower probability of local failure (HR: 0.33; 95% CI: 0.14-0.78) and regional or distant recurrence (HR: 0.58; 95% CI: 0.35-0.93) in the group that received the boost.[10] There was no difference between groups in toxicity.

Observational studies have found comparable results.[11]

Regarding patients undergoing surgery, despite the accuracy with which MRI can detect index lesions, extraprostatic extension, and seminal vesicle involvement, and the frequency with which treatment plan is altered by MRI findings, the evidence regarding whether preoperative MRI lowers positive surgical margin rates or subsequent biochemical recurrence is mixed.[12-15] A 2019 meta-analysis of 6 studies that directly compared preoperative MRI to no preoperative MRI, including one randomized controlled trial (RCT), showed an absolute risk reduction of 5.2% in the likelihood of positive margins at final pathology in patients who had undergone preoperative MRI compared to those who had not (OR: 0.74; 95% CI: 0.63-0.87; $P < .001$).[13] Additionally, these studies have consistently shown increased use of nerve-sparing among patients who underwent preoperative MRI, suggesting that there may also be benefits in terms of functional outcomes.

In reviewing these studies, the Panel concluded that clinicians may use MRI for local staging in any risk category, not only to refine patient selection for active surveillance and to direct focal therapy, but also to guide treatment in ways that may improve oncologic and functional outcomes. It must be acknowledged, however, that access to MRI may be limited in some settings, and MRI scanner quality and radiologist expertise may influence the utility of MRI and the rate of false-positives and false-negatives.

Clinicians should not routinely perform prostate-specific membrane antigen positron emission tomography (PSMA PET) scan, cross-sectional imaging (contrast-enhanced abdomino-pelvic computed tomography [CT] scan or MRI), or bone scan for nodal or metastatic staging in asymptomatic patients with low- or favorable intermediate-risk prostate cancer. (Expert Opinion)

Imaging studies are intended to define the local extent of disease as well as determine the presence of nodal and distant metastases and thereby inform management. Clinicians should use a risk-based approach to stage patients with newly diagnosed prostate cancer, considering the probability of the patient harboring metastatic disease as well as the sensitivity and specificity of the imaging modality. For asymptomatic patients with low- or favorable intermediate-risk prostate cancer, the probability of nodal or distant metastasis is low.[16-18] Therefore, molecular imaging (ie, PSMA PET-CT scan), bone scan, or cross-sectional imaging (CT scan or MRI) for nodal and metastatic staging are unlikely to be helpful and should not be routinely obtained. However, even in the low- and favorable intermediate-risk patients, there may be instances in which symptoms, laboratory abnormalities, or disease characteristics warrant further investigation with imaging.

Clinicians should stage unfavorable intermediate- and high-risk localized prostate cancer using either PSMA PET scan or a combination of bone scan and cross-sectional imaging. (Strong Recommendation; Evidence Level: Grade B)

In patients with unfavorable intermediate- or high-risk localized prostate cancer who have negative conventional imaging, clinicians may obtain PSMA PET scan to evaluate for metastases. (Expert Opinion)

Historically, prostate cancer has been staged with conventional imaging (bone scan plus either CT or MRI). Since many of the studies supporting therapeutic interventions for prostate cancer are predicated on the results of conventional imaging (bone scan plus either CT or MRI), there remains some uncertainty regarding the potential for improved outcomes based on PSMA PET imaging modalities. Nonetheless, there is ample evidence of the greater sensitivity of PSMA PET as compared with conventional imaging for identification of nodal and distant disease and evidence that findings of PSMA PET imaging can substantially alter the treatment plan and expectations regarding outcomes of treatment (eg, finding small volume metastatic disease on PSMA PET in a patient otherwise thought to have localized disease by conventional imaging).[19]

PET imaging using F-18 piflufolastat or gallium-68 PSMA-11 is approved by the FDA for staging prostate cancer, and additional agents are approved for detection of recurrence and metastatic disease. PSMA PET imaging with these tracers is performed in conjunction with CT or MRI for localization. PSMA PET imaging is standard of care for staging in the setting of recurrence after primary treatment as well as in certain scenarios of advanced disease.[20]

In localized disease, the data regarding sensitivity of PSMA PET for nodal staging vary widely depending on the study. For example, a single-arm study of 764 men with unfavorable intermediate- and high-risk disease using gallium-68 PSMA-11 PET CT showed a relatively low sensitivity for lymph node involvement (40%) with a specificity of 95%.[21] Meanwhile, the proPSMA trial, which enrolled 302 men with similar disease characteristics, showed far higher sensitivity for lymph node involvement using gallium-68 PSMA-11 PET CT (91%).[19] By contrast, in detection of nodal metastasis, MRI has been found to be associated with a low to moderate sensitivity (range 0.09-0.44) and

