



Clinically Localized Prostate Cancer: AUA/ASTRO Guideline 2022

Endorsed by SUO

James A. Eastham, MD; Gregory B. Aufferberg, MD, MS; Daniel A. Barocas, MD, MPH; Roger Chou, MD; Tony Crispino; John W. Davis, MD, Scott Eggener, MD; Eric M. Horwitz, MD; Christopher J. Kane, MD; Daniel W. Lin, MD; Sean M. McBride, MD, MPH; Alicia K. Morgans, MD, MPH; Phillip M. Pierorazio, MD; George Rodrigues, MD; William W. Wong, MD; Stephen A. Boorjian, MD

EXECUTIVE SUMMARY

Purpose

The recommendations discussed herein for the management of clinically localized prostate cancer provide a framework stratified by risk to facilitate care decisions and guide clinicians in the implementation of selected management options.

Methodology

The systematic review that informs this Guidelines was based on searches in Ovid MEDLINE (September 2021), Cochrane Central Register of Controlled Trials (August 2021), and Cochrane Database of Systematic Reviews (September 2021). Searches were supplemented by reviewing reference lists of relevant articles. Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. The target population was patients with clinically localized prostate cancer, defined as up to clinical stage T3 (by digital rectal examination [DRE]) prostate cancer without nodal or distant metastasis (N0M0) on conventional imaging.

GUIDELINE STATEMENTS

RISK ASSESSMENT

1. Clinicians should use clinical T stage, serum prostate-specific antigen (PSA), Grade Group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong Recommendation; Evidence Level: Grade A)
2. Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)
3. Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)
4. Clinicians should perform an assessment of patient and tumor risk factors to guide the decision to offer germline testing that includes mutations known to be associated with aggressive prostate cancer and/or known to have implications for treatment. (Expert Opinion)

STAGING

5. Clinicians should not routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or intermediate-risk prostate cancer. (Expert Opinion)
6. Clinicians should obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer. (Strong Recommendation; Evidence Level: Grade B)
7. In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases. (Expert Opinion)

RISK-BASED MANAGEMENT

8. Clinicians should inform patients that all prostate cancer treatments carry risk. The risks of treatment, in particular 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 a shared decision-making approach to management. (Clinical Principle)
9. Clinicians should provide an individualized risk estimate of post-treatment prostate cancer recurrence to patients with prostate cancer. (Clinical Principle)
10. For patients with low-risk prostate cancer, clinicians should recommend active surveillance as the preferred management option. (Strong Recommendation; Evidence Level: Grade A)
11. In asymptomatic patients with prostate cancer and limited life expectancy (determined on a patient-specific basis), clinicians should recommend watchful waiting. (Strong Recommendation; Evidence Level: Grade A)
12. For patients with favorable intermediate-risk prostate cancer, clinicians should discuss active surveillance, radiation therapy, and radical prostatectomy. (Strong Recommendation; Evidence Level: Grade A)
13. Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion)
14. For patients with unfavorable intermediate- or high-risk prostate cancer and estimated life expectancy greater than 10 years, clinicians should offer a choice between radical prostatectomy or radiation therapy plus androgen deprivation therapy (ADT). (Strong Recommendation; Evidence Level: Grade A)
15. Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial. (Expert Opinion)
16. Clinicians may recommend palliative ADT alone for patients with high-risk prostate cancer, local symptoms, and limited life expectancy. (Expert Opinion)

PRINCIPLES OF MANAGEMENT

Principles of Active Surveillance

17. Patients managed with active surveillance should be monitored with serial PSA values and repeat prostate biopsy. (Expert Opinion)

18. In patients selecting active surveillance, clinicians should utilize mpMRI to augment risk stratification, but this should not replace periodic surveillance biopsy. (Expert Opinion)

Principles of Surgery

19. In patients electing radical prostatectomy, nerve-sparing, when oncologically appropriate, should be performed. (Moderate Recommendation; Evidence Level: Grade B)
20. Clinicians should inform patients that pelvic lymphadenectomy provides staging information, which may guide future management, but does not have consistently documented improvement in metastasis-free, cancer-specific, or overall survival. (Moderate Recommendation; Evidence Level: Grade B)
21. Clinicians should use nomograms to select patients for lymphadenectomy. The potential benefit of identifying lymph node positive disease should be balanced with the risk of complications. (Clinical Principle)
22. Clinicians performing pelvic lymphadenectomy should perform an extended dissection, which improves staging accuracy compared to a limited dissection. (Moderate Recommendation; Evidence Level: Grade: B)
23. Clinicians should complete a radical prostatectomy if suspicious regional nodes are encountered intraoperatively. (Moderate Recommendation; Evidence Level: Grade C)
24. Clinicians should risk stratify patients with positive lymph nodes identified at radical prostatectomy based on pathologic variables and postoperative PSA. (Expert Opinion)
25. Clinicians may offer patients with positive lymph nodes identified at radical prostatectomy and an undetectable post-operative PSA adjuvant therapy or observation. (Conditional Recommendation; Evidence Level: Grade C)
26. Clinicians should not routinely recommend adjuvant radiation therapy after radical prostatectomy. (Strong Recommendation; Evidence Level: Grade A)

Principles of Radiation

27. Clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of external beam radiation therapy (EBRT) delivered for prostate cancer. (Clinical Principle)
28. Clinicians should utilize dose escalation when EBRT is the primary treatment for patients with prostate cancer. (Strong Recommendation; Evidence Level: Grade A)
29. 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)
30. Clinicians should offer moderate hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (Strong Recommendation; Evidence Level: Grade A)
31. Clinicians may offer ultra hypofractionated EBRT for patients with low- or intermediate risk prostate cancer who elect EBRT. (Conditional Recommendation; Evidence Level: Grade B)
32. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary

high-dose rate (HDR) prostate implant as equivalent forms of treatment. (Strong Recommendation; Evidence Level: Grade B)

33. In patients with low- or intermediate-risk prostate cancer electing radiation therapy, clinicians should not electively radiate pelvic lymph nodes. (Strong Recommendation; Evidence Level: Grade B)
34. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should not routinely use ADT. (Moderate Recommendation; Evidence Level: Grade B)
35. In patients with unfavorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer the addition of short-course (four to six months) ADT with radiation therapy. (Strong Recommendation; Evidence Level: Grade A)
36. Clinicians should offer moderate hypofractionated EBRT for patients with high-risk prostate cancer who are candidates for EBRT. (Moderate Recommendation; Evidence Level: Grade C)
37. In patients with unfavorable intermediate- or high-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT or combined EBRT + brachytherapy (LDR, HDR) along with a risk-appropriate course of ADT. (Strong Recommendation; Evidence Level: Grade A/B)
38. In patients with high-risk prostate cancer electing radiation therapy, clinicians may offer radiation to the pelvic lymph nodes. (Conditional Recommendation; Evidence Level: Grade B)
39. When treating the pelvic lymph nodes with radiation, clinicians should utilize intensity-modulated radiation therapy (IMRT) with doses between 45 Gy to 52 Gy. (Strong Recommendation; Evidence Level: Grade B)
40. In patients with high-risk prostate cancer electing radiation therapy, clinicians should recommend the addition of long-course (18 to 36 months) ADT with radiation therapy. (Strong Recommendation; Evidence Level: Grade A)
41. When combined ADT and radiation are used, ADT may be initiated neoadjuvantly, concurrently, or adjuvantly. (Conditional Recommendation; Evidence Level: Grade C)
42. When combining ADT with radiation therapy, clinicians may use combined androgen suppression (luteinizing hormone-releasing hormone [LHRH] agonist with an antiandrogen), an LHRH agonist alone, or an LHRH antagonist alone. (Expert Opinion)

FOLLOW-UP AFTER TREATMENT

43. Clinicians should monitor patients with prostate cancer post therapy with PSA and symptom assessment. (Clinical Principle)
44. Clinicians should support patients with prostate cancer through continued symptom management and encouraging engagement with professional or community-based resources. (Clinical Principle)

INTRODUCTION

METHODOLOGY

The Localized Prostate Cancer Guideline Panel was created in 2019 by the American Urological Association (AUA). This guideline was developed in collaboration with the American Society for Radiation Oncology (ASTRO) with additional representation from the American Society of Clinical Oncology (ASCO) and Society of Urologic Oncology (SUO). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the additional panel members with specific expertise in this area in conjunction with ASTRO, ASCO, and SUO. Additionally, the Panel included patient representation. Funding of the Panel was provided by AUA and ASTRO; panel members received no remuneration for their work.

Primary methodology was provided by the Pacific Northwest Evidence-based Practice Center of Oregon Health & Science University (OHSU).¹ The Panel also utilized the systematic review developed by the Agency for Healthcare Research and Quality (AHRQ) on *Therapies for Clinically Localized Prostate Cancer*.^{2,3}

Data Sources and Searches. A research librarian conducted searches in Ovid MEDLINE (September 2021), Cochrane Central Register of Controlled Trials (August 2021), and Cochrane Database of Systematic Reviews (September 2021). Searches were supplemented by reviewing reference lists of relevant articles.

Study Selection. Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. The target population was patients with clinically localized prostate cancer, defined as up to clinical stage T3 (by digital rectal examination [DRE]) prostate cancer without nodal or distant metastasis (N0M0) on conventional imaging. Studies of patients with low-, intermediate-, or high-risk clinically localized prostate cancer were included.

For evaluation of prognostic factors, OHSU included primary studies and systematic reviews that reported risk estimates and controlled for potential confounders, evaluated patients that did not undergo curative treatment or who underwent radical prostatectomy or radiation

therapy, and recruited patients in or after 1990. OHSU restricted inclusion to large ($n > 1,000$) studies, unless no such studies were available. Such sample size criterion was only applied to studies of prognosis. For diagnosis, the methodology team included primary studies and systematic reviews that reported diagnostic accuracy or discrimination (e.g., the area under the receiver operating characteristic curve). For evaluation of treatments/management, OHSU focused on randomized trials; if no randomized trials were available, methodologists also included recent, large cohort studies that evaluated comparisons of interest and controlled for confounders. OHSU excluded uncontrolled studies of treatments, case reports, narrative reviews, and non-English language articles. In vitro and animal studies were also excluded. Articles must have been published in a peer-reviewed journal.

Using the pre-specified criteria, two investigators independently reviewed titles and abstracts of all citations. OHSU used a two-phase method for screening full-text articles identified during review of titles and abstracts. In the first phase, OHSU reviewed full-text articles to identify relevant systematic reviews for inclusion. When there were many primary studies or the primary studies were primarily observational, OHSU utilized systematic reviews that addressed Key Questions, were higher quality, and published within the last five years. The second phase reviewed full-text articles to identify primary studies for key questions not sufficiently answered by previously published systematic reviews, and new studies published after the systematic reviews.

Data Abstraction. For primary studies that met inclusion criteria, a single investigator abstracted information on study design, year, setting, country, sample size, eligibility criteria, dose and duration of the intervention, population characteristics (age, race, tumor stage, tumor grade, prostate-specific antigen [PSA] level, performance status, prostate cancer risk category), results, and source of funding. For systematic reviews, OHSU abstracted characteristics of the included studies (number, design, and sample sizes of included studies, study settings), population characteristics (inclusion and exclusion criteria), interventions, methods, and ratings for the risk of bias of included studies, synthesis methods, and results. For survival and progression-free survival (PFS), risk estimates were based on the number of deaths or cases of progression, so that estimates < 1 indicate improved

survival; if necessary, reported risk estimates were converted to this format. Data abstractions were reviewed by a second investigator for accuracy and discrepancies were resolved through discussion and consensus.

Risk of Bias Assessment. Two investigators independently assessed risk of bias using predefined criteria. Disagreements were resolved by consensus. For randomized trials and cohort studies, the methodology team adapted criteria for assessing risk of bias from the U.S. Preventive Services Task Force.⁴ Criteria for randomized trials included use of appropriate randomization and allocation concealment methods, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. For cohort studies on prognostic factors, criteria included methods for assembling cohorts, attrition, blinding assessment of outcomes, and adjustment for potential confounding. OHSU assessed systematic reviews using AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) criteria.⁵ Criteria included use of pre-specified methods, appropriate search methods, assessment of risk of bias, and appropriate synthesis methods. For diagnostic accuracy studies, OHSU adapted criteria from QUADAS-2 to assess risk of bias related to patient selection, interpretation of the index test, selection and interpretation of the reference standard, and flow and timing (e.g., interval between index test and reference standard, receipt of the reference standard, and exclusion of patients from the analysis).⁶ Studies were rated as “low risk of bias,” “medium risk of bias,” or “high risk of bias” based on the presence and seriousness of methodological shortcomings.

Studies rated “low risk of bias” are generally considered valid. “Low risk of bias” randomized trials include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; blinding of patients, care providers, and outcome assessors; and appropriate analysis of outcomes.

Studies rated “medium risk of bias” are susceptible to some bias, though not necessarily enough to invalidate the results. These studies do not meet all the criteria for a rating of low risk of bias, but no flaw is likely to cause major bias. Studies may be missing information, making it difficult

to assess limitations and potential problems. The “medium risk of bias” category is broad, and studies with this rating vary in their strengths and weaknesses. Therefore, the results of some medium risk of bias studies are likely to be valid, while others may be only possibly valid.

Studies rated “high risk of bias” have significant flaws that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of high risk of bias studies could be as likely to reflect flaws in study design and conduct as true difference between compared interventions. OHSU did not exclude studies rated high risk of bias a priori, but high risk of bias studies were considered less reliable than low or medium risk of bias studies.

Data Synthesis and Determination of Evidence Strength. OHSU constructed evidence tables with study characteristics, results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. OHSU reported pooled estimates and other results from systematic reviews and examined whether the findings of new studies were consistent with the reviews.

The AUA employs a three-tiered strength of evidence system to underpin evidence-based guideline statements. (Table 1) The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable randomized controlled trials [RCTs] or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.⁷

Table 1: Strength of Evidence Definitions

AUA Evidence Category	Strength of	GRADE Certainty Rating	Definition
A		High	<ul style="list-style-type: none"> • Very confident that the true effect lies close to that of the estimate of the effect
B		Moderate	<ul style="list-style-type: none"> • Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C		Low	<ul style="list-style-type: none"> • Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
		Very Low	<ul style="list-style-type: none"> • Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel’s judgment regarding the balance between benefits and risks/burdens. (Table 2) Strong Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. Moderate Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. Conditional Recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, when benefits and harms are finely balanced, or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and

that future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but that better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but that better evidence is likely to change confidence. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens; therefore, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion emerged.⁸ A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence.

Peer Review and Document Approval. An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and management of Clinically Localized Prostate Cancer. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from ASTRO, ASCO, and SUO as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from December 3-17, 2021 to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and representation from prostate cancer patient and advocacy organizations to open the document further to the patient perspective. The draft guideline document was distributed to 115 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 78 reviewers provided comments, including 61 external reviewers. At the end of the peer review process, a total of 668 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD as well as ASTRO for final approval.

BACKGROUND

Prostate cancer remains the most common non-cutaneous cancer among US men, with an estimated 268,490 new cases and 34,500 deaths in 2022.⁹ As the vast majority of newly-diagnosed prostate cancer patients have clinically-localized disease,⁹ providing evidence-based guideline statements to support clinical decision-making represents an important component of facilitating the delivery of standardized, high-quality care.

Given the breadth of investigation into various aspects of the evaluation and management of clinically-localized disease that has occurred over the past several years, with the resultant emergence of data relevant to patient care delivery, the AUA, in collaboration with ASTRO, undertook to re-evaluate and update the organization's prior prostate cancer guidelines.^{10,11}

An important component of the updated guidelines 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 shared decision-making (SDM) for treatment recommendations, and facilitates clinical trial enrollment. Recognizing that various risk classifications have been described,¹⁰⁻¹⁴ the Panel elected to maintain a risk group model (Table 3). Of note, the Panel did combine the prior risk categories of "very low-risk" and "low-risk" disease together, as the recommended management for these patients is consistent. 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 intended to address indications for staging in the newly-diagnosed patient, provide risk-based treatment approaches to be reviewed by the clinician with the patient, and offer 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, fields, and concurrent androgen deprivation therapy (ADT) usage, as well as principles of conducting 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.

TABLE 3: 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
	<ul style="list-style-type: none"> Favorable: Grade Group 1 with PSA 10-<20 ng/mL or clinical stage T2b-c and <50%* 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 ≥50%* biopsy cores positive OR Grade Group 3 with PSA <20 ng/mL
High-Risk	PSA ≥20 ng/mL OR Grade Group 4-5 OR clinical stage T3

*Percent biopsy cores positive is the total number of cores containing cancer divided by total number of cores obtained x 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 (i.e., 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 highest Gleason score used for risk stratification.¹⁶

GUIDELINE STATEMENTS

RISK ASSESSMENT

- Clinicians should use clinical T stage, serum PSA, Grade Group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong Recommendation; Evidence Level: Grade B)**

The risk of disease progression and adverse oncologic outcomes of prostate cancer varies widely based on clinicopathologic characteristics. Disease risk stratification is vital at the outset of patient counseling to align the aggressiveness of management to the severity of disease. Several risk stratification systems have been described and have been variously utilized, including risk groups, risk

scores, and nomograms.¹⁰⁻¹⁴ The Panel did conduct a systematic review of the literature to verify that the individual features of the risk groups remain associated with likelihood of adverse pathologic findings, biochemical recurrence, metastases, and death, and to evaluate whether mature data exist to support inclusion of additional parameters to enhance risk stratification. In total, 30 studies on prognostic factors in localized prostate cancer met inclusion criteria.¹⁷⁻⁴⁹ Sample sizes ranged from 1,062 to 19,684 patients.

Nineteen cohort studies evaluated baseline PSA level as a prognostic factor in patients with clinically localized prostate cancer who underwent curative treatment (typically radical prostatectomy or radiation therapy).

Higher PSA level was associated with increased risks of biochemical recurrence,^{18,21-23,25,27-31,33,36,38,41,44,45,47} prostate cancer-specific mortality,^{18,26,32,35,47} and all-cause mortality.^{32,35,40} Similarly, a separate series evaluated baseline PSA level as a prognostic factor in patients with clinically localized prostate cancer who did not undergo curative treatment and noted an association between higher PSA level and increased risk of prostate cancer mortality.²⁴ Overall, PSA level was deemed to be an important risk factor that should be assessed, documented, and used to categorize patient risk.

Clinical T-stage is determined by DRE and is defined according to the American Joint Committee on Cancer (AJCC) system.^{16,50} Higher clinical T-stage was found to be associated with increased risk of biochemical recurrence,^{18,21,23,33,36,38,41,46} prostate cancer-specific mortality,^{18,26,35,47} and all-cause mortality,^{32,35} including among patients who did not undergo definitive treatment.^{17,24} Thus, clinical T-stage should be ascertained by DRE, documented in the chart, and used to categorize patient risk. Of note, prostate imaging (ultrasound or MRI) is not at this time used to assign clinical T-stage for risk classification. Nevertheless, the Panel acknowledges that imaging (e.g., MRI) findings may provide additional information regarding local tumor extent,⁵¹ and may be utilized in disease prognostication/treatment planning.

Cancer grade on biopsy is assigned using the World Health Organization/ International Society of Urologic Pathologists (WHO/ISUP) Grade Group system or the older Gleason score system. ISUP recommends that Gleason scores 6, 3 + 4 = 7, 4 + 3 = 7, 8 and 9-10, be reported as ISUP grades 1-5, respectively.⁵² Fourteen cohort studies evaluated baseline Gleason score as a prognostic factor in patients with clinically localized prostate cancer who underwent curative treatment. Higher Gleason score was associated with increased risks of biochemical recurrence,^{21,23,33,36-38,41,46} metastatic disease,^{39,42,43} prostate cancer-specific mortality,^{26,32,35,42,43,47} and all-cause mortality.^{32,35,40} Gleason score was also a strong predictor of prostate cancer mortality in patients who did not undergo curative treatment.^{17,24} As such, Grade Group is included in risk assessment. The Panel acknowledges that certain histologic features, such as intraductal and cribriform patterns, have likewise been associated with worse prognosis.⁵³⁻⁵⁵ Such features, when available, should be considered when counseling an individual patient.

Of note, the Panel did not include PSA density (serum PSA [ng/mL] divided by imaging measured prostate volume [cc]) in the systematic literature review. However, an ad-hoc literature review demonstrated that a PSA density ≥ 0.15 ng/mL/cc has been associated with the risk of upgrading on subsequent biopsy among patients on active surveillance.⁵⁶ As such, the Panel believes that PSA density remains an important component of disease risk assessment. Of note, the Panel does recognize the continuous nature of risk associated with the spectrum of PSA density values and cautions against use of threshold values in isolation for management decision-making.

- 2. Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)**
- 3. Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)**

Regarding tissue-based genomic biomarkers, several currently available commercial tests, including Prolaris, Oncotype Dx, and Decipher, variously offer prediction of adverse pathology as well as the risks of biochemical recurrence, metastasis, and prostate cancer death. However, most of the reported studies to date that evaluated the prognostic ability of these genomic tests did not meet inclusion criteria for the systematic review as the studies used surgical (i.e., prostatectomy) rather than biopsy specimens. Notably, two studies using biopsy data have shown that a cell cycle progression panel (Prolaris) score was associated with the risks of biochemical recurrence, metastatic disease, and prostate cancer death; however, only one of those studies met inclusion criteria for the systematic review.^{19,20,57} The Oncotype Dx assay has been validated on needle biopsy tissue and found to be associated with adverse pathology, biochemical recurrence, metastasis, and prostate cancer death; again, however, the studies did not meet inclusion criteria for the systematic review.⁵⁸⁻⁶¹ Meanwhile, a multi-institutional evaluation of Decipher Biopsy testing found that a high-risk Decipher score was associated with conversion from active surveillance to definitive treatment.⁴⁸

Thus, based on the level of existing data, the Panel concluded that clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making; however, clinicians may use such tests selectively when added risk stratification may alter SDM. These recommendations are largely consistent with recent ASCO Guidelines as well.⁶² Examples of patients for whom tissue-based genomic markers may help clarify risk include patients with high-volume (multiple involved cores) Gleason score 6 cancer as well as select men with favorable intermediate-risk prostate cancer who are interested in active surveillance. Examples of patients for whom tissue-based genomic markers are not recommended including the majority of men with low-volume (few involved cores) Gleason score 6 cancer and men with favorable intermediate-risk prostate cancer who are interested in treatment.

The Panel recognizes that this is an active area of research. Most notably, prospective validation of the predictive capacity of genomic classifiers (GC) in localized disease will be important to support widespread use for treatment selection. Additional discussion on GCs may be found in Future Directions.

4. Clinicians should perform an assessment of patient and tumor risk factors to guide the decision to offer germline testing that includes

mutations known to be associated with aggressive prostate cancer and/or known to have implications for treatment. (Expert Opinion)

Germline testing in patients with clinically localized prostate cancer has several potential goals, including enhanced risk stratification, identification of genes that may guide treatment decisions, and providing information to determine the need for personal and family member cancer screening. Identified prostate cancer associated genes to date include *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, and *TP53*. For example, studies have demonstrated that men with prostate cancer harboring *BRCA2* genetic aberrations are more likely to have worse disease and a poorer prognosis.⁶³ Testing is typically performed via a saliva or blood sample. Patient education, testing, and referral to a genetic counselor should be considered. Establishing specific indications for genetic testing is beyond the scope of this Guideline; indeed, such recommendations have recently been outlined by a large expert-panel consensus conference.⁶⁴ A number of the indications for germline testing are provided in Table 4. Importantly, patient and family history risk factors should be investigated by the clinician through careful history taking, while pathology from biopsy or radical prostatectomy should be reviewed in the consideration of germline testing.

TABLE 4: Indications for Germline Testing in Patients with Localized Prostate Cancer*

Strong family history of prostate cancer	Examples: first-degree relative or multiple second-degree relatives diagnosed with Grade Group 2 or higher prostate cancer, particularly at early age (< 60 years), particularly if metastatic or lethal
Strong personal or family history of related cancers	Examples: breast, colorectal, ovarian, pancreatic, upper tract urothelial carcinoma
Known family history of familial cancer risk mutation	Examples: <i>BRCA1</i> , <i>BRCA2</i> , <i>ATM</i> , Lynch-syndrome associated genes
Ashkenazi Jewish ancestry	Particularly in patients with Grade Group 2 or higher disease
Adverse tumor characteristics	Examples: High-risk disease; intermediate-risk disease with intraductal or cribriform morphology
*The Panel recognizes that this list is not exhaustive.	

STAGING

- 5. Clinicians should not routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or 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 staging 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 intermediate-risk prostate cancer, the probability of nodal or distant metastasis is low.^{65 - 67} Therefore, abdomino-pelvic computed tomography (CT) scan and bone scan are unlikely to be helpful and should not be routinely obtained.

- 6. Clinicians should obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer. (Strong Recommendation; Evidence Level: Grade B)**

For patients with high-risk prostate cancer, CT scan or multi-parametric magnetic resonance imaging (mpMRI) scan should be obtained to evaluate the loco-regional extent of disease and presence of distant metastasis. For detection of extracapsular extension or seminal vesicle invasion, MRI scan has a low to moderate sensitivity (approximately 0.6) and high specificity (approximately 0.9).^{51, 68-78} mpMRI is preferred for local tumor staging, which may thereby inform therapy.⁷⁹⁻⁸¹ For both mpMRI scan and CT scan, the assessment of nodal metastasis is based on size criteria, and these modalities have similar accuracy. For example, in detection of nodal metastasis, MRI has been found to be associated with a low to moderate sensitivity (range 0.09 to 0.44) and high specificity (range 0.88 to 1.0).^{71,75,76,82,83} To evaluate for the presence of bone metastasis, conventional bone scan should be obtained as the initial staging study. As robust evidence to support an imaging evaluation in unfavorable intermediate-risk disease remains lacking, the Panel offers

that clinicians may consider obtaining staging imaging for patients within this risk classification.

- 7. In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases. (Expert Opinion)**

The role of molecular imaging, also referred to as next generation imaging (NGI), continues to evolve as new and more sensitive radiotracers become available. Recently, both the Gallium 68 prostate-specific membrane antigen (PSMA)-11 (Ga 68 PSMA-11) and piflufolostat F-18 PSMA (18F-DCFPyL) PET scanning have been FDA approved for initial staging for patients at high risk of metastasis (as well as for evaluation of biochemical relapse after treatment).^{84,85} In a multicenter randomized trial, Ga-68 PSMA PET scan was compared with conventional imaging using CT scan and bone scan in patients with high-risk prostate cancer before definitive therapy. Ga-68 PSMA PET scan was found to have a 27% greater accuracy than conventional imaging, with better sensitivity and specificity, in the detection of nodal or distant metastasis.⁸⁶ While data to date supporting a clinical benefit to novel imaging modalities for patients with negative conventional imaging remain quite limited, the Panel did conclude that clinicians may offer molecular imaging in patients at high risk for metastatic disease based on the demonstrated enhanced staging accuracy. This recommendation is consistent with recent ASCO Guidelines as well.⁸⁷ The Panel recognizes that the identification of disease with molecular imaging may influence treatment (e.g., the addition of systemic therapy or metastases-directed therapy) and underscores the current uncertainty regarding an incremental oncologic benefit of altering treatment based on the identification of metastases with molecular imaging among patients with negative conventional imaging. The Panel further acknowledges that the role of NGI is an active area of investigation, availability remains inconsistent, and the impact on patient outcomes remains to be determined in order to guide its place in clinical decision making. Further discussion on this topic is provided in the Future Directions section.

RISK-BASED MANAGEMENT

- 8. Clinicians should inform patients that all prostate cancer treatments carry risk. The**

risks of treatment, in particular 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 a shared decision-making approach to management. (Clinical Principle)

The selection of a management strategy for clinically localized prostate cancer is preference-sensitive and very often based on patients' 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. 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.⁸⁸⁻⁹¹ RCTs of SDM versus 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.^{88,92} The Institute 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.^{93, 94} Key components of SDM in selecting a management option for localized prostate cancer are provided in Table 5.

Clinicians should counsel patients regarding the severity of disease and documented natural history to provide perspective regarding the tradeoff between treatment-related side effects and the likelihood of disease progression. Furthermore, risk level dictates the intensity of the staging evaluation and the intensity of treatment, so a discussion of risk level sets the foundation for patient understanding of these decisions. Similarly, as the intensity of treatment is also tied to the patient's life expectancy, an estimate of life expectancy should factor into the SDM discussion.