high specificity (range 0.88-1.0).[22-26] Therefore, most studies in which PSMA PET has been compared with conventional imaging for nodal staging have shown greater sensitivity and overall accuracy for PSMA PET. In the proPSMA trial, sensitivity for pelvic lymph nodes was 59% for conventional imaging, a 32% absolute difference compared to 91% for gallium-68 PSMA-11 PET CT; PSMA PET also had an advantage in sensitivity for detection of metastatic disease (74% vs 95%).[21] A meta-analysis including 31 studies (2431 patients) of patients with intermediate- and high-risk disease, showed PSMA PET to be more sensitive and specific than mpMRI (73.7% vs 38.9% and 97.5% vs 82.6%) and CT (73.2% vs 38.5% and 97.8% vs 83.6%) for detection of nodal involvement.[27] Additionally, PSMA PET was more sensitive and specific than bone scan for skeletal metastases (98.0% vs 73.0% and 96.2% vs 79.1%, respectively). Because of the incremental predictive value of PSMA PET, it has been incorporated into nomograms designed to predict lymph node metastases.[28] Importantly, however, the studies showing low sensitivity of PSMA PET imaging for nodal metastases (eg, the Hope study, which showed only 40% sensitivity) indicate that a negative PSMA PET scan does not rule out nodal involvement.[21]

Taken together, the Panel recommends staging imaging for patients with unfavorable intermediate- and high-risk prostate cancer. PSMA PET imaging, where available, provides improved sensitivity for identification of lymph node involvement and metastatic disease and, therefore, may be preferred. However, many of the treatment paradigms are predicated on conventional imaging, and the association between staging with PSMA PET imaging and downstream oncologic outcomes has not been established. While some studies of PSMA PET for initial staging have included all intermediate-risk patients,[29] the evidence is strongest for the high-risk and unfavorable intermediate-risk patients. Therefore, the Panel determined that data were insufficient to warrant recommending routine use of staging imaging in favorable intermediate-risk patients.

Risk-Based Management

Clinicians should inform patients that all prostate cancer treatments carry risk. The risks of treatment to patients' urinary, sexual, and bowel function must be incorporated with the risk posed by the cancer, patient life expectancy, comorbidities, pre-existing medical conditions, and patient preferences to facilitate an SDM approach to management. (Clinical Principle)

The selection of a management strategy for clinically localized prostate cancer is preference-sensitive and very often based on patient interpretation of the balance between treatment-specific risks and benefits.

With that in mind, clinicians must inform patients thoroughly regarding the risks and benefits of the various management options. Clinicians also must elicit from patients their values, preferences, and concerns about outcomes of treatment and seek their engagement in the decision-making process. The clinician then helps the patient arrive at a decision and evaluate that decision. This collaborative SDM process is designed to yield a well-informed, high-quality decision that is consistent with patients' preferences and values.

SDM aims to improve the quality of medical decisions by helping patients choose options consistent with their own values and in accordance with the best available scientific evidence.[30-33] RCTs of SDM vs routine care have demonstrated that patients engaged in SDM are more knowledgeable, have more realistic expectations, participate more actively in the care process, and more frequently arrive at decisions aligned with their personal preferences.[32,34] The National Academy of Medicine and the AUA have both articulated strong support for the use of SDM for complex decisions such as treatment for localized prostate cancer.[35,36] Key components of SDM are illustrated by the Agency for Healthcare Research and Quality SHARE approach in Table 2.[37]

Clinicians should inform patients with low- and intermediate-risk prostate cancer that whole gland or focal ablation remains investigational without high-quality data comparing ablation outcomes to standard of care therapies such as surgery, radiation therapy, and active surveillance. (Expert Opinion)

Current ablative modalities include high-intensity focused ultrasound (HIFU), cryoablation, focal laser, irreversible electroporation (IRE), and photodynamic therapy (PDT), which are FDA approved for the treatment of prostate tissue only.[38] Patient selection criteria in reported studies have varied widely as has treatment planning approach (eg, lesion-based focal therapy, hemi-ablation, whole-gland). An early randomized trial demonstrated that focal PDT lowered the likelihood of cancer progression and rates of surgery compared to active surveillance.[39] However, active surveillance remains the preferred approach for patients with low-risk prostate cancer.

Table 2. *AHRQ SHARE Approach to Shared Decision-Making*

Seek your patient's participation
Help your patient explore and compare treatment options
Assess your patient's values and preferences
Reach a decision with your patient
Evaluate your patient's decision

Several institutional, multi-site, and population-based studies have reported outcomes of various ablative therapies for intermediate-risk disease; however, in the absence of randomization, non-standardized protocols, and insufficient follow-up, the role of ablative therapy in the management of clinically localized prostate cancer remains to be defined.[40] Several studies report in-field recurrence rates of 10 to 40% for any disease, and generally < 20% for residual pattern 4 across treatment modalities. However, no trials have compared ablative approaches to each other and detailed outcomes including frequency of salvage radical treatment, and long-term oncologic outcomes are lacking.

Prospective trials publishing early results in focal therapy for prostate cancer demonstrate feasibility and safety. The HIFI study was a nonrandomized prospective study of over 3300 patients with predominantly intermediate-risk prostate cancer comparing radical prostatectomy to HIFU. The study demonstrated that 30-month salvage treatment-free survival with whole gland or subtotal HIFU was non-inferior to that of radical prostatectomy with fewer urinary and sexual side effects. Evidence remains very limited by 2 to 3 years of follow up, lack of randomization, and large age difference (median 74.7 vs 65.1 years in HIFU vs radical prostatectomy groups, respectively).[41] In another single-arm phase 2b multicenter study, MRI-guided focused ultrasound focal therapy for intermediate-risk prostate cancer achieved a 24-month in-field disease-free rate of ~88% (defined as Grade Group ≥ 2 cancer in the treated area) with potential to safely delay or eliminate the need for radical whole-gland treatment in the long term. There are no RCTs comparing HIFU to standard of care treatment modalities including radical prostatectomy, radiation, or active surveillance. While HIFU may have benefit in select patients, its long-term efficacy relative to standard treatments remains unproven, and the appropriate patient population remains undefined. The Panel cautions against wide implementation of HIFU in the absence of high-level evidence.