The expected harms of treatment include immediate risks (e.g., perioperative risks associated with surgery), short-term side effects, and long-term (typically quality of life [QOL]) implications. Local treatments are associated with differing profiles of urinary, sexual, and bowel side effects (variously termed 'functional outcomes'), which may evolve or resolve over time.⁹⁵ Meanwhile, hormonal therapy, which is sometimes used in conjunction with radiation therapy, is associated with systemic side effects, some of which are symptomatic (e.g., hot flashes, fatigue, cognitive changes, sexual dysfunction) and some of which remain asymptomatic (e.g., changes in metabolic syndrome parameters). The patient must be informed about the expected risks and side effects of each management option in order to compare the options and to facilitate clear expectations. Specifying the likelihood of various outcome scenarios with each treatment can facilitate SDM, and there are tools available to estimate the likelihood of functional outcomes with each treatment.⁹⁶

Since baseline function is one of the strongest predictors of functional outcomes,⁹⁷ the clinician should ascertain the patient's pre-treatment urinary, bowel, and sexual function (and hormone therapy-related domains if concurrent hormone therapy and radiation is being considered). These functional domains are best assessed using standardized instruments to minimize clinician bias and to facilitate longitudinal comparisons. The Expanded Prostate Cancer Index Composite (EPIC)-26 is one such validated instrument, and it has been selected by the International Consortium on Health Outcomes Measurement (ICHOM) as part of the 'standard set' of data that should be collected on each patient with clinically localized prostate cancer. A shorter instrument tailored to clinical care is the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP).^{98,99} The 5-item Sexual Health Inventory for Men (SHIM)¹⁰⁰ is an instrument designed to assess erectile function as is the longer 15-item International Index of Erectile Function (IIEF).¹⁰¹ Alternative questionnaires for assessment of urinary continence include the International Continence Society Male Short-Form (ICSmaleSF)¹⁰² and International Consultation on Incontinence Questionnaires (ICIQ).¹⁰³ The EORTC has developed and validated QOL instruments pertinent to a general oncology population (QLQ-C30) and has refined sets for specific cancers, including prostate cancer. The EORTC-QLQ-PR25 assesses urinary function, sexual function, bowel function, and hormone therapy symptoms.¹⁰⁴ Similarly, the

Functional Assessment of Cancer Therapy (FACT) measurement system has developed a 12-item prostate cancer subscale (PCS), appended to the 35-item FACT-G for the general oncology population.¹⁰⁵ The Patient-Reported Outcomes Measurement Information System (PROMIS), initiated by the National Institutes of Health, curates a wide variety of QOL measures, and some have been used to assess symptoms after prostate cancer treatment.¹⁰⁶

9. Clinicians should provide an individualized risk estimate of post-treatment prostate cancer recurrence to patients with prostate cancer. (Clinical Principle)

Post-treatment cancer recurrence risk is dependent on a number of clinicopathologic factors, including most notably tumor grade and stage, as well as pretreatment PSA and, for patients undergoing radical prostatectomy, surgical margin status.¹⁰⁷ Multiple predictive models and nomograms have been developed to estimate the risks of biochemical recurrence, metastases, and death from prostate cancer.^{12,13,108-110} These tools may be used to support discussions with patients regarding their personalized risk. In addition, competing risks of mortality from patient age and comorbidity status should be considered. Discussion of risk is a particularly important aspect of patient counseling and SDM.

TABLE 5: Components of Shared Decision-Making for Localized Prostate Cancer Treatment Selection

Informing patients about the severity of their cancer (risk level)*
Assessing patients' relevant comorbidities and life expectancy**
Informing patients about the likelihood of cure, recurrence, and other oncologic endpoints of each management strategy/treatment option (ideally using a risk calculator or nomogram)
Assessing patients' baseline disease-specific function (e.g., urinary, sexual, and bowel function) and the value or utility they place on each (ideally using standardized instruments, with or without decision aids)
Informing patients about their likelihood of specific short- and long-term side effects of each management strategy/treatment option
*see Table 3 and associated text
** An accurate determination of a man's life expectancy based on age and comorbidities is difficult. Methods available to determine life expectancy include clinician prediction, model prediction, and publicly available calculators (e.g., https://www.ssa.gov/OACT/population/longevity.html). Life expectancy may be assessed in conjunction with a patient's primary care physician.

10. For patients with low-risk prostate cancer, clinicians should recommend active surveillance as the preferred management option. (Strong Recommendation; Evidence Level: Grade A)

The intent of active surveillance is to maintain patients' QOL by deferring or delaying definitive treatment when prostate cancer is unlikely to cause mortality or significant morbidity, while simultaneously maintaining the potential to implement definitive treatment with curative intent should this become necessary. Relevant data to inform

management for patients with low-risk prostate cancer may be found in the ProtecT trial,¹¹¹ which randomized 1,643 patients with clinically localized prostate cancer to surgery, radiation therapy, or active surveillance (referred to as active monitoring in the trial). In total, 77% of patients in the trial had a Gleason score of 6, 76% had clinical stage T1c (non-palpable) disease, and approximately two-thirds of patients had low-risk prostate cancer.¹⁸ The incidence of all-cause mortality for radical prostatectomy, radiation therapy, and active monitoring was 10.1, 10.3, and 10.9 per 1,000 person-years, respectively (P=0.87). Moreover, no significant differences were identified in prostate

cancer-specific mortality. As such, the trial provides high-level evidence supporting the concept that selected patients with prostate cancer can delay or altogether avoid treatment. These results from ProtecT reinforced numerous cohort studies that have documented the outcomes of patients managed with active surveillance for low-risk prostate cancer and consistently demonstrated low rates of metastases (<1.5%) and prostate cancer related death (<1%) within 10 years after diagnosis.¹¹²⁻¹¹⁸

Given the demonstrated relative safety of active surveillance, the Panel believes that the benefits of aggressive treatment do not outweigh the risk of treatment-related harms for most patients with low-risk disease. Indeed, the potential adverse events associated with prostate cancer treatment, predominantly urinary morbidity, bowel complications, and sexual dysfunction, have been well documented.¹¹⁹⁻¹²¹ The Panel nevertheless acknowledges that select patients with low-risk disease may elect definitive local therapy after an informed discussion between clinician and patient. In particular, clinicians may offer immediate treatment to select patients who are fully informed as to all options and risks with low-risk prostate cancer such as those who have a high probability of disease risk reclassification on active surveillance (e.g., high-volume cancer, higher PSA density) or other risk factors for harboring higher-risk disease (e.g., family history of lethal prostate cancer, germline mutation associated with adverse pathology).¹²²

Patients electing to proceed with active surveillance should be informed of the importance of regular cancer surveillance to avoid missing the window of curability. Strategies for monitoring disease in patients electing active surveillance are detailed further in Principles of Active Surveillance.

11. In asymptomatic patients with prostate cancer and limited life expectancy (determined on a patient-specific basis), clinicians should recommend watchful waiting. (Strong Recommendation; Evidence Level: Grade A)

Patients with a life expectancy of ≤ 5 years do not benefit from prostate cancer screening, diagnosis, or treatment¹²³ as prostate cancer treatment does not improve survival within five years of follow-up.¹²⁴ The PIVOT and SPCG-4 randomized trials of radical prostatectomy versus observation/watchful waiting collectively demonstrate the relative importance of competing risks of mortality and of

patient longevity (minimum estimated life expectancy of 8-10 years) in order for treatment to result in a reduction in the risk of death.^{125,126}

Watchful waiting does not involve routine cancer surveillance, but rather aims to deliver palliative therapy for relief of symptoms should they develop. The critical goal of watchful waiting is to maintain the patient's QOL by avoiding treatment when prostate cancer is unlikely to cause mortality or significant morbidity. One of the principal aims of watchful waiting is avoidance of side effects from local treatment or ADT. Watchful waiting is appropriate for elderly patients or patients with significant comorbidities in whom competing risks of mortality are considerably greater than the risk of death from prostate cancer.

The Panel acknowledges that life expectancy is difficult to predict and notes the existence of several predictive tools to help with this assessment, such as the Kent model.¹²⁷

12. For patients with favorable intermediate-risk prostate cancer, clinicians should discuss active surveillance, radiation therapy, and radical prostatectomy. (Strong Recommendation; Evidence Level: Grade A)

The management of patients with intermediate-risk disease may likewise be informed in part by the ProtecT trial, as approximately one third of patients therein had intermediate- or high-risk disease.¹¹¹ Of note, in the trial, active monitoring was found to be associated with an increased risk of clinical progression compared to radical prostatectomy or radiotherapy (22.9 per 1,000 person-years versus 8.9 per 1,000 person-years for radical prostatectomy and 9.0 per 1,000 person-years for radiation therapy, $P < 0.001$). Similarly, an increased risk of metastatic disease was seen for patients managed with active monitoring (6.3 per 1,000 person-years versus 2.4 per 1,000 person-years for radical prostatectomy and 3.0 per 1,000 person-years for radiation therapy, $P = 0.004$). Nevertheless, all-cause mortality was low in each treatment arm, and no difference was noted in prostate cancer deaths. As such, the Panel believes that, with appropriate counseling, favorable intermediate-risk patients should be offered active surveillance, radical prostatectomy, and radiation therapy. Patients with favorable intermediate-risk disease who may be considered for active surveillance include those with a low PSA density, low tumor volume, as well as a low percentage of Gleason pattern 4 disease on biopsy. The

Panel does recognize the noted increased risk of disease progression with active surveillance among intermediate-risk (versus low-risk) patients, particularly those with Grade Group 2 disease,^{114,128} as well as the relatively limited data on very long-term follow-up of such patients, and thereby emphasizes the importance of informed SDM. Again, patients electing active surveillance should be informed of the importance of regular cancer surveillance to avoid missing the window of curability. Further, for favorable intermediate-risk patients electing treatment with radiation, at this time, ADT should not be used. The Panel recognizes the ongoing accumulation of evidence on this topic (e.g., NRG RTOG 08-15 trial, the results of which have been presented but not yet to date published). Thus, it remains unclear at this time what the benefit for these patients will be in adding ADT to their radiation treatment. Evolving evidence will inform future practice for these patients.

13. Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion)

Numerous ablative modalities, relying on differing energy sources/differing mechanisms of action, are currently available to patients with clinically localized prostate cancer.¹²⁹ Patient selection criteria in reported studies have varied widely as has treatment planning approach (e.g., lesion-based focal therapy, hemi-ablation, whole-gland). The only properly powered randomized trial reported to date on prostate ablation was restricted to patients with low-risk prostate cancer and demonstrated that focal photodynamic therapy (PDT) lowered the likelihood of cancer progression and rates of surgery/radiation compared to active surveillance, at an expense of an increased likelihood of mild urinary or erectile dysfunction.¹³⁰ However, PDT is not approved in the United States. Further, active surveillance is the preferred approach for patients with low-risk prostate cancer.

A number of institutional, multi-site, and population-based studies have reported outcomes of various ablative therapies; however, with 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.¹³¹ Fortunately, randomized trials are ongoing and more are anticipated.

Currently, the Panel believes that ablation may be considered in select, appropriately informed patients (with clinical trial enrollment prioritized). Patients being considered for ablation should have intermediate-risk prostate cancer,¹³² as data supporting treatment of high-risk disease with ablation are lacking, while patients with low-risk cancers should be preferentially managed with active surveillance. Patients considering ablation should be counseled regarding side effects and recurrence risk and should be followed post-ablation with PSA, DRE, MRI, and biopsy tailored to their specific health and cancer characteristics.¹³³

14. For patients with unfavorable intermediate- or high-risk prostate cancer and estimated life expectancy greater than 10 years, clinicians should offer a choice between radical prostatectomy or radiation therapy plus androgen deprivation therapy (ADT). (Strong Recommendation; Evidence Level: Grade A)

For patients with unfavorable intermediate- or high-risk clinically localized prostate cancer, definitive local therapy is advised.¹³⁴⁻¹³⁷ The optimal treatment for these patients remains a topic of active study, and prior published meta-analyses have reported relatively disparate findings as to comparative survival following each of these treatment approaches.^{138,139} The Panel supports offering patients with unfavorable intermediate- and high-risk disease either radical prostatectomy or radiation with ADT (see Principles of Surgery and Principles of Radiation). For patients with sufficiently high-risk disease (clinically node positive, or with 2 of 3 of the following criteria: clinical stage T3 or T4, PSA \geq 40 ng/mL, or \geq Gleason 8), treatment with radiation and ADT can include two years of concurrent abiraterone acetate plus prednisone as well.¹⁴⁰

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

As previously discussed, the only properly powered randomized trial reported to date on prostate ablation included only patients with low-risk prostate cancer. Currently, patients being considered for ablation should

have intermediate-risk prostate cancer,¹³² as there is a lack of data supporting treatment of high-risk disease with ablation, while again, patients with low-risk cancers should be managed with surveillance.

16. Clinicians may recommend palliative ADT alone for patients with high-risk prostate cancer, local symptoms, and limited life expectancy. (Expert Opinion).

Due to the lack of evidence indicating a significant oncologic benefit to treatment with primary ADT for clinically localized prostate cancer, the Panel concluded primary ADT should only be recommended for palliation of local disease-related symptoms in select patients with a limited life expectancy for whom definitive local therapy is not advised. Indeed, among eight cohort studies evaluating survival outcomes between primary ADT and observation in prostate cancer populations of various risk categories - all of which were rated as having a moderate risk of bias - none demonstrated improvements in all-cause or prostate cancer-specific survival.¹⁴¹⁻¹⁴⁸ Moreover, in a cohort study of patients with unfavorable intermediate- or high-risk clinically localized prostate cancer, no significant differences were identified between immediate treatment with primary ADT versus observation with regard to all-cause (adjusted HR 0.69, 95% CI 0.45 to 1.07) or prostate cancer-specific mortality (adjusted HR 2.69, 95% CI 0.77 to 9.32).¹⁴² Likewise, in a population-based analysis of patients with poorly differentiated tumors using Surveillance, Epidemiology, and End Results Program (SEER)-Medicare data, no significant differences were noted between immediate treatment with primary ADT versus observation with regard to overall mortality (adjusted HR 1.04, 95% CI 0.97 to 1.13) or prostate cancer-specific mortality (adjusted HR 1.12, 95% CI 0.96 to 1.29).¹⁴⁴ Of note, in one trial, patients with clinically localized prostate cancer who were unfit for (or declined) local treatment were randomized to immediate versus delayed (at the time of symptomatic progression or metastatic disease) ADT.¹⁴⁹ Although the trial did not report outcomes specifically for patients with high-risk prostate cancer, immediate treatment with ADT was associated with a decrease in overall mortality (HR 0.80, 95% CI 0.68 to 0.95), but not prostate cancer-specific mortality (10-year incidence 24.8% versus 26.0%, $p=0.44$) or disease progression. Further, the study was rated as having moderate risk of bias due to open-label design and unclear blinding of outcomes.

For such patients, the primary goals of care include symptom control/palliation and maintenance of QOL. As such, ADT may be used to manage urinary tract sequelae of local tumor growth through (albeit transient) cytoreduction.

PRINCIPLES OF MANAGEMENT

PRINCIPLES OF ACTIVE SURVEILLANCE

17. Patients managed with active surveillance should be monitored with serial PSA values and repeat prostate biopsy. (Expert Opinion)

Patients managed with active surveillance need to be counseled regarding the importance of continued follow-up as part of this management strategy. Indeed, active surveillance is distinct as a management strategy from watchful waiting, or passive surveillance, by the incorporation of follow-up cancer testing, including prostate biopsy. While the intensity of monitoring has varied among the various reported large active surveillance cohorts to date,^{112,114,118, 150, 151} critical components include following PSA values, which the Panel advises be in general obtained no more frequently than every six months and updating a symptom assessment and physical examination with DRE every one to two years.

Notably, the monitoring regimen for patients managed with active surveillance may be individualized. For example, among patients at low risk of progression or with a more limited life expectancy, a less intense follow-up schedule may be implemented.¹⁵² With regard to the use of genomic testing, as previously noted, while biopsy-based genomic testing may impact the decision of surveillance versus treatment, robust data are currently lacking for meaningful long-term outcomes among contemporary patients managed with active surveillance. In addition, serial genomic testing among patients on active surveillance should be discouraged.

An increase in PSA in a patient being managed with active surveillance should initially prompt re-testing of PSA as transient PSA elevations are common and PSA kinetics have variably been associated with pathology among patients on surveillance.^{153,154} Serial PSA increases, new DRE abnormalities, or other concerns for clinical progression should prompt re-evaluation with MRI and

possible prostate biopsy; less frequently, direct conversion to treatment may be considered. Detection of significantly higher-volume or higher-grade disease on surveillance biopsy should then prompt discussion of definitive therapy. The decision to continue surveillance versus proceed with treatment should incorporate the principles of SDM and include the factors of age, comorbidity status, estimated life expectancy, cancer characteristics, and patient preference, balancing the relative risks of impacting quality-of-life with treatment and disease progression.

18. In patients selecting active surveillance, clinicians should utilize mpMRI to augment risk stratification, but this should not replace periodic surveillance biopsy. (Expert Opinion)

The purpose of active surveillance for suitable patients is to maintain patients' QOL by deferring or delaying definitive treatment when prostate cancer is unlikely to cause mortality or significant morbidity, while simultaneously ensuring the appropriate potential to implement definitive treatment with curative intent should this become necessary. As such, a critical component of management with active surveillance for patients with newly diagnosed prostate cancer is an assessment of the patient's risk for harboring more aggressive disease in the prostate than was detected on biopsy, which would thereby render the patient at increased risk for experiencing subsequent disease progression. mpMRI has been utilized as one such tool for risk assessment in this setting,^{155,156} particularly among patients whose initial prostate biopsy was performed without prior mpMRI guidance. The purported rationale here has been to obtain complete gland imaging, potentially allowing detection of more aggressive disease in the prostate in regions not sampled on the patient's diagnostic biopsy. Patients with positive mpMRI findings have been found to be more likely to contain clinically significant disease (typically, higher Grade Group).¹⁵⁷

A role for mpMRI prior to confirmatory biopsy among patients on active surveillance for low-risk prostate cancer was investigated in the prospective, randomized ASIST trial.¹⁵⁸ Although the initial report of the trial did not find a statistically significant difference in the rate of biopsy upgrading among patients with versus without a pre-confirmatory biopsy mpMRI, a follow-up report from the trial found that patients who underwent mpMRI had fewer active surveillance failures and less grade progression at

two years follow-up post biopsy.¹⁵⁹ Thus, the Panel believes that an mpMRI should be obtained if the initial (diagnostic) prostate biopsy was performed without mpMRI guidance. If the mpMRI demonstrates findings suspicious for clinically-significant prostate cancer (PIRADS 4 or 5), then timely repeat (confirmatory) targeted biopsy is recommended, with disease risk re-established based on these biopsy results. Conversely, if the mpMRI is assessed as PIRADS 1, 2, or 3, then repeat biopsy may be performed within approximately 12 months after diagnosis. Thereafter, serial surveillance biopsies are recommended every one to four years depending on patient age, health, risk of progression, and preference.¹⁶⁰⁻¹⁶²

Evidence for the utility of serial prostate mpMRI to evaluate for changes in disease risk among patients on surveillance remains mixed; as such, mpMRI cannot be recommended as a stand-alone replacement for periodic repeat biopsy.¹⁶³ For example, a recent cohort study demonstrated that a surveillance strategy using mpMRI or clinical changes as the sole indicator for repeat biopsy would have missed upgrading to Grade Group 2 or higher in 169 of every 1,000 patients on surveillance, leading to the conclusion by the authors that periodic biopsy should remain a component of the management of patients on surveillance.¹⁶⁴ A subsequent meta-analysis found a pooled sensitivity and specificity for detecting Grade Group of 2 or more of 0.59 (95% CI 0.44 to 0.73) and 0.75 (95% CI 0.66 to 0.84), respectively.¹⁶⁵ It should be noted that interobserver variability in interpreting mpMRI may be a limitation. Therefore, while the Panel recognizes that mpMRI may be utilized in patients electing active surveillance, further study is warranted to determine the optimal timing and incorporation of continued imaging for patient management.

PRINCIPLES OF SURGERY

19. In patients electing radical prostatectomy, nerve-sparing, when oncologically appropriate, should be performed. (Moderate Recommendation; Evidence Level: Grade B)

Preservation of the neurovascular bundles during radical prostatectomy has consistently been associated with a lower likelihood of postoperative erectile dysfunction, has variously but favorably been associated with improved urinary continence after surgery, and has not been found to significantly compromise the rates of positive surgical

margins or biochemical recurrence.¹⁶⁶⁻¹⁶⁹ The Panel does acknowledge, however, that the systematic review did not identify RCTs of nerve-sparing versus non-nerve sparing radical prostatectomy. The Panel also recognizes the balance between nerve preservation and optimizing cancer control. Indeed, the decision to perform nerve-sparing is frequently multifactorial, and may include PSA, DRE, biopsy findings (grade, tumor volume, and location), MRI findings, as well as the patient's baseline erectile function and stated prioritization of sexual function. The Panel further asserts that MRI should not be used in isolation to determine nerve-sparing, as the ability of MRI to predict extracapsular extension, particularly when microscopic, is suboptimal.¹⁷⁰ Importantly, the Panel notes that nerve-sparing does not necessarily entail an "all or none" decision, and both partial nerve preservation and unilateral nerve-sparing may be utilized.

20. Clinicians should inform patients that pelvic lymphadenectomy provides staging information, which may guide future management, but does not have consistently documented improvement in metastasis-free, cancer-specific, or overall survival. (Moderate Recommendation; Evidence Level: Grade B)

21. Clinicians should use nomograms to select patients for lymphadenectomy. The potential benefit of identifying lymph node positive disease should be balanced with the risk of complications. (Clinical Principle)

The systematic review supporting this guideline identified 44 studies (N=244,889 patients) detailing the outcomes of patients who variously did or did not undergo pelvic lymph node dissection (PLND) at the time of radical prostatectomy for clinically localized prostate cancer. Of note, the absence of robust prospective clinical trials comparing the results of patients undergoing PLND versus not, as well as significant methodological issues (e.g., heterogeneity in risk of harboring lymph node positive disease among the populations studied, lack of standardized dissection templates) and bias limit the level of evidence from the reported outcome data. That said, from the existing literature, no consistent benefit to PLND can be derived with regard to oncologic outcomes such as biochemical recurrence, metastasis-free, cancer-specific, and overall survival.¹⁷¹⁻¹⁷⁶ Two recent prospective trials randomized patients undergoing radical prostatectomy to

limited versus extended PLND.^{177, 178} In both trials, no statistically significant difference in subsequent biochemical recurrence-free survival was identified between the treatment arms, although one of the trials did note improved biochemical recurrence-free survival with extended lymph node dissection in an exploratory subgroup analysis of patients with Grade Group 3 to 5 tumors.¹⁷⁷ At the same time, the systematic review did demonstrate a higher risk of adverse perioperative outcomes in patients undergoing PLND (operating time, blood loss, length of stay) and post-operative complications – most notably lymphocele.¹⁷⁹

Nevertheless, as PLND (specifically, an extended PLND) does facilitate identification of positive nodes,^{177, 180} the Panel concluded that patients should be counseled regarding the staging benefit of PLND. Identifying positive nodes not only contributes to refined risk stratification/patient counseling, but may further be used to guide the selective application of secondary therapies.^{181, 182} Given the uncertain oncologic benefit and noted – albeit small – increased risk of complications with PLND, the Panel believes that PLND should be advised according to a risk stratified approach, using nomograms for risk assessment. Several nomograms exist to facilitate selection of patients for PLND.¹⁸³⁻¹⁸⁵ When selecting a model, it is important that clinicians consider the risk profile of the patients included in model development (e.g., percentage of high-risk patients) as well as the reference standard (e.g., extended versus limited PLND) utilized to establish the model's predictive capacity. Existing national and organizational guidelines have proposed various thresholds of nomogram-predicted probability of lymph node positive disease for clinicians to perform a PLND at the time of radical prostatectomy. Recognizing varying individual risk tolerance, the Panel believes that the patient's calculated risk of harboring positive nodes should be discussed along with the utility of establishing the presence of positive nodes to inform future management and the risks associated with PLND and to facilitate the SDM approach to performing lymph node dissection.

22. Clinicians performing pelvic lymphadenectomy should perform an extended dissection, which improves staging accuracy compared to a limited dissection. (Moderate Recommendation; Evidence Level: Grade: B)

Using anatomic landmarks, PLND templates may be considered as follows:¹⁷¹

- Limited = obturator fossa
- Standard = limited plus external iliac lymph nodes
- Extended = Standard plus internal iliac lymph nodes
- Super-extended = Extended plus common iliac, presacral and/or other nodes

Extended PLND results in higher lymph node counts as well as a greater positive lymph node yield.^{177,179,180,186} While a more extensive lymph node dissection increases operative time as well as the risk of lymphocele,¹⁷⁹ the Panel believes that the demonstrated staging benefit supports that extended dissection should be performed for appropriately risk-selected patients undergoing PLND.

23. Clinicians should complete a radical prostatectomy if suspicious regional nodes are encountered intraoperatively. (Moderate Recommendation; Evidence Level: Grade C)

The Panel acknowledges the absence of prospective trial testing in this setting. Numerous retrospective series – largely in historic cohorts of patients from an era during which frozen section analysis of pelvic lymph nodes at the time of prostatectomy was routine – have reported a benefit to completion of radical prostatectomy among patients found to have positive nodes versus patients whose surgery was aborted and who were then treated with ADT alone.^{187 - 190} Recognizing the design/methodologic limitations of these studies, the Panel believes that completion of surgery remains warranted among patients for whom lymph nodes suspicious for harboring malignancy are encountered during surgery, particularly given the overall demonstrated safety of radical prostatectomy in contemporary series.¹⁹¹

24. Clinicians should risk stratify patients with positive lymph nodes identified at radical prostatectomy based on pathologic variables and postoperative PSA. (Expert Opinion)

25. Clinicians may offer patients with positive lymph nodes identified at radical prostatectomy and an undetectable postoperative PSA adjuvant therapy or observation. (Conditional Recommendation; Evidence Level: Grade C)

Importantly, the documented postoperative natural history of patients with lymph node positive disease at radical prostatectomy is relatively heterogeneous. In fact, up to 30% of patients with positive lymph nodes may remain free of disease long-term following surgery without further therapy.^{192 - 194} As such, assessment of the risk for subsequent disease progression among patients with positive lymph nodes is warranted to guide the judicious use of secondary therapy. Various clinicopathologic features have been associated with oncologic outcomes in this setting, particularly the number of positive nodes identified.¹⁹⁵

Further, while salvage therapy would be appropriate for such patients with a persistently detectable PSA after radical prostatectomy, the Panel believes that patients with an undetectable PSA may be offered adjuvant treatment versus continued PSA surveillance. Of note, a randomized trial in 98 patients assessed the use of immediate, indefinite ADT after radical prostatectomy for patients with lymph node positive disease versus delayed treatment with ADT (largely at the time of systemic progression).¹⁸¹ At the median 11.9 year follow-up, immediate ADT was associated with improved PFS (HR 3.42, 95% CI 1.96 to 5.98), prostate cancer-specific survival (HR 4.09, 95% CI 1.76 to 9.49), and overall survival (HR 1.84, 95% CI 1.01 to 3.35). However, relevant to contemporary management, the trial did not assess the comparative outcomes of adjuvant ADT versus ADT initiated at the time of biochemical recurrence, thus the optimal timing to initiate postoperative ADT for patients with lymph node positive disease remains to be determined. Interestingly, six cohort studies investigating this topic have reported mixed findings.^{196 - 201} Three studies found no significant association between treatment with adjuvant ADT¹⁹⁶⁻¹⁹⁸ and oncologic outcomes including biochemical recurrence-free survival, metastasis-free survival, prostate cancer-specific survival, and overall survival, while three studies found improvement in various cancer-specific outcomes in certain populations.¹⁹⁹⁻²⁰¹

The role of postoperative radiation for patients with lymph node positive disease has not to date been addressed in the prospective clinical trial setting. Rather, a number of cohort studies have reviewed the outcomes of patients with lymph node positive disease treated with adjuvant ADT with or without adjuvant radiation as well.^{197,200-206} Five of those studies demonstrated improvements in a variety of oncologic outcomes, including overall and cause-specific

survival when adjuvant radiation therapy was added to ADT.^{197,200,203-205} In addition, a retrospective analysis noted superior metastases-free survival among patients with lymph node positive disease treated with adjuvant radiation versus a cohort who received no treatment/salvage radiation.¹⁹⁷ Nevertheless, the absence of prospective data preclude definitive recommendations regarding the optimal timing of radiation in patients with lymph node involvement at surgery.

Therefore, the Panel believes that both adjuvant therapies (e.g., ADT, radiation) as well as surveillance with the option for early salvage therapy should the patient experience PSA relapse may be utilized for patients with positive lymph nodes at radical prostatectomy and an undetectable postoperative PSA. The approach taken should be based on SDM, including an assessment of disease risk stratification (e.g., number of positive nodes, primary tumor features) as well as the potential toxicities of additional therapies.

26. Clinicians should not routinely recommend adjuvant radiation therapy after radical prostatectomy. (Strong Recommendation; Evidence Level: Grade A)

Three recent randomized trials (GETUG-AFU 17, RAVES, RADICALS) evaluated adjuvant radiation therapy versus surveillance with early salvage radiation therapy for PSA increase in patients with high-risk localized prostate cancer following radical prostatectomy.²⁰⁷⁻²⁰⁹ The criteria for early salvage therapy was a PSA >0.1 ng/mL or >0.2 ng/mL depending on the trial; the proportion of patients in the early salvage therapy groups that received radiation therapy ranged from one third to one half. All three trials demonstrated no significant difference in oncological outcomes between patients who received adjuvant radiation therapy versus patients managed with surveillance and early salvage therapy. Moreover, a prospectively planned systematic review of these trials found no evidence of improvement in event-free survival (pooled HR 0.95, 95% CI 0.75 to 1.21) with receipt of adjuvant therapy and noted that adjuvant radiation was associated with increased risk of genitourinary toxicity.²¹⁰ Given these findings, together with the observation that between one third and one half of the patients in the surveillance arm of the trials did not require salvage therapy, the Panel concluded adjuvant radiation therapy should not be routinely recommended, and patients should

be initially managed with PSA surveillance after radical prostatectomy. The Panel does recognize the relatively limited number of patients included in the aforementioned trials with particularly high-risk features (e.g., Gleason 8 to 10 disease with extraprostatic extension, positive lymph nodes) and thereby acknowledges a potential role for adjuvant radiation in such select patients.²¹¹

PRINCIPLES OF RADIATION

27. Clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of external beam radiation therapy (EBRT) delivered for prostate cancer. (Clinical Principle)

As is common with other tumor systems in which radiation therapy is delivered for therapeutic benefit, an overarching paradigm in prostate cancer radiation therapy is the application of appropriate evidence-based dosages to the cancer target while simultaneously avoiding sensitive adjacent normal tissues. In this way, the therapeutic ratio between tumor control and normal tissue injury is established to maximize therapeutic benefit while minimizing toxicity, morbidity, and potentially treatment-related mortality. Over the past few decades, the specialty of radiation oncology has leveraged various technologies to achieve this goal of improved cancer outcomes with equal or improved toxicity profiles.