Retrospective SEER studies have examined population-based outcomes from cryoablation compared to radiation in low- and intermediate-risk patients, and differences in patient selection temper any conclusions.[42,43] There are no rigorous, contemporary trials comparing cryoablation to surgery or radiation therapy. The Panel considers cryotherapy to be a non-standard option for intermediate-risk patients.

Similarly, published data on focal laser ablation are limited to single center retrospective series comparing selected patients to younger and healthier patients undergoing prostatectomy or radiation therapy. No clear difference in cancer-specific survival is demonstrated. Other modalities including IRE and PDT are being tested in intermediate-risk prostate cancer. Early functional outcomes show minimal urinary and sexual side effects, but oncologic outcomes comparing their use to standard of care are not proven.

Currently, the Panel believes that broader use of ablative techniques should be limited to clinical trial enrollment. They can be used in appropriately informed patients with intermediate-risk prostate cancer declining standard therapies, and ideally in a prospective study.[44] Patients with low-risk cancers should still be offered active surveillance. Patients considering ablation should be counseled regarding side effects and recurrence risk and should be followed post-ablation with routine PSA, MRI, and biopsy tailored to their specific health and cancer characteristics to detect disease, persistence, or recurrence.[45]

Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial. (Expert Opinion)

Currently, patients being considered for ablation should have intermediate-risk prostate cancer.[44] Patients with high-risk disease should not be recommended ablative techniques due to lack of evidence and risk of missing or delaying definitive approaches with proven benefit.

PRINCIPLES OF MANAGEMENT

Principles of Radiation

Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (Conditional Recommendation; Evidence Level: Grade C)

To date, no prospective study has demonstrated improved disease control or side effects with proton beam radiation therapy (PBRT) compared to intensity-modulated radiotherapy (IMRT). Proponents of PBRT have offered that it has dosimetric advantages compared to IMRT. That is, while the target volume for both techniques includes the prostate and a margin of normal tissue (bladder and rectum) that is irradiated to the prescribed dose, proton beam delivers lower integral doses and mean doses to normal tissues compared to IMRT.[46] However, this dosimetric difference has not been shown to result in fewer side effects or better patient reported quality of life (QOL). Indeed, the existing peer reviewed literature suggests that clinical outcomes (eg, complications, patient reported QOL) are similar.[47]

Comparative effectiveness studies have been published to evaluate relative toxicity and oncologic outcomes between proton and photon therapies. Three studies comparing patients treated with proton therapy or photon therapy reported similar toxicity rates and patient reported outcomes. A prospective comparison of patients treated with IMRT (n = 204) and patients treated with proton therapy (n = 1234) with regard to patient-reported outcomes measured using the EPIC instrument concluded that "no differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts" after up to 2 years of follow-up.[48] Meanwhile, a retrospective analysis of Medicare data from 421 patients treated with proton therapy and a matched cohort of 842 patients treated with IMRT showed less genitourinary toxicity at 6 months with proton therapy, although the difference disappeared after 1 year.[49] No other significant differences were seen between the groups. A more recent large observational study of 772 low- or intermediate-risk group prostate cancer patients treated with either PBRT or IMRT compared patient-reported gastrointestinal and genitourinary toxicities.[50] Authors found no significant difference in late gastrointestinal or genitourinary toxicities between the 2 treatment modalities at 12 and 24 months. After adjusting for factors such as age and risk group, both PBRT and IMRT demonstrated low rates of toxicity.

A report compared PBRT to IMRT using a case-matched approach.[51] This observational study of 177 patients found that oncological outcomes (long-term biochemical failure-free survival, prostate cancer-specific survival and overall survival [OS]) were similar between PBRT and IMRT (all $P > .05$).

Randomized trials are ongoing comparing IMRT and PBRT using long-term side effects and QOL as the primary endpoints. The PARTIQoL trial, which has a primary endpoint of bowel function at 24 months, has 3 preliminary reports including a description of baseline characteristics of the study participants.[52-54]

When combined ADT and radiation are used, ADT may be initiated neoadjuvantly or concurrently. (Conditional Recommendation; Evidence Level: Grade C)

The optimal sequencing of ADT and radiation has not been clearly defined, but RCT data, meta-analyses, and a systematic review have been published to provide some information on this topic.