A variety of approaches exist to optimize the therapeutic ratio in radiation oncology. A non-exhaustive list of these approaches include the following:

- Simulation procedures: Bladder/rectum filling instructions, patient immobilization, placement of fiducial markers, and use of rectal spacers
- Imaging procedures: CT simulations, integrations of fusion imaging (e.g., MRI prostate), image-guided radiation therapy approaches (e.g., cone-beam CT)
- Planning procedures: Use of highly conformal radiation therapy such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and

stereotactic body radiation therapy (SBRT), combined with published target and normal tissue dose objectives to optimize planning

Most of these approaches have not been subject to prospective randomized phase III trial testing. One exception is the use of rectal spacers, which was evaluated in a trial that randomized 222 patients 2:1 to either a rectal spacer or control group prior to 79.2 Gy in 1.8 Gy fractions to the prostate ± seminal vesicles.^{212,213} With a median follow-up of three years, improvements in low-grade (one and two) rectal toxicity, no difference in urinary toxicity, and improvements in bowel health-related QOL were identified.²¹³ Device-related toxicity events were not detected in this trial.²¹² Of note, the utility of this technology in conjunction with hypofractionated or ultra hypofractionated radiation therapy has not been reported in prospective randomized clinical trials to date.

28. Clinicians should utilize dose escalation when EBRT is the primary treatment for patients with prostate cancer. (Strong Recommendation; Evidence Level: Grade A)

With the introduction of modern treatment planning software and CT scans in the late 1980s and early 1990s, radiation oncology techniques evolved from basic conventional techniques using simple 2-dimensional planning. Prior to the implementation of sophisticated treatment planning software and CT scans, radiation doses used in the treatment of prostate cancer were limited to between 65-70 Gy.

Advances in radiation treatment planning software and imaging technology have allowed delivery of higher doses to the prostate while limiting doses to the surrounding normal tissues such as rectum and bladder, thus improving the therapeutic ratio.^{214,215} The current standard technique of external beam radiation therapy (EBRT) is IMRT, which allows dose escalation to greater than 80 Gy safely.

Since the 1990s, multiple phase III randomized prospective studies have compared dose-escalated EBRT (DE-EBRT) using both 3-D conformal radiation therapy (3DCRT) and IMRT with standard dose EBRT and have consistently demonstrated improved biochemical PFS with dose escalation. Multiple randomized trials (sample sizes 126 to 1,499) compared escalated versus conventional dose radiation therapy in patients with localized prostate cancer.^{216 - 230} The trials enrolled a mix of low-,

intermediate-, and high-risk patients. Escalated doses ranged from 74 to 79.2 Gy, while conventional doses ranged from 64 to 70.2 Gy. The trials consistently demonstrated that escalated dose radiation therapy was associated with decreased rates of biochemical failure or recurrence. Of note, the Panel acknowledges that estimates from these trials for the endpoints of metastatic-disease free survival, prostate cancer-specific survival, and overall survival were imprecise and did not indicate a benefit to dose escalation, with the exception of one trial^{224,225,227} that did report reduced risks of distant metastatic failure (HR 0.33, 95% CI 0.13 to 0.82) and prostate cancer mortality (HR 0.52, 95% CI 0.27 to 0.98). The largest of the trials was NRG-RTOG 0126 (n=1,499) which looked at standard versus dose-escalated radiation therapy in patients with intermediate-risk prostate cancer.²³⁰ This trial demonstrated improvements in biochemical failure and distant metastases; however, the dose-escalated radiation therapy arm was not associated with improvements in overall survival. Furthermore, higher radiation doses were also associated with lower rates of post-radiation salvage at the expense of higher rates of late toxicity. Importantly, this trial has provided clinicians valuable information about radiation dose constraints for the safe planning of dose-escalated radiation therapy for intermediate-risk prostate cancer.²³¹

29. 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 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 than IMRT.²³² However, this dosimetric difference has not been shown to result in fewer side effects or better patient reported QOL. Indeed, the existing peer-reviewed literature suggests that clinical outcomes (e.g., complications, patient reported QOL) are similar.²³³

Comparative effectiveness studies have been published in an attempt to evaluate relative toxicity and oncologic outcomes between proton and photon therapies. Two such studies comparing patients treated with proton therapy or photon therapy reported similar toxicity rates. For one, a prospective comparison of patients treated with IMRT (n=204) and patients treated with proton therapy (n=1,234) 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.²³⁴ 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.²³⁵ No other significant differences were seen between the groups. Randomized trials are ongoing comparing IMRT and PBRT using long-term side effects and QOL as the primary endpoints (e.g., PARTIQoL, which has a primary endpoint of bowel function at 24 months).

30. Clinicians should offer moderate hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (Strong Recommendation; Evidence Level: Grade A)

31. Clinicians may offer ultra hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (Conditional Recommendation; Evidence Level: Grade B)

Using fewer (but larger dose) radiation treatments (i.e., hypofractionation) may be more convenient for patients with prostate cancer electing radiation therapy.²³⁶ Nevertheless, demonstrating equivalent cancer control and toxicity profiles with such an approach is paramount.

A systematic review compared hypofractionated (>2 Gy per fraction, range 2.35 to 3.4 Gy) versus conventionally fractionated (1.8 to 2 Gy) EBRT in patients with localized prostate cancer.²³⁶ This review included 10 randomized trials (N=8,278); seven trials used highly conformal radiation therapy, six used image-guided radiation therapy (IGRT), and two trials reported some form of motion management. In pooled analyses, no differences were noted between hypofractionation versus conventional

fractionation with regard to biochemical recurrence-free survival (HR 0.88, 95% CI 0.68 to 1.13, 5 trials), metastasis-free survival (HR 1.07, 95% CI 0.65 to 1.76, 5 trials), prostate cancer-specific survival (HR 1.00, 95% CI 0.72 to 1.39, 8 trials), or overall survival (HR 0.94, 95% CI 0.83 to 1.07, 10 trials). There were also no differences identified with regard to acute genitourinary radiation therapy toxicity (Relative Risk [RR] 1.03, 95% CI 0.95 to 1.11, 4 trials), late genitourinary radiation therapy toxicity (RR 1.05, 95% CI 0.93 to 1.18), or late gastrointestinal radiation therapy toxicity (RR 1.10, 95% CI 0.68 to 1.78). Findings were consistent in stratified analyses based on radiation therapy dose (≥ 74 Gy or < 74 Gy), difference in radiation therapy doses between hypofractionation and conventional fractionation, radiation therapy technique (highly conformal versus 3DCRT), and use of ADT ($\leq 50\%$ of $> 50\%$). Moreover, three trials (n=92, 139, and 303) published subsequent to the systematic review likewise found no clear differences between moderate hypofractionation (fraction size 2.25 to 2.7 Gy, total 70 to 72 Gy) versus conventional fractionation (fraction size 2.0 Gy, total 74 to 80 Gy) in oncological outcomes, QOL, or adverse events, though some estimates were imprecise.²³⁷⁻²⁴⁰

One randomized trial (HYPO-RT, n=1,200) compared ultra hypofractionation (42.7 Gy in 7 fractions, fraction size 6.1 Gy) versus conventional fractionation (78.0 Gy in 39 fractions, fraction size 2 Gy) in patients undergoing radiation therapy with image-guided 3DCRT, IMRT, or VMAT for intermediate- or high-risk localized prostate cancer.^{241, 242} Ultra fractionation was found to be non-inferior to conventional fractionation with regard to failure-free survival (HR 1.00, 95% CI 0.76 to 1.32), prostate cancer mortality (incidence at 5 years 2% versus 1%, p=0.46), and overall survival (HR 1.11, 95% CI 0.73 to 1.69). In addition, although ultra hypofractionation was associated with increased incidence of acute urinary and bowel symptoms, no differences were found in late symptoms or QOL.

Currently, data on long-term control with ultra hypofractionated compared to moderate hypofractionation is less well documented; however, data to date support the use of hypofractionated EBRT. Of note, the recommendations herein are consistent with existing guidance provided by ASTRO/ASCO/AUA.²⁴³

32. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment. (Strong Recommendation; Evidence Level: Grade B)

Trial data support the use of dose-escalated hypofractionated EBRT or brachytherapy including temporary high-dose rate (HDR) or permanent low-dose rate (LDR) prostate implants as appropriate treatment options for patients with low- or favorable intermediate-risk prostate cancer.²⁴⁴

Importantly, the systematic review undertaken for guideline development identified no randomized trials comparing EBRT to brachytherapy. Of note, a recent retrospective analysis among patients with intermediate-risk prostate cancer (n=684) found no difference between EBRT (75.3 Gy) versus brachytherapy (radioactive iodine seeds at minimum peripheral dose of 145 Gy), with or without neoadjuvant ADT, in propensity score adjusted 10-year metastasis-free survival (91% versus 94%), prostate cancer-specific survival (96% versus 95%), or overall survival (76% versus 78%).²⁴⁵ EBRT was associated with decreased likelihood of freedom from biochemical failure (57% versus 80%).

To note as well, in a Phase II trial of 170 patients randomized to receive HDR as either a single (19 Gy) fraction or as two fractions (13.5 Gy), the 5-year biochemical disease-free survival and cumulative incidence of local failure was 73.5% and 29% in the single fraction arm and 95% (p = 0.001) and 3% (p < 0.001) in the 2-fraction arm, respectively.²⁴⁶ Toxicity results from this study were reported separately; in the single fraction arm, the 5-year cumulative incidence of Grade 2 or higher genitourinary and gastrointestinal toxicity was 62% and 12%, and was 47% and 9% in the two-fraction arm. Grade 3 genitourinary toxicity was only seen in the single fraction arm. No significant differences in mean urinary health related QOL were seen compared to baseline in the two-fraction arm, in contrast to the single-fraction arm, wherein a decline in urinary health-related QOL was seen at 4 and 5 years. The authors ultimately concluded that both single

fraction and 2-fraction HDR monotherapy were well tolerated.²⁴⁷

33. In patients with low- or intermediate-risk prostate cancer electing radiation therapy, clinicians should not electively radiate pelvic lymph nodes. (Strong Recommendation; Evidence Level: Grade B)

A prior trial (n=446) that compared whole pelvis (46 Gy with cone-down to prostate) to prostate only (66 to 70 Gy) radiation therapy among low-, intermediate-, and high-risk patients with clinical stage T1b-T3 localized prostate cancer found no difference in PFS (adjusted HR 0.96, 95% CI 0.64 to 1.43) or overall survival between the treatment arms.^{248, 249} Similarly, the RTOG 9413 trial, which contained intermediate-risk patients and utilized a 2 x 2 factorial design, demonstrated no significant difference in biochemical failure when comparing whole pelvic radiation therapy to prostate only radiation.²⁵⁰⁻²⁵² As these are the only prospective trials with sub-groups of intermediate-risk patients, and no benefit was found with nodal radiation, the Panel recommends against the routine use of elective pelvic nodal irradiation for low- and intermediate-risk patients electing radiation therapy.

34. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should not routinely use ADT. (Moderate Recommendation; Evidence Level: Grade B)

ADT is associated with well-recognized side effects and may significantly impact patients' health-related QOL.^{253,254} These side effects commonly include (but are not limited to) decreased libido, erectile dysfunction, hot flashes, depression and other mood disturbances, fatigue, and weight gain. In addition, treatment with ADT may result in significant changes in metabolic function, including reduction in bone mineral density, increased insulin resistance, and changes in blood lipid profiles.²⁵⁵

Given the potential deleterious short- and long-term effects of ADT, its application in the treatment of localized prostate cancer must be based on an individualized risk-benefit balance. While a number of randomized trials have investigated the use of ADT in combination with radiation therapy versus radiation therapy alone,²⁵⁶⁻²⁶⁹ most of these studies have investigated intermediate- and high-risk cancer populations. However, in a large trial (n=2,028) that

included patients in all risk strata, the use of ADT was not associated with improved overall survival outcome for low-risk patients (HR 0.93, 95% CI 0.72 to 1.20).²⁶⁴ Moreover, although trials have demonstrated a benefit to ADT with radiation for intermediate-risk patients, these trials have not consistently sub-stratified intermediate-risk patients into favorable and unfavorable risk for separate outcome reporting. In line with recommendations of other organizations,¹⁴ the Panel believes that routine use of ADT in favorable intermediate-risk patients is not recommended given the observed positive cancer outcomes of radiotherapeutic monotherapy for this patient population (acknowledging the exception of unique circumstances such as planned prostate gland volume reduction prior to definitive radiation therapy, in which ADT may be useful). At the same time, the Panel recognizes that the utility of ADT for favorable intermediate-risk localized prostate cancer is currently under investigation (e.g., NRG Oncology/RTOG 0815).

35. In patients with unfavorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer the addition of short-course (four to six months) ADT with radiation therapy. (Strong Recommendation; Evidence Level: Grade A)

Given the higher risk of local and distant relapse with unfavorable intermediate-risk disease, the use of ADT is recommended for this patient population. Eight randomized trials have evaluated the role of ADT with radiation therapy versus radiation therapy alone.²⁵⁶⁻²⁶⁹ All eight trials included intermediate-risk patients, with one trial including patients from all risk strata²⁶⁴ and one trial exclusive to intermediate-risk patients only.²⁶⁹ These trials were heterogeneous in terms of radiation therapy dosage (ranging from 65 to 78 Gy) and technique (3DCRT and IMRT), as well as ADT duration (three to six months in all trials except one trial, which treated for three years), ADT timing (neoadjuvant in five trials, concurrent in two trials, and unknown in one trial), and ADT type (luteinizing hormone-releasing hormone [LHRH] agonist plus antiandrogen in six trials, LHRH agonist alone in one trial, and antiandrogen in one trial). Regardless, these studies collectively demonstrated a consistent benefit with regard to oncologic outcomes among the patients who received ADT with radiation. In an analysis stratified by prostate cancer risk category from one of these trials (n= 2,028), radiation therapy plus short-term ADT was associated with

improved overall survival among patients with intermediate-risk disease (HR 0.81, 95% CI 0.67 to 0.98).²⁶⁴ The benefit of hormonal therapy was also demonstrated in the recently published MARCAP meta-analysis, which demonstrated that the addition of ADT to radiotherapy significantly improved metastasis-free survival (HR 0.83, 95% CI 0.77 to 0.89, p<0.0001).²⁷⁰

Toxicity was assessed in seven of the trials indicated above.^{256-261,263-269} The use of ADT was associated with expected toxicities during ADT administration. These effects generally diminished or resolved after discontinuation of ADT treatment.²⁶⁹ Notably, late gastrointestinal and genitourinary effects were not impacted by the use of ADT with radiation therapy.^{258,265,269}

With regard to the duration of ADT with radiation in unfavorable intermediate-risk disease, six clinical trials assessed very short course ADT (eight weeks to three months) versus standard short course ADT (six months) in intermediate-risk disease, five of which demonstrated that the six-month approach had superior cancer outcomes, including all-cause mortality and/or prostate cancer-specific mortality.^{259,262, 271 - 280} Nevertheless, the Panel acknowledges that a four-month course of ADT is also commonly given to patients with radiation therapy for intermediate-risk disease in an effort to mitigate the deleterious effects of ADT while maintaining the benefit of combination therapy for cancer control.