In the randomized Ottawa 0101 study, neoadjuvant and concurrent ADT for 6 months was compared with concurrent and adjuvant ADT for 6 months.[55] No differences were detected in biochemical relapse-free survival or OS. Meanwhile, in NRG/RTOG 9413, a 2 × 2 factorial design was used whereby patients with prostate cancer were randomized to 4 months of neoadjuvant and concurrent ADT (starting 2 months before radiation) vs 4 months of adjuvant ADT, with a second randomization to prostate-only vs whole pelvis irradiation.[56,57] Interestingly, among patients who underwent prostate-only radiation, adjuvant ADT was associated with improved progression-free survival (PFS) compared to neoadjuvant ADT. However, among patients who received whole pelvis radiation, adjuvant ADT was associated with worse PFS compared to neoadjuvant ADT.

In a 2021 meta-analysis by Spratt et al (including data from Ottawa 0101 and NRG/RTOG 9413), patients receiving neoadjuvant and concurrent ADT and prostate-only radiation were combined into the neoadjuvant group, and patients receiving concurrent and adjuvant ADT were combined into the adjuvant group.[58] After a median follow-up of 14.9 years, the adjuvant group had significantly better biochemical control, PFS, and metastasis-free survival (MFS) compared to the neoadjuvant group. Of note, patients receiving whole pelvic nodal radiation in NRG/RTOG 9413 were not included in the analysis. There were also systematic differences between the 2 trials (eg, duration of ADT, inclusion of more aggressive disease in the NRG/RTOG 9413). As a result, the authors acknowledged that their ability to soundly perform comparative subset analyses was hindered.

A 2023 systematic review assessed the question of optimal timing to start ADT in localized prostate cancer.[59] A total of 24 studies were included, with 5 studies specifically assessing ADT sequencing with radiotherapy in either the neoadjuvant, concurrent, or adjuvant setting. Included studies were made up of 2 RCTs, 2 retrospective studies, and one individual patient data meta-analysis. Studies were qualitatively synthesized, and the review found conflicting results. One included study found no difference in any oncological outcomes between adjuvant and neoadjuvant ADT and radiotherapy, while others found that neoadjuvant ADT improved OS, PFS and biochemical failure. Two included studies, however, found that a concurrent adjuvant sequence of ADT improved biochemical relapse-free survival, PFS, biochemical failure and distant metastasis.[59]

The authors acknowledged several methodological issues with this systematic review, including a limited number of trials comparing neoadjuvant vs concurrent ADT, lack of trials assessing ADT timing in high-risk prostate cancer patients treated with pelvic radiotherapy and ADT, as well as significant heterogeneity of trials in terms of inclusion criteria, risk stratification, and radiation protocols. Despite these methodological shortcomings,

the authors supported the use of concurrent ADT for intermediate-risk patients (with neoadjuvant ADT initiation as an acceptable option particularly for patients who may benefit from pre-radiotherapy prostate volume reduction). Short-term neoadjuvant ADT followed by concurrent and long-term adjuvant ADT is recommended (versus concurrent initiation) for high-risk prostate cancer patients. Due to the evolving data in this space, the initiation of adjuvant ADT is no longer recommended.

When treating a subgroup of high-risk localized patients (≥2 of the following: PSA ≥ 40 ng/dL, ≥ Gleason 8, ≥ cT3) or locally advanced prostate cancer (cN1) with radiation therapy, clinicians should combine ADT with abiraterone acetate and prednisone for 24 months. (Strong Recommendation; Evidence Level: Grade B)

A meta-analysis of phase 3 STAMPEDE trials included patients with high-risk prostate cancer (having $\geq$ 2 of the following: PSA $\geq$ 40 ng/dL, $\geq$ Gleason 8, $\geq$ cT3) or clinical evidence of pelvic lymph node involvement. In this investigation, patients treated with ADT plus abiraterone acetate 1000 mg PO daily with prednisolone 5 mg PO daily for 24 months in combination with definitive radiation treatment had improved MFS and OS when compared with patients receiving ADT for 24 months with definitive radiation alone.[60]

FUTURE DIRECTIONS

Treatment Intensification for High-Risk Disease

Multiple trials evaluating next generation androgen signaling inhibitors in high-risk clinically localized disease have accrued and are awaiting results. In the Apa-RP trial, adjuvant apalutamide for high-risk prostatectomy patients has demonstrated excellent biochemical control.[61] This phase 2 trial showed a 100% biochemical recurrence-free survival at 24 months among 108 high-risk prostate cancer patients who received 12 months of apalutamide combined with ADT following radical prostatectomyPROTEUS, a randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide plus ADT vs placebo plus ADT prior to radical prostatectomy in patients with localized high-risk or locally advanced prostate cancer has also completed enrollment. PROTEUS aims to improve pathologic complete response rates and MFS. Final outcomes should be available in late 2028. Further, DASL-HiCaP randomized in a 1:1 fashion 1100 patients with planned radiation therapy with very high-risk localized prostate cancer on conventional imaging or very high-risk features with PSA persistence or rise within 12 months of radical prostatectomy. Patients were randomized to receive darolutamide or placebo twice daily for 96 weeks in combination with 96 weeks of ADT plus radiation therapy starting 8 to 24 weeks from randomization. The primary endpoint is MFS.