36. Clinicians should offer moderate hypofractionated EBRT for patients with high-risk prostate cancer who are candidates for EBRT. (Moderate Recommendation; Evidence Level: Grade C)

As noted above, moderate hypofractionation holds important advantages in terms of patient convenience and resource utilization. Moreover, multiple large-scale randomized prospective clinical trials have been completed comparing moderately hypofractionated and conventionally fractionated EBRT.^{239,281-283} These studies have demonstrated that moderate hypofractionation confers similar prostate-cancer-control outcomes and similar rates of late toxicity compared to conventional fractionation. In one study, men with intermediate- to high-risk prostate adenocarcinoma were randomized to receive C-IMRT (76 Gy in 38 fractions; n=152) or H-IMRT (70.2 Gy in 26 fractions; n=151).²³⁹ High-risk patients were prescribed 24 months of ADT. Intermediate-risk patients

were prescribed 4 months of ADT at the discretion of the treating physician. The primary end point was the cumulative incidence of biochemical and/or clinical disease failure. Median follow up was 130 months (range 7 to 181 months). Ten-year biochemical disease free survival was similar in both arms (25.9% in the C-IMRT arm and 30.6% in the H-IMRT arm; HR 1.31, 95% CI 0.82 to 2.11). The two treatment groups also had similar rates of 10-year freedom from metastatic disease, prostate cancer-specific, and overall survival. The authors concluded that H-IMRT demonstrated no difference in disease outcomes when compared to C-IMRT at 10 years.²³⁹

Of note, ultra hypofractionation in high-risk patients receiving EBRT with elective nodal coverage is not currently recommended outside a clinical trial or multi-institutional registry due to insufficient comparative evidence.²⁴³

37. In patients with unfavorable intermediate- or high-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT or combined EBRT + brachytherapy (LDR, HDR) along with a risk-appropriate course of ADT. (Strong Recommendation; Evidence Level: Grade A/B)

Trials have demonstrated a benefit in clinical control for unfavorable intermediate- or high-risk prostate cancer patients who receive either dose-escalated moderately hypofractionated IMRT or EBRT plus a brachytherapy boost (HDR temporary prostate implant or LDR permanent prostate implant).^{284 - 289} Combining EBRT and brachytherapy has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials.²⁸⁴⁻²⁸⁷

Interestingly, the phase III randomized ASCENDE-RT trial compared two methods of dose escalation in 398 patients with intermediate- or high-risk prostate cancer: dose-escalated EBRT boost to 78 Gy or LDR brachytherapy boost.²⁸⁷⁻²⁸⁹ All patients were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. The primary endpoint of control (biochemical, no evidence of disease) was 89% versus 84% at 5 years; 86% versus 75% at 7 years; and 83% versus 62% at 9 years for the LDR versus EBRT boost arms (log-rank $P < .001$). However, toxicity was higher in the brachytherapy arm, with a cumulative incidence of grade 3 genitourinary events at 5 years of 18.4% for brachytherapy boost and 5.2% for EBRT boost

($P < .001$). In addition, increased gastrointestinal toxicity among patients treated with a brachytherapy boost was also seen (cumulative incidence of grade 3 events at 5 years, 8.1% versus 3.2%; $P = .12$).

38. In patients with high-risk prostate cancer electing radiation therapy, clinicians may offer radiation to the pelvic lymph nodes. (Conditional Recommendation; Evidence Level: Grade B)

The recently published POP-RT trial randomized patients ($n=214$) with NCCN high- (~50%) and very high-risk (~50%) prostate cancer²⁹⁰ to IMRT to the whole pelvis (68 Gy in 25 fractions to prostate with 50 Gy to pelvic lymph nodes) versus prostate-only (68 Gy). This currently represents the only trial of elective pelvic nodal irradiation that delivered both modern standard-of-care radiotherapy doses and ADT duration while looking exclusively at high-risk patients.

All patients received ADT (surgical or medical) starting eight weeks prior to radiation therapy; medical ADT was via an LHRH agonist and was administered for two years. The trial demonstrated improved 5-year biochemical failure-free survival (HR 0.23, 95% CI 0.10 to 0.52; trial's primary endpoint), distant metastasis-free survival (HR 0.35, 95% CI 0.15 to 0.82), and disease-free survival (HR 0.40, 95% CI 0.22 to 0.73) with whole pelvis IMRT, although no difference was detected in overall survival (HR 0.92, 95% CI 0.41 to 2.05).

Despite not showing an overall survival benefit, the Panel notes that elective nodal irradiation for high-risk patients may be offered given the reasonable morbidity (higher late grade II genitourinary toxicity with whole pelvis radiation but no difference in late gastrointestinal toxicity and no difference in grade III/IV genitourinary or gastrointestinal toxicity noted) as well as the reductions in biochemical failure and distant metastases. The Panel recognizes that neither the previous GETUG-01²⁴⁹ nor RTOG 9413²⁵¹ trials demonstrated a benefit to elective nodal irradiation, but submits that those studies included variably-defined high-risk sub-groups (and lower risk than the POP-RT trial), used simpler radiation technologies with more limited pelvic fields, included a shorter duration of ADT, and delivered lower doses of radiation to the prostate; collectively, these differences may have blunted the impact of elective regional irradiation; as such, may be less relevant to inform contemporary practice.

39. When treating the pelvic lymph nodes with radiation, clinicians should utilize intensity-modulated radiation therapy (IMRT) with doses between 45 Gy to 52 Gy. (Strong Recommendation; Evidence Level: Grade B)

As the POP-RT trial²⁹⁰ outlined above utilized IMRT for the treatment of the pelvic lymph nodes, the Panel concludes that clinicians should utilize IMRT when treating the nodes electively in high-risk patients. Meanwhile, various reported trials that included pelvic nodal irradiation treated the nodes with doses from 45 Gy to 52 Gy (50 Gy in POP-RT);²⁹⁰ as such, the Panel supports this range when nodal radiation is utilized.

40. In patients with high-risk prostate cancer electing radiation therapy, clinicians should recommend the addition of long-course (18 to 36 months) ADT with radiation therapy. (Strong Recommendation; Evidence Level: Grade A)

Multiple prospective RCTs have informed the management of high-risk localized prostate cancer to include ADT with radiation based on improved cancer outcomes.²⁵⁶⁻²⁶⁹ In particular, the primary evidence for the use of ADT with radiation in high-risk disease comes from EORTC 22863, a trial that randomized 415 patients with locally advanced prostate cancer to 3 years of ADT plus 70 Gy of prostate radiation therapy versus radiation therapy alone.²⁵⁶⁻²⁵⁹ Benefits were noted in the combination treatment arm with regard to both prostate cancer-specific survival (HR 0.38, 95% CI 0.24 to 0.60) and overall survival (HR 0.60, 95% CI 0.45 to 0.80). From this study, three years of ADT was established as a reference standard ADT treatment for the duration of combined ADT with radiation therapy in the treatment of patients with high-risk prostate cancer. A subsequent RCT among high-risk patients tested 18 versus 36 months of ADT.²⁸⁰ This trial did not demonstrate differences in disease-free survival (HR 0.84, 95% CI 0.68 to 1.02), disease-specific survival (HR 0.95, 95% CI 0.58 to 1.55), or overall survival (HR 1.02, 95% CI 0.81 to 1.29) between the treatment durations, and has thereby introduced a minimum threshold duration of ADT when combined with radiation therapy for the management of high-risk disease. The recently published MARCAP meta-analysis further demonstrates the benefit of ADT in patients treated with radiation therapy.²⁷⁰

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

The optimal sequencing of ADT and radiation has not been clearly defined. In the randomized Ottawa 0101 study, neoadjuvant and concurrent ADT for six months was compared with concurrent and adjuvant ADT for six months.²⁹¹ No differences were detected in biochemical relapse-free survival or overall survival. Meanwhile, in NRG/RTOG 9413, a 2 x 2 factorial design was used whereby^{250,251} patients with prostate cancer were randomized to four months of neoadjuvant and concurrent ADT (starting two months before radiation) versus four months of adjuvant ADT, with a second randomization to prostate only versus whole pelvis irradiation. Interestingly, among patients who underwent prostate only radiation, adjuvant ADT was associated with improved PFS compared to neoadjuvant ADT. However, among patients who received whole pelvis radiation, adjuvant ADT was associated with worse PFS compared to neoadjuvant ADT. Meanwhile, in a meta-analysis 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 arm were combined into the adjuvant group.²⁹² After a median follow-up of 14.9 years, the adjuvant group had significantly better biochemical control, PFS, and metastasis-free survival 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 two trials (e.g., 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. Thus, while this study suggested that adjuvant ADT is associated with improved disease control relative to neoadjuvant ADT in patients receiving (prostate only) radiation, the findings should not be considered definitive. Further, a separate, retrospective cohort study found no difference between neoadjuvant ADT and adjuvant ADT in biochemical recurrence-free survival or distant metastasis-free survival.²⁹³ Importantly, by initiating ADT concurrently or adjuvantly, radiation therapy can begin without delay and may thereby be more convenient for patients as compared to neoadjuvant ADT.

42. When combining ADT with radiation therapy, clinicians may use combined androgen suppression (luteinizing hormone-releasing hormone [LHRH] agonist with an antiandrogen), an LHRH agonist alone, or an LHRH antagonist alone. (Expert Opinion)

Various compositions of ADT have been used in combination with radiation in the randomized trials to date. For example, a number of studies used combined androgen suppression for the entire course of treatment,^{258-260,275,277} while other series used an LHRH agonist for the duration of treatment with an initial short course of antiandrogen at the early phase of treatment,^{278,280} and some trials used LHRH agonists alone.^{269,272} The Panel believes that clinicians may use any one of these options in combination with radiation.

FOLLOW-UP AFTER TREATMENT

43. Clinicians should monitor patients with prostate cancer post therapy with PSA and symptom assessment. (Clinical Principle)

Monitoring after treatment for clinically localized disease with serial PSA measurements and symptom assessments is necessary to identify recurrence as well as complications from treatment, and thereby facilitate early intervention as appropriate. The specific intervals for PSA follow-up may be tailored to disease risk based on clinicopathologic features. Initial monitoring should in general be performed more frequently and is recommended every three to six months for the first two years after treatment. Subsequent monitoring between years two and five should occur every six months, with monitoring annually thereafter. The duration and interval of follow-up beyond 10 years for patients with an undetectable PSA at that time should be a shared decision based on patient disease risk, age, comorbidity status, and preference. Urinary, bowel, and sexual function should likewise be routinely queried, with the use of standardized/validated instruments recommended, in order to monitor the QOL impact from therapy.

44. Clinicians should support patients with prostate cancer through continued symptom management and encouraging engagement with professional or community-based resources. (Clinical Principle)

Multiple resources for support exist for patients with prostate cancer and their loved ones. These resources may be engaged at any time in the patient's clinical course, including at the time of diagnosis (pre-treatment) as well as following definitive local therapy. Important psychosocial support can be provided through social work services and local virtual and in-person prostate cancer support groups, as well as through national patient advocacy organizations (e.g., Active Surveillance Patients International [aspatients.org], AnCan Foundation [ancan.org], Prostate Cancer Foundation [pcf.org], Prostate Cancer Research Institute [PCRI.org], Prostate Cancer Supportive Care Program [pcscprogram.ca], the Prostate Health Education Network [prostatehealthed.org], the Urology Care Foundation [urologyhealth.org], ZERO/UsTOO – the End of Prostate Cancer [zero.org]). Additional physical and lifestyle survivorship support may be provided through referrals to dietary and nutrition services, physical therapists, pelvic floor rehabilitation specialists, and psychosexual therapists. The array of survivorship needs for an individual patient and caregiver may be broad and should be explored by the clinician and team to ensure that appropriate support, especially peer support, is offered.

FUTURE DIRECTIONS

Clinically localized prostate cancer remains among the most active areas of investigation in urology. As such, patient care will likely continue to be refined – and enhanced – in the near future. A few topics of ongoing study are highlighted herein.

TREATMENT INTENSIFICATION FOR HIGH-RISK DISEASE

The STAMPEDE trial results showing a benefit to the addition of abiraterone to ADT in very high-risk localized and node positive disease has ignited interest in treatment intensification in this patient population.¹⁴⁰

Multiple trials evaluating next generation androgen signaling inhibitors in high-risk clinically localized disease have either fully accrued or are currently accruing. For example, ENZARAD completed accrual in 2020, while PROTEUS, a randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide plus ADT versus placebo plus ADT prior to radical prostatectomy in patients with localized high-risk or locally advanced prostate

cancer, is recruiting at multiple centers internationally. Further, DASL-HiCaP is investigating the impact of the novel androgen receptor antagonist darolutamide on metastasis-free survival in very high-risk localized and biochemically recurrent/persistent disease.

GENOMIC CLASSIFIERS

The ability for commercially available GCs (e.g., Prolaris, Decipher, Oncotype DX) to improve the outcomes of patients with clinically localized prostate cancer has not been validated in prospective clinical trials to date. Thus, as noted, 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 under-sampling on the prognostic ability of GCs for assessing the risks of recurrence, metastasis, and death from prostate cancer 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.²⁹⁴ 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 overall survival.²⁹⁵

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 (e.g. 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.

ADVANCED IMAGING

A number of novel imaging radiotracers utilizing PET-based technology have emerged over the past several years and have been demonstrated to improve detection

of disease over conventional imaging. Broadly, these imaging modalities have been referred to as NGI, and among these, PSMA-based PET scanning has received the most attention. This interest has been bolstered by recent US FDA approval of two PSMA based tracers: Gallium 68 PSMA-11 (Ga 68 PSMA-11) and piflufolastat F-18 (18F-DCFPyL).^{84,85} Moreover, continued evaluation of novel PSMA PET agents remains ongoing.²⁹⁶ As such, PSMA PET may become 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 stem from patients evaluated with conventional imaging. For example, in the recent OSPREY trial in which patients underwent F-18 DCFPyL-PET/CT followed by radical prostatectomy and extended 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.²⁹⁷ 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.²⁹⁷ 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.