Surgical Innovation

Intraoperative imaging for robotic surgery has the potential to improve functional outcomes, margin status, and node dissection. PSMA targeting fluorophores and radioguided surgery enable real-time tumor visualization. Early studies show safety and feasibility. Fluorescence-guided prostatectomy (first-in-human) for margin status and nerve preservation demonstrate early improvements in surgical technique, particularly in reoperative or node-positive settings.[62] Focal therapy in prostate cancer including all modalities such as HIFU, IRE, PDT, and cryoablation are undergoing extensive evaluation in prospective studies. Future practice must balance long-term oncologic outcomes with preserving urinary and sexual function.

Biomarkers

The ability of commercially available genomic classifiers (GCs) to improve the outcomes of patients with clinically localized prostate cancer has not been validated in prospective clinical trials to date. Thus, routine use is not recommended at this time. A specific important limitation of the existing data supporting the prognostic capacity of GCs is that studies have been primarily based on tissue analysis of radical prostatectomy specimens. As such, the impact of tissue heterogeneity and undersampling on the prognostic ability of GCs for assessing the risks of recurrence, metastasis, and death from prostate cancer biopsies remains uncertain. Of note, accumulating evidence has indicated that GC scores, specifically Decipher, derived from biopsy specimens do correlate with cancer outcomes. For example, Nguyen et al reported on 235 radical prostatectomy/radiation therapy patients for whom Decipher was run on biopsy specimens and found that, on multivariable analysis, Decipher score was associated with both the risks of metastasis and prostate cancer-specific mortality.[63] In addition, the prognostic capacity of biopsy-based Decipher was validated using prospectively collected, banked specimens from RTOG 9202, 9413, and 9902. After adjusting for age, PSA, Gleason score, cT-stage, trial and randomized treatment arm, Decipher score was associated with distant metastases, prostate cancer-specific mortality, and OS.[64]

Prospective validation of the predictive capacity of GCs in localized disease will be important to support widespread use for treatment selection. Several ongoing clinical trials (eg, NRG GU009 and

GU 010) are indeed evaluating treatment intensification and de-intensification based on GC (Decipher) results in both intermediate- and high-risk patient populations.

Artificial intelligence for interpretation of hematoxylin and eosin slides will also be practice-changing. Artera AI's multimodal artificial intelligence biomarker test applies a deep learning algorithm to digitized biopsy slides developed and validated in large cooperative group trials such as NRG/RTOG 9202, 9408, 9413, 9910, and 0126.[65] Artera AI not only stratifies risk, but also predicts which patients benefit from adding ADT to radiation, enabling more precise personalization of therapy while reducing overtreatment and toxicity.

Imaging

The PRIME study demonstrated that a two-sequence (bi-parametric) MRI was non-inferior to standard contrast-enhanced multiparametric MRI for detecting clinically significant prostate cancer, which may reduce cost, improve access, and increase screening efficiency. Utilization of bi-parametric MRI is likely to increase diagnosis, improve monitoring during active surveillance, and treatment planning.[7]

High-resolution micro-ultrasonography (microUS) is an alternative to mpMRI for detecting clinically significant prostate cancer.[66] While MRI is still standard, microUS can be considered when MRI is inconclusive, if the patient is claustrophobic, or the patient has metal implants.

As noted in the updated guideline statements, PSMA PET has greater sensitivity than conventional imaging for identification of nodal and distant disease, and evidence that PSMA PET imaging can substantially alter the treatment plan and expectations regarding outcomes of treatment[19] (eg, finding small volume metastatic disease on PSMA PET in a patient otherwise thought to have localized disease by conventional imaging). PSMA PET is a first-line option for staging in patients with unfavorable intermediate-risk or high-risk prostate cancer.

Several imaging radiotracers utilizing PET-based technology have been demonstrated to improve detection of disease over conventional imaging. Broadly, these imaging modalities have been referred to as next-generation imaging (NGI); among these, PSMA-based PET scanning has received the most attention. This interest has been bolstered by FDA approval of 2 PSMA based tracers: Gallium 68 PSMA-11 (Ga 68 PSMA-11) and piflufolastat F-18 (18F-DCFPyL).[67,68] Moreover, continued evaluation of novel PSMA PET agents remains ongoing.[69] As such, PSMA PET is an accepted standard in the staging evaluation of patients with localized high-risk prostate cancer. Nevertheless, future studies are needed to determine how the information from NGI should be incorporated into clinical decision-making due to both the limitations of these advanced imaging techniques and the fact that the data to date on outcomes following treatment upon which management recommendations are based on patients evaluated with conventional imaging. For example, in the OSPREY trial in which patients underwent F-18 DCFPyl-PET/CT followed by radical prostatectomy and extended pelvic lymph node dissection (PLND), the sensitivity of the scan for detection of pelvic lymph node disease was only 40.3%, suggesting this study alone could not be used to triage patients as to whether or not to undergo lymph node dissection at the time of surgery.[70] At the same time, in 12.3% of high-risk patients, F-18 DCFPyl identified extra-pelvic disease, indicating patients for whom additional therapy would be indicated.[70] Prospective studies incorporating NGI as staging will be required to determine clinical utility. Until such data are available, clinicians should exercise caution when using PSMA PET results to justify substantial alterations in standard-of-care treatments the utility of which has been established among patients who were staged with conventional imaging.

REFERENCES

1. Siegel RL, Kratzer TB, Wagle NS, Sung H, Jemal A. Cancer statistics, 2026. *CA Cancer J Clin.* 2026;76(1):e70043. doi:10.3322/caac.70043

2. de Rooij M, Hamoen EH, 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

3. Soeterik TFW, van Melick HHE, Dijksman LM, Biesma DH, Witjes JA, van Basten JPA. Multiparametric magnetic resonance imaging should be preferred over digital rectal examination for prostate cancer local staging and disease risk classification. *Urology.* 2021;147:205-212. doi:10.1016/j.urology.2020.08.089

4. Kayat Bittencourt L, Litjens G, Hulsbergen-van de Kaa CA, Turkbey B, Gasparetto EL, Barentsz JO. Prostate cancer: the European Society of Urogenital Radiology Prostate Imaging Reporting and Data System criteria for predicting extraprostatic extension by using 3-t multiparametric mr imaging. *Radiology.* 2015;276(2):479-489. doi:10.1148/radiol.15141412

5. Futela D, Bhargava M, Rama S, et al. 10 mm (pi-rads v2.1) versus 15 mm (pi-rads v1.0) tumor capsule contact length in predicting extracapsular extension in prostate cancer: meta-analysis and systematic review. *Abdom Radiol (NY).* 2025;50(12):6106-6118. doi:10.1007/s00261-025-04998-6

6. Mehralivand S, Shih JH, Harmon S, et al. A grading system for the assessment of risk of extraprostatic extension of prostate cancer at multiparametric mri. *Radiology.* 2019;290(3):709-719. doi:10.1148/radiol.2018181278

7. Ng A, Asif A, Agarwal R, et al. Biparametric vs multiparametric mri for prostate cancer diagnosis: the prime diagnostic clinical trial. *JAMA*. 2025;334(13):1170-1179. doi:10.1001/jama.2025.13722

8. 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

9. Menne Guricová K, Draulans C, Pos FJ, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: 10-year outcomes of the flame trial. *J Clin Oncol*. 2025;43(28):3065-3069. doi:10.1200/JCO-25-00274

10. Groen VH, Haustermans K, Pos FJ, et al. Patterns of failure following external beam radiotherapy with or without an additional focal boost in the randomized controlled flame trial for localized prostate cancer. *Eur Urol*. 2022;82(3):252-257. doi:10.1016/j.eururo.2021.12.012

11. Onal C, Guler OC, Erbay G, Demirhan B, Elmali A, Yavuz M. Propensity score matched analysis of external beam radiotherapy with or without focal boost to intraprostatic lesions in prostate cancer. *Prostate*. 2025;85(8):805-813. doi:10.1002/pros.24888

12. Kozikowski M, Malewski W, Michalak W, Dobruch J. Clinical utility of mri in the decision-making process before radical prostatectomy: systematic review and meta-analysis. *PLoS One*. 2019;14(1):e0210194. doi:10.1371/journal.pone.0210194

13. Patel HD, Okabe Y, Rac G, et al. Mri versus non-mri diagnostic pathways before radical prostatectomy: impact on nerve-sparing, positive surgical margins, and biochemical recurrence. *Urol Oncol*. 2023;41(2):104.e19-104.e27. doi:10.1016/j.urolonc.2022.10.012

14. Jäderling F, Akre O, Aly M, et al. Preoperative staging using magnetic resonance imaging and risk of positive surgical margins after prostate-cancer surgery. *Prostate Cancer Prostatic Dis*. 2019;22(3):391-398. doi:10.1038/s41391-018-0116-z

15. Bonebrake BT, Parr E, Huynh LM, et al. Predictive value of multiparametric magnetic resonance imaging in risk group stratification of prostate adenocarcinoma. *Adv Radiat Oncol*. 2024;9(6):101493. doi:10.1016/j.adro.2024.101493

16. Merdan S, Womble PR, Miller DC, et al. Toward better use of bone scans among men with early-stage prostate cancer. *Urology*. 2014;84(4):793-798. doi:10.1016/j.urology.2014.06.010

17. Risko R, Merdan S, Womble PR, et al. Clinical predictors and recommendations for staging computed tomography scan among men with prostate cancer. *Urology*. 2014;84(6):1329-1334. doi:10.1016/j.urology.2014.07.051

18. Makarov DV, Trock BJ, Humphreys EB, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy gleason score (partin tables) based on cases from 2000 to 2005. *Urology*. 2007;69(6):1095-1101. doi:10.1016/j.urology.2007.03.042

19. 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

20. 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

21. Hope TA, Eiber M, Armstrong WR, et al. Diagnostic accuracy of 68ga-psma-11 pet for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: a multicenter prospective phase 3 imaging trial. *JAMA Oncol*. 2021;7(11):1635-1642. doi:10.1001/jamaoncol.2021.3771

22. Colvin SD, Cason DE, Galgano SJ, et al. Fusion of high b-value diffusion-weighted and t2-weighted mr images increases sensitivity for identification of extraprostatic disease in prostate cancer. *Clin Imaging*. 2020;68:202-209. doi:10.1016/j.clinimag.2020.08.022

23. Jager GJ, Barentsz JO, de la Rosette JJ, Rosenbusch G. Preliminary results of endorectal surface coil magnetic resonance imaging for local staging of prostate cancer. *Radiologe*. 1994;34(3):129-133.