ABBREVIATIONS

3DCRT	3-D conformal radiation therapy	PGC	Practice Guidelines Committee
ADT	Androgen deprivation therapy	PICOTS	Populations, interventions, comparators, outcomes, timing, types of studies and settings
AHRQ	Agency for Healthcare Research & Quality	PLND	Pelvic lymph node dissection
AJCC	American Joint Committee on Cancer	PROMIS	Patient-Reported Outcomes Measurement Information System
ASCO	American Society of Clinical Oncology	PSA	Prostate-specific antigen
ASTRO	American Society for Radiation Oncology	PSMA	Prostate-specific membrane antigen
AUA	American Urological Association	QOL	Quality of life
BOD	Board of Directors	RCT	Randomized controlled trial
CI	Confidence interval	RR	Relative Risk
CT	Computed tomography	SBRT	Stereotactic body radiation therapy
DE-EBRT	Dose-escalated external beam radiation therapy	SDM	Shared decision-making
DRE	Digital rectal exam	SEER	Surveillance, Epidemiology, and End Results
EBRT	External beam radiation therapy	SHIM	Sexual Health Inventory for Men
EPIC	Expanded Prostate Cancer Index Composite	SQC	Science & Quality Council
EPIC-CP	Expanded Prostate Cancer Index Composite for Clinical Practice	SUO	Society of Urologic Oncology
FACT	Functional Assessment of Cancer Therapy	VMAT	Volumetric modulated arc therapy
GC	Genomic classifier	WHO	World Health Organization
HDR	High-dose rate		
HR	Hazard ratio		
ICHOM	International Consortium on Health Outcomes Measurement		
ICIQ	International Consultation on Incontinence Questionnaires		
ICSmaleSF	International Continence Society Male Short-Form		
IGRT	Image-guided radiation therapy		
IIEF	International Index of Erectile Function		
IMRT	Intensity-modulated radiation therapy		
ISUP	International Society of Urologic Pathologists		
LDR	Low-dose rate		
LHRH	Luteinizing hormone-releasing hormone		
mpMRI	Multi-parametric magnetic resonance imaging		
MRI	Magnetic resonance imaging		
NCCN	National Comprehensive Cancer Network		
NGI	Next generation imaging		
OHSU	Oregon Health & Science University		
PBRT	Proton beam radiation therapy		
PCS	Prostate cancer subscale		
PDT	Photodynamic therapy		
PET	Positron emission tomography		
PFS	Progression-free survival		

CLINICALLY LOCALIZED PROSTATE CANCER PANEL, CONSULTANTS AND STAFF

PANEL

James A. Eastham, MD (Chair)
Memorial Sloan Kettering Cancer Center

Stephen A. Boorjian, MD (Vice Chair)
Mayo Clinic

Phillip M. Pierorazio, MD
Penn Medicine

Tony Crispino (Patient Advocate)
UsTOO

Gegory B. Auffenberg, MD, MS
Urology of St. Louis

Daniel A. Barocas, MD, MPH
Vanderbilt University Medical Center

John W. Davis, MD
MD Anderson Cancer Center

Scott Eggener, MD
UChicago Medicine

Eric M Horwitz, MD
Fox Chase Cancer Center

Christopher J. Kane, MD
UC San Diego Health Physician Group

Daniel W. Lin, MD
UW Medicine

Sean M. McBride, MD, MPH
Memorial Sloan Kettering Cancer Center

Alicia K. Morgans, MD, MPH
Dana-Farber Cancer Institute

George Rodrigues, MD
London Health Sciences Centre

William W. Wong
Mayo Clinic

CONSULTANTS

Roger Chou, MD
Jessica C. Griffin, MS
Tamara P. Cheney, MD
Sara Grusing, MPH
Rebecca S. Holmes, MD, MS

STAFF

Marybeth Farquhar, PhD, MSN, RN
Erin Kirkby, MS
Leila Rahimi, MHS
Brooke Bixler, MPH
Sennett Kim
Chelsi Matthews

CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic- and non-topic-related relationships. Panel members not listed below have nothing to disclose.

Consultant/Advisor: **Stephen Boorjian**, Ferring, ArTara, FerGene, Prokarium; **John Davis**, Medtronic; **Scott Eggener**, Profound Medical, Sophiris, Insightec; **Christopher Kane**, Stratify Genomics/ Invitae; **Daniel Lin**, Astellas, Clovis; **Alicia Morgans**, Bayer, Astra Zeneca, Astellas, Sanofi, Genentech, Janssen, Clovis, Dendreon, Merck, BMS, Pfizer, Myovant, Advanced Accelerator Applications, Progenics, Lantheus, Myriad, Telix, Novartis; **Phillip Pierorazio**, NCCN, Urogen, Ethicon

Meeting Participant or Lecturer: **Daniel Barocas**, Progenics, Ambu, Pacific Edge Diagnostics, Optum Health; **John Davis**, Intuitive Surgical; **Scott Eggener**, Janssen, Francis Medical

Scientific Study or Trial: **Stephen Boorjian**, SUO-CTC; **John Davis**, Janssen, GenomeDx; **Scott Eggener**, Steba Biotech, Candel; **Daniel Lin**, NIH/NCI, Department of Defense, Genomic Health, GenomeDx, MDxHealth, MagForce USA; **Sean McBride**, Janssen, Genentech, Astra Zeneca, Bayer

Investment Interest: **James Eastham**, 3DBiopsy (C)

Health Publishing: **John Davis**, British Journal of Urology International; **Scott Eggener**, ASCO; **Christopher Kane**, NCCN; **Phillip Pierorazio**, Wolters Kluwer; **George Rodrigues**, Demos Medical Publishers

Leadership Position: **Phillip Pierorazio**, Testicular Cancer Awareness Foundation

REFERENCES

- 1 Chou R, Griffin J, Cheney T et al: Management of clinically localized prostate cancer: a systematic evidence review. Portland, OR: Pacific Northwest Evidence-based Practice Center; 2022.
- 2 Dahm P, Brasure M, Ester E et al: Therapies for Clinically Localized Prostate Cancer. Comparative Effectiveness Review No. 230. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-0000-81) AHRQ Publication No. 20-EHC022. Rockville, MD: Agency for Healthcare Research and Quality; September 2020.
- 3 Wilt TJ, Ullman KE, Linskens EJ et al: Therapies for clinically localized prostate cancer: a comparative effectiveness review. J Urol 2020. [Epub ahead of print.]
- 4 Harris RP, Helfand M, Woolf SH et al: Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001; **20**:21.
- 5 Shea BJ, Reeves BC, Wells G et al: AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017; **358**:j4008.
- 6 Whiting PF, Rutjes AW, Westwood ME et al: QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; **155**:529.
- 7 Faraday M, Hubbard H, Kosiak B et al: Staying at the cutting edge: a review and analysis of evidence reporting and grading; the recommendations of the American Urological Association. BJU Int 2009; **104**: 294.
- 8 Hsu C and Sandford BA: The Delphi technique: making sense of consensus. Practical Assessment, Research & Evaluation 2007; **12**: 1.
- 9 Siegel RL, Miller KD, Fuchs HE et al: Cancer statistics, 2022. Ca Cancer J Clin 2022; **72**: 7.
- 10 Sanda MG, Cadeddu JA, Kirkby E et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. part I: risk stratification, shared decision making, and care options. J Urol 2018; **199**:683.
- 11 Sanda MG, Cadeddu JA, Kirkby E et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. part II: recommended approaches and details of specific care options. J Urol 2018; **199**:990.
- 12 Cooperberg MR, Pasta DJ, Elkin EP et al: The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005; **173**:1938.
- 13 D'Amico AV, Whittington R, Malkowicz SB et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; **280**:969.
- 14 National Comprehensive Cancer Network: Prostate Cancer Version 2.2022. November 30, 2021.
- 15 D'Amico AV, Whittington R, Malkowicz SB et al: Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. J Clin Oncol 2000; **16** 1164.
- 16 Amin MB, Edge S, Greene F et al. (Eds.): AJCC Cancer Staging Manual, 8th edition. Chapter 58: Prostate. Springer International Publishing: American Joint Commission on Cancer; 2017.
- 17 Akre O, Garmo H, Adolfsson J et al: Mortality among men with locally advanced prostate cancer managed with noncurative intent: a nationwide study in PCBaSe Sweden. Eur Urol 2011; **60**:554.
- 18 Bryant RJ, Oxley J, Young GJ et al: The ProtecT trial: analysis of the patient cohort, baseline risk stratification and disease progression. BJU Int 2020; **125**:506.
- 19 Canter DJ, Freedland S, Rajamani S et al: Analysis of the prognostic utility of the cell cycle progression (CCP) score generated from needle biopsy in men treated with definitive therapy. Prostate Cancer Prostatic Dis 2020; **23**:102.
- 20 Canter DJ, Reid J, Latsis M et al: Comparison of the prognostic utility of the cell cycle progression score for predicting clinical outcomes in African American and non-African American men with localized prostate cancer. Eur Urol 2019; **75**: 515.
- 21 Chun FK, Graefen M, Zacharias M et al: Anatomic radical retropubic prostatectomy-long-term recurrence-

- free survival rates for localized prostate cancer. *World J Urol* 2006; **24**:273.
- 22 Cole AI, Morgan TM, Spratt DE et al: Prognostic value of percent Gleason grade 4 at prostate biopsy in predicting prostatectomy pathology and recurrence. *J Urol* 2016; **196**:405.
- 23 Cooperberg MR, Pasta DJ, Elkin EP et al: The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J Urol* 2005; **173**:1938.
- 24 Cuzick J, Fisher G, Kattan MW et al: Long-term outcome among men with conservatively treated localised prostate cancer. *Br J Cancer* 2006; **95**:1186.
- 25 Dash A, Sanda MG, Yu M et al: Prostate cancer involving the bladder neck: recurrence-free survival and implications for AJCC staging modification. *American Joint Committee on Cancer. Urology* 2002; **60**:276.
- 26 Dess RT, Suresh K, Zelefsky MJ et al: Development and validation of a clinical prognostic stage group system for nonmetastatic prostate cancer using disease-specific mortality results from the international staging collaboration for cancer of the prostate. *JAMA Oncol* 2020; **6**:1912.
- 27 Fajkovic H, Mathieu R, Lucca I et al: Validation of lymphovascular invasion is an independent prognostic factor for biochemical recurrence after radical prostatectomy. *Urol Oncol* 2016; **34**:233.e1.
- 28 Galiabovitch E, Hovens CM, Peters JS et al: Routinely reported 'equivocal' lymphovascular invasion in prostatectomy specimens is associated with adverse outcomes. *BJU Int* 2017; **119**:567.
- 29 Garcia-Barreras S, Nunes I, Srougi V et al: Predictors of early, intermediate and late biochemical recurrence after minimally invasive radical prostatectomy in a single-centre cohort with a mean follow-up of 8 years. *Actas Urol Esp* 2018; **42**:516.
- 30 Garcia-Barreras S, Sanchez-Salas R, Mejia-Monasterio C et al: Biochemical recurrence-free conditional probability after radical prostatectomy: a dynamic prognosis. *Int J Urol* 2019; **26**:725.
- 31 Ginzburg S, Nevers T, Staff I et al: Prostate cancer biochemical recurrence rates after robotic-assisted laparoscopic radical prostatectomy. *J Soc Laparoendosc Surg* 2012; **16**:443.
- 32 Kibel AS, Ciezki JP, Klein EA et al: Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol* 2012; **187**:1259.
- 33 Korets R, Seager CM, Pitman MS et al: Effect of delaying surgery on radical prostatectomy outcomes: a contemporary analysis. *BJU Int* 2012; **110**:211.
- 34 Lamy PJ, Allory Y, Gauchez AS et al: Prognostic biomarkers used for localised prostate cancer management: a systematic review. *Eur Urol Focus* 2018; **4**:790.
- 35 Liu J, Shi L, Sartor O et al: Androgen-deprivation therapy versus radical prostatectomy as monotherapy among clinically localized prostate cancer patients. *Onco Targets Ther* 2013; **6**:725.
- 36 Potters L, Fearn P, Kattan MW: External radiotherapy and permanent prostate brachytherapy in patients with localized prostate cancer. *Brachytherapy* 2002; **1**:36.
- 37 Potters L, Klein EA, Kattan MW et al: Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol* 2004; **71**:29.
- 38 Reese AC, Pierorazio PM, Han M et al: Contemporary evaluation of the National Comprehensive Cancer Network prostate cancer risk classification system. *Urology*. 2012; **80**:1075.
- 39 Ross AE, Yousefi K, Davicioni E et al: Utility of risk models in decision making after radical prostatectomy: lessons from a natural history cohort of intermediate- and high-risk men. *Eur Urol* 2016; **69**:496.
- 40 Schymura MJ, Kahn AR, German RR et al: Factors associated with initial treatment and survival for clinically localized prostate cancer: results from the CDC-NPCR Patterns of Care Study (PoC1). *BMC Cancer* 2010; **10**:152.
- 41 Sivaraman A, Sanchez-Salas R, Prapotnich D et al: Learning curve of minimally invasive radical prostatectomy: comprehensive evaluation and cumulative summation analysis of oncological outcomes. *Urol Oncol* 2017; **35**:149.e1.
- 42 Taira AV, Merrick GS, Butler WM et al: Long-term outcome for clinically localized prostate cancer treated with permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2011; **79**:1336.
- 43 Taira AV, Merrick GS, Galbreath RW et al: Distant metastases following permanent interstitial brachytherapy for patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**:e225.
- 44 Walz J, Chun FK, Klein EA et al: Risk-adjusted hazard rates of biochemical recurrence for prostate cancer

- patients after radical prostatectomy. *Eur Urol* 2009;**55**:412.
- 45 Walz J, Chun FK, Klein EA et al: Nomogram predicting the probability of early recurrence after radical prostatectomy for prostate cancer. *J Urol* 2009;**181**:601.
- 46 Warner A, Pickles T, Crook J et al: Development of ProCaRS clinical nomograms for biochemical failure-free survival following either low-dose rate brachytherapy or conventionally fractionated external beam radiation therapy for localized prostate cancer. *Cureus* 2015;**7**:e276.
- 47 Wattson DA, Chen MH, Moran BJ et al: The number of high-risk factors and the risk of prostate cancer-specific mortality after brachytherapy: implications for treatment selection. *Int J Radiat Oncol Biol Phys* 2012;**82**:e773.
- 48 Vince RA, Jr., Jiang R, Qi J et al: Impact of Decipher Biopsy testing on clinical outcomes in localized prostate cancer in a prospective statewide collaborative. *Prostate Cancer Prostatic Dis* 2021;**20**:20.
- 49 Wibmer AG, Chaim J, Lakhman Y et al: Oncologic outcomes after localized prostate cancer treatment: associations with pretreatment prostate magnetic resonance imaging findings. *J Urol* 2021;**205**:1055.
- 50 Buyyounouski MK, Choyke PL, McKenney JK et al: Prostate cancer- major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J clin* 2017.
- 51 de Rooij M, Hamoen EHJ, Witjes JA et al: Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. *Eur Urol* 2016;**70**:233.
- 52 Egevad L, Delahunt B, Srigley JR et al: International Society of Urological Pathology (ISUP) grading of prostate cancer – an ISUP consensus on contemporary grading. *APMIS* 2016; **124**: 433.
- 53 Hesterberg AB, Gordetsky JB, Hurley PJ: Cribriform prostate cancer: clinical pathologic and molecular considerations. *Urology* 2021;**155**:47.
- 54 Epstein JI, Amin MB, Fine SW et al: The 2019 Genitourinary Pathology Society (GUPS) white paper on contemporary grading of prostate cancer. *Arch Pathol Lab Med* 2021;**145**:461.
- 55 van Leenders GJLH, van der Kwast TH, Grignon DJ et al: The 2019 International Society of Urological Pathology (ISUP) consensus conference on grading of prostatic carcinoma. *Am J Surg Pathol* 2020;**44**:e87.
- 56 Loeb S, Bruinsma SM, Nicholson J et al: Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. *Eur Urol* 2015; **67**:619.
- 57 Bishoff JT, Freedland SJ, Gerber L et al: Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. *J Urol* 2014;**192**:409.
- 58 Knezevic D, Goddard AD, Natraj N et al: Analytical validation of the Oncotype DX prostate cancer assay - a clinical RT-PCR assay optimized for prostate needle biopsies. *BMC Genomics* 2013;**14**:690.
- 59 Eggner S, Karsh LI, Richardson T et al: A 17-gene panel for prediction of adverse prostate cancer pathologic features: prospective clinical validation and utility. *Urology* 2019;**126**:76.
- 60 Klein EA, Cooperberg MR, Magi-Galluzzi C et al: A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol* 2014;**66**:550.
- 61 Van Den Eeden SK, Lu R, Zhang N et al: A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. *Eur Urol* 2018;**73**:129.
- 62 Eggner SE, Rumble RB, Armstrong AJ et al: Molecular biomarkers in localized prostate cancer: ASCO guideline. *J Clin Oncol* 2020;**38**:1474.
- 63 McNevin CS, Cadoo K, Baird AM et al: Pathogenic BRCA variants as biomarkers for risk in prostate cancer. *Cancers (Basel)*. 2021;**13**:5697.
- 64 Giri VN, Knudsen KE, Kelly WK et al: Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol* 2020;**38**:2798.
- 65 Merdan S, Womble PR, Miller DC et al: Toward better use of bone scans among men with early-stage prostate cancer. *Urology* 2014;**84**:793.
- 66 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**:1329.
- 67 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 (Partins tables) based on cases from 2000-2005. *Urology* 2007;**69**:1095.
- 68 Salerno J, Finelli A, Morash C et al: Multiparametric magnetic resonance imaging for pre-treatment local

- staging of prostate cancer: a Cancer Care Ontario clinical practice guideline. *Can Urol Assoc J* 2016;**10**:E332.
- ⁶⁹ Silva RC, Sasse AD, Matheus WE et al: Magnetic resonance image in the diagnosis and evaluation of extra-prostatic extension and involvement of seminal vesicles of prostate cancer: a systematic review of literature and meta-analysis. *Int Braz J Urol* 2013;**39**:155.
- ⁷⁰ Zhang F, Liu CL, Chen Q et al: Accuracy of multiparametric magnetic resonance imaging for detecting extracapsular extension in prostate cancer: a systematic review and meta-analysis. *Br J Radiol* 2019;**92**:20190480.
- ⁷¹ 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.
- ⁷² Cornud F, Belin X, Flam T et al: Local staging of prostate cancer by endorectal MRI using fast spin-echo sequences: prospective correlation with pathological findings after radical prostatectomy. *Br J Urol* 1996;**77**:843.
- ⁷³ Counago F, Recio M, Del Cerro E et al: Role of 3.0 T multiparametric MRI in local staging in prostate cancer and clinical implications for radiation oncology. *Clin Transl Oncol* 2014; **16**:993.
- ⁷⁴ Ikonen S, Karkkainen P, Kivisaari L et al: Magnetic resonance imaging of clinically localized prostatic cancer. *J Urol* 1998;**159**:915.
- ⁷⁵ Jager GJ, Barentsz JO, de la Rosette JJ et al: Preliminary results of endorectal surface coil magnetic resonance imaging for local staging of prostate cancer. *Radiologe* 1994;**34**:129.
- ⁷⁶ 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**:297.
- ⁷⁷ Lawrence EM, Gallagher FA, Barrett T et al: Preoperative 3-T diffusion-weighted MRI for the qualitative and quantitative assessment of extracapsular extension in patients with intermediate- or high-risk prostate cancer. *AJR Am J Roentgenol* 2014;**203**:W280.
- ⁷⁸ Pompe RS, Kuhn-Thoma B, Nagaraj Y et al: Validation of the current eligibility criteria for focal therapy in men with localized prostate cancer and the role of MRI. *World J Urol* 2018; **36**:705.
- ⁷⁹ Abrams-Pompe RS, Fanti S, Schoots IG et al: The role of magnetic resonance imaging and positron emission tomography/computed tomography in the primary staging of newly diagnosed prostate cancer: a systematic review of the literature. *Eur Urol Oncol* 2021; **4**:370.
- ⁸⁰ Somford DM, Hamoen EH, Fütterer JJ et al: The predictive value of endorectal 3 Tesla multiparametric magnetic resonance imaging for extraprostatic extension in patients with low, intermediate and high risk prostate cancer. *J Urol* 2013;**190**:1728.
- ⁸¹ Park BH, Jeon HG, Jeong BC et al: Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy. *J Urol* 2014;**192**:82.
- ⁸² Selnaes KM, Krüger-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**:3151.
- ⁸³ 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**:743.
- ⁸⁴ US Food & Drug Administration: FDA approves second PSMA-targeted PET imaging drug for men with prostate cancer. 2021.
- ⁸⁵ US Food & Drug Administration: FDA approves first PSMA-targeted PET imaging drug for men with prostate cancer. 2020
- ⁸⁶ 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**: 1208.
- ⁸⁷ Trabulsi EJ, Rumble RB, Jadvar H et al: optimum imaging strategies for advanced prostate cancer: ASCO guideline *J Clin Oncol* 2020;**38**:1963.
- ⁸⁸ Stacey D, Legare F, Col NF et al: Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2014; **1**: CD001431.
- ⁸⁹ 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.
- ⁹⁰ 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**: 239.

- 91 Légaré F, Stacey D, Krygoruchko J et al: Interventions for improving the adoption of shared decision making by healthcare professionals. *Cochrane Database Syst Rev* 2010; **5**: CD006732.
- 92 O'Connor AM, Llewellyn-Thomas HA, and Flood AB: Modifying unwarranted variations in health care: shared decision making using patient decision aids. *Health Aff (Millwood)* 2004; Suppl Variation: VAR63.
- 93 Institute of Medicine: Crossing the quality chasm: a new health system for the 21st century. Washington, DC: The National Academies Press, 2001.
- 94 Makarov DV, Chrouser K, Gore JL et al: AUA white paper on implementation of shared decision making into urological practice. *Urology Practice* 2016; **3**: 355.
- 95 Hoffman KE, Penson DF, Zhao Z et al: Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer *JAMA* 2020; **323**: 149.
- 96 Laviana AA, Zhao Z, Huang LC et al: Development and internal validation of a web-based tool to predict sexual, urinary, and bowel function longitudinally after radiation therapy, surgery, or observation. *Eur Urol* 2020; **78**: 248.
- 97 Hoffman KE, Penson DF, Zhao Z et al: Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer *JAMA* 2020; **323**: 149.
- 98 Szymanski KM, Wei JT, Dunn RL et al: Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology* 2010; **76**:1245.
- 99 Chang P, Szymanski KM, Dunn RL et al: Expanded prostate cancer index composite for clinical practice: development and validation of a practical health related quality of life instrument for use in the routine clinical care of patients with prostate cancer. *J Urol* 2011; **186**: 865.
- 100 Rosen RC Cappelleri JC, Smith MD et al: Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999; **11**: 319.
- 101 Rosen RC, Riley A, Wagner G et al: The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* **1997**; **49**: 822.
- 102 Donovan JL, Peters TJ, Abrams P et al: Scoring the short form ICSmaleSF questionnaire. *J Urol* 2000; **164**:1948.
- 103 Avery K, Donovan J, Peters TJ: ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* 2004; **23**:322.
- 104 van Andel G, Bottomley A, Fosså SD et al: An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. *Eur J Cancer*. 2008; **44**:2418.
- 105 Esper P, Mo F, Chodak G et al: Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology* 1997; **50**:920.
- 106 Agochukwu NQ, Wittmann D, Boileau NR et al: Michigan Urological Surgery Improvement Collaborative. Validity of the Patient-Reported Outcome Measurement Information System (PROMIS) Sexual Interest and Satisfaction Measures in men following radical prostatectomy. *J Clin Oncol* 2019; **37**:2017.
- 107 Surveillance, Epidemiology, and End Results Program: Cancer Stat Facts: Prostate Cancer. Accessed January 2022.
- 108 Cooperberg MR, Hilton JF, Carroll PR: The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. *Cancer* 2011; **117**:5039.
- 109 Stephenson AJ, Scardino PT, Eastham JA et al: Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst* 2006; **98**:715.
- 110 Zelefsky MJ, Kattan MW, Fearn P et al: Pretreatment nomogram predicting ten-year biochemical outcome of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer. *Urology* 2007; **70**:283.
- 111 Hamdy FC, Donovan JL, Lane JA et al: 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Eng J Med* 2016; **375**:1415.
- 112 Newcomb LF, Thompson IM, Jr., Boyer HD et al: Outcomes of active surveillance for clinically localized prostate cancer in the prospective, multi-institutional Canary PASS Cohort. *J Urol* 2016; **195**:313.

- ¹¹³ Tosoian JJ, Mamawala M, Epstein JI et al: Active surveillance of Grade Group 1 prostate cancer: long-term outcomes from a large prospective cohort. *Eur Urol* 2020;**77**:675.
- ¹¹⁴ Klotz L, Vesprini D, Sethukavalan P et al: Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol* 2015;**33**:272.
- ¹¹⁵ Soloway MS, Soloway CT, Eldefrawy A, Acosta K, Kava B, Manoharan M. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. *Eur Urol* 2010;**58**:831.
- ¹¹⁶ Carlsson S, Benfante N, Alvim R et al: Long-term outcomes of active surveillance for prostate cancer: the Memorial Sloan Kettering Cancer Center experience. *J Urol* 2020;**203**:1122.
- ¹¹⁷ Bokhorst LP, Valdagni R, Rannikko A et al: A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. *Eur Urol* 2016;**70**:954.
- ¹¹⁸ Welty CJ, Cowan JE, Nguyen H et al: Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. *J Urol* 2015;**193**:807.
- ¹¹⁹ Barocas DA, Alvarez J, Resnick MJ et al: Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. *JAMA* 2017;**317**:1126.
- ¹²⁰ Chen RC, Basak R, Meyer AM et al: association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA* 2017;**317**:1141.
- ¹²¹ Donovan JL, Hamdy FC, Lane JA et al: patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Eng J Med* 2016; **375**:1425.
- ¹²² Carter HB, Helfand B, Mamawala M et al: Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol* 2019;**75**:743.
- ¹²³ Schroder FH, Hugosson J, Roobol MJ et al: Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012; **366**: 981.
- ¹²⁴ Wilt TJ, Brawer MK, Jones KM: Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; **367**:203.
- ¹²⁵ Wilt T, Jones KM, Barry MJ et al: Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med* 2017;**377**:132.
- ¹²⁶ Bill-Axelsson A, Holmberg L, Garmo H et al: radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014;**370**:932.
- ¹²⁷ Kent M, Penson DF, Albertsen PC et al: Successful external validation of a model to predict other cause mortality in localized prostate cancer. *BMC Med* 2016;**14**:25.
- ¹²⁸ Musunuru HB, Yamamoto T, Klotz L et al: Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook experience. *J Urol* 2016;**196**:1651.
- ¹²⁹ Hopstaken JS, Bomers JGR, Sedelaar MJ et al: An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years? *Eur Urol* 2022; **81**: 5.
- ¹³⁰ 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**:786.
- ¹³¹ 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**:405.
- ¹³² 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**: 115.
- ¹³³ 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**:371.
- ¹³⁴ Abdollah F, Sun M, Thuret R et al: A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* 2011;**59**:88.
- ¹³⁵ Widmark A, Klepp O, Solberg A et al: Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009; **373**: 301.

- ¹³⁶ Mason MD, Parulekar WR, Sydes MR et al: Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol* 2015; **33**:2143
- ¹³⁷ Chin JL, Al-Zahrani AA, Autran-Gomez AM et al: Extended followup oncologic outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). *J Urol* 2012; **188**: 1170.
- ¹³⁸ Wallis CJD, Saskin R, Choo R et al: Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2016;**70**:21.
- ¹³⁹ Guy DE, Chen H, Boldt RG et al: Characterizing surgical and radiotherapy outcomes in non-metastatic high-risk prostate cancer: a systematic review and meta-analysis. *Cureus* 2021;**13**:e17400.
- ¹⁴⁰ 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**: 447.
- ¹⁴¹ Schymura MJ, Kahn AR, German RR et al: Factors associated with initial treatment and survival for clinically localized prostate cancer: results from the CDC-NPCR Patterns of Care Study (PoC1). *BMC Cancer* 2010;**10**:152.
- ¹⁴² Lee HJ, Lee A, Huang HH et al: Primary androgen deprivation therapy as monotherapy in unfavourable intermediate- and high-risk localised prostate cancer: a Singaporean single-centre perspective. *Int Urol Nephrol* 2018;**50**:665.
- ¹⁴³ Lu-Yao GL, Albertsen PC, Li H et al: Does primary androgen-deprivation therapy delay the receipt of secondary cancer therapy for localized prostate cancer? *Eur Urol* 2012;**62**:966.
- ¹⁴⁴ Lu-Yao GL, Albertsen PC, Moore DF et al: Survival following primary androgen deprivation therapy among men with localized prostate cancer. *JAMA* 2008;**300**:173.
- ¹⁴⁵ Lu-Yao GL, Albertsen PC, Moore DF et al: Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. *JAMA Intern Med* 2014;**174**:1460.
- ¹⁴⁶ Potosky AL, Haque R, Cassidy-Bushrow AE et al: Effectiveness of primary androgen-deprivation therapy for clinically localized prostate cancer. *J Clin Oncol* 2014;**32**:1324.
- ¹⁴⁷ Seikkula H, Boström PJ, Seppä K et al: Survival and mortality of elderly men with localized prostate cancer managed with primary androgen deprivation therapy or by primary observation. *BMC Urol* 2020;**20**:25.
- ¹⁴⁸ Wong YN, Freedland SJ, Egleston B et al: The role of primary androgen deprivation therapy in localized prostate cancer. *Eur Urol* 2009; **56**:609.
- ¹⁴⁹ Studer UE, Whelan P, Albrecht W et al: Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol* 2006;**24**:1868.
- ¹⁵⁰ Tosoian JJ, Mamawala M, Epstein JI et al: Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. *J Clin Oncol* 2015;**33**:3379.
- ¹⁵¹