24. Kam J, Yuminaga Y, Krelle M, et al. Evaluation of the accuracy of multiparametric mri for predicting prostate cancer pathology and tumour staging in the real world: an multicentre study. *BJU Int*. 2019;124(2):297-301. doi:10.1111/bju.14696

25. Selnaes KM, Kruger-Stokke B, Elschot M, et al. (18)f-fluciclovine pet/mri for preoperative lymph node staging in high-risk prostate cancer patients. *Eur Radiol*. 2018;28(8):3151-3159. doi:10.1007/s00330-017-5213-1

26. Wang L, Hricak H, Kattan MW, et al. Combined endorectal and phased-array mri in the prediction of pelvic lymph node metastasis in prostate cancer. *AJR Am J Roentgenol*. 2006;186(3):743-748. doi:10.2214/AJR.04.1682

27. 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

28. Vis AN, Meijer D, Roberts MJ, et al. Development and external validation of a novel nomogram to predict the probability of pelvic lymph-node metastases in prostate cancer patients using magnetic resonance imaging and molecular imaging with prostate-specific membrane antigen positron emission tomography. *Eur Urol Oncol*. 2023;6:553-563. doi:10.1016/j.euo.2023.03.010

29. Rosales JJ, Betech Antar V, Minguez F, et al. Comparison of staging using [(68)ga]ga-psma-11 pet/ct and histopathological results in intermediate- and high-risk prostate cancer patients treated with radical prostatectomy and pelvic lymph node dissection. *Rev Esp Med Nucl Imagen Mol (Engl Ed)*. 2025;44(2):500076. doi:10.1016/j.remnie.2024.500076

30. Légaré F, Ratté S, Stacey D, et al. Interventions for improving the adoption of shared decision making by healthcare professionals. *Cochrane Database Syst Rev*. 2010;5:Cd006732. doi:10.1002/14651858.CD006732.pub2

31. Légaré F, Stacey D, Turcotte S, et al. Interventions for improving the adoption of shared decision making by healthcare professionals. *Cochrane Database Syst Rev*. 2014;9:Cd006732. doi:10.1002/14651858.CD006732.pub3

32. Stacey D, Légaré F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2017;4:Cd001431. doi:10.1002/14651858.CD001431.pub5

33. Violette PD, Agoritsas T, Alexander P, et al. Decision aids for localized prostate cancer treatment choice: systematic review and meta-analysis. *CA Cancer J Clin*. 2015;65(3):239-251. doi:10.3322/caac.21272

34. O'Connor AM, Llewellyn-Thomas HA, Flood AB. Modifying unwarranted variations in health care: shared decision making using patient decision aids. *Health Aff (Millwood)*. 2004;23(Suppl 2):Var63. doi:10.1377/hlthaff.var.63

35. Institute of Medicine (US) Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. National Academies Press (US) Copyright 2001 by the National Academy of Sciences, 2001.

36. Makarov DV, Chrouser K, Gore JL, et al. Aua white paper on implementation of shared decision making into urological practice. *Urol Pract*. 2016;3(5):355-363. doi:10.1016/j.urpr.2015.10.006

37. Agency for Healthcare Research and Quality. *The Share Approach*, 2024.

38. Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years? *Eur Urol*. 2022;81(1):5-33. doi:10.1016/j.eururo.2021.08.005

39. Gill IS, Azzouzi AR, Emberton M, et al. Randomized trial of partial gland ablation with vascular targeted phototherapy versus active surveillance for low risk prostate cancer: extended followup and analyses of effectiveness. *J Urol*.

2018;200(4):786-793. doi:10.1016/j.juro.2018.05.121

40. Bates AS, Ayers J, Kostakopoulos N, et al. A systematic review of focal ablative therapy for clinically localised prostate cancer in comparison with standard management options: limitations of the available evidence and recommendations for clinical practice and further research. *Eur Urol Oncol.* 2021;4(3):405-423. doi:10.1016/j.euo.2020.12.008

41. Ploussard G, Coloby P, Chevallier T, et al. Whole-gland or subtotal high-intensity focused ultrasound versus radical prostatectomy: the prospective, noninferiority, nonrandomized hifi trial. *Eur Urol.* 2025;87(5):526-533. doi:10.1016/j.eururo.2024.11.006

42. Li H, Xu Z, Lv Z, Wang M, Liu M. Survival after cryotherapy versus radiotherapy in low and intermediate risk localized prostate cancer. *Clin Genitourin Cancer.* 2023;21(6):679-693. doi:10.1016/j.clgc.2023.06.009

43. Karkov J, Jensen BN. ultrastructural markers in patients with aids. *Ugeskr Laeger.* 1988;150(26):1595-1597.

44. Weinstock C, Suzman D, Kluetz P, et al. Development of treatments for localized prostate cancer in patients eligible for active surveillance: U.S. Food and drug administration oncology center of excellence public workshop. *J Urol.* 2020;203(1):115-119. doi:10.1097/JU.0000000000000532

45. Lebastchi AH, George AK, Polascik TJ, et al. Standardized nomenclature and surveillance methodologies after focal therapy and partial gland ablation for localized prostate cancer: an international multidisciplinary consensus. *Eur Urol.* 2020;78(3):371-378. doi:10.1016/j.eururo.2020.05.018

46. Cella L, Lomax A, Miralbell R. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2001;49(1):217-223. doi:10.1016/s0360-3016(00)01368-7

47. Coen JJ, Paly JJ, Niemierko A, et al. Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;82(2):e201–e209. doi:10.1016/j.ijrobp.2011.03.048

48. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer.* 2014;120(7):1076-1082. doi:10.1002/cncr.28536

49. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst.* 2013;105(1):25-32. doi:10.1093/jnci/djs463

50. Lukez A, Handorf E, Mendenhall NP, et al. A pooled patient-reported outcomes analysis of moderately hypofractionated proton beam therapy and photon-based intensity modulated radiation therapy for low- or intermediate-risk prostate cancer. *Prostate.* 2024;84(4):395-402. doi:10.1002/pros.24660

51. Bao A, Barsky AR, Both S, et al. Case-matched outcomes of proton beam and intensity-modulated radiation therapy for localized prostate cancer. *Int J Part Ther.* 2023;10(1):1-12. doi:10.14338/IJPT-23-00002.1

52. Wisdom AJ, Yeap BY, Michalski JM, et al. Setting the stage: feasibility and baseline characteristics in the partiqol trial comparing proton therapy versus intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2025;121(3):741-751. doi:10.1016/j.ijrobp.2024.09.043

53. Wisdom AJ, Yeap BY, Michalski JM, et al: Prostate advanced radiation technologies investigating quality of life (partiqol): a phase iii randomized clinical trial of proton therapy vs. Imrt for low or intermediate risk prostate cancer.

54. Wisdom AJ, Yeap BY, Michalski JM, et al: Baseline characteristics of patients enrolled on the prostate advanced radiation technologies investigating quality of life (partiqol) trial comparing proton therapy vs. Imrt for low or intermediate risk prostate cancer.

55. Malone S, Roy S, Eapen L, et al. Sequencing of androgen-deprivation therapy with external-beam radiotherapy in localized prostate cancer: a phase iii randomized controlled trial. *J Clin Oncol.* 2020;38(6):593-601. doi:10.1200/JCO.19.01904

56. Roach M, 3rd, DeSilvio M, Lawton C, et al. Phase iii trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: radiation therapy oncology group 9413. *J Clin Oncol.* 2003;21(10):1904-1911. doi:10.1200/JCO.2003.05.004

57. 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

58. Spratt DE, Malone S, Roy S, et al. Prostate radiotherapy with adjuvant androgen deprivation therapy (adt) improves metastasis-free survival compared to neoadjuvant adt: an individual patient meta-analysis. *J Clin Oncol.* 2021;39(2):136-144. doi:10.1200/JCO.20.02438

59. Cartes R, Karim MU, Tisseverasinghe S, et al. Neoadjuvant versus concurrent androgen deprivation therapy in localized prostate cancer treated with radiotherapy: a systematic review of the literature. *Cancers (Basel).* 2023;15(13):3363. doi:10.3390/cancers15133363

60. 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

61. Shore N, Hafron J, Saltzstein D, et al. Apalutamide for high-risk localized prostate cancer following radical prostatectomy (apa-rp). *J Urol.* 2024;212(5):682-691. doi:10.1097/JU.0000000000004163

62. Nguyen HG, van den Berg NS, Antaris AL, et al. First-in-human evaluation of a prostate-specific membrane antigen-targeted near-infrared fluorescent small molecule for fluorescence-based identification of prostate cancer in patients with high-risk prostate cancer undergoing robotic-assisted prostatectomy. *Eur Urol Oncol.* 2024;7(1):63-72. doi:10.1016/j.euo.2023.07.004

63. Nguyen PL, Haddad Z, Ross AE, et al. Ability of a genomic classifier to predict metastasis and prostate cancer-specific mortality after radiation or surgery based on needle biopsy specimens. *Eur Urol.* 2017;72(5):845-852. doi:10.1016/j.eururo.2017.05.009

64. Nguyen PL, Huang HC, Davicioni E, et al. Validation of a 22-gene genomic classifier in the nrg oncology/rtog 9202, 9413 and 9902 phase iii randomized trials: a biopsy-based individual patient meta-analysis in high-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* 2021;111:S50.

65. Spratt DE, Tang S, Sun Y, et al. Artificial intelligence predictive model for hormone therapy use in prostate cancer. *NEJM Evid.* 2023;2(8):EVIDoa2300023. doi:10.1056/EVIDoa2300023

66. Kinnaird A, Luger F, Cash H, et al. Microultrasonography-guided vs mri-guided biopsy for prostate cancer diagnosis: the optimum randomized clinical trial. *JAMA.* 2025;333(19):1679-1687. doi:10.1001/jama.2025.3579

67. US Food and Drug Administration. *FDA Approves Second PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer.* 2021.

68. US Food and Drug Administration. *FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer.* 2020.

69. Sprute K, Kramer V, Koerber SA, et al. Diagnostic accuracy of (18)f-psma-1007 pet/ct imaging for lymph node staging of prostate carcinoma in primary and biochemical recurrence. *J Nucl Med.* 2021;62(2):208-213. doi:10.2967/jnumed.120.246363

70. 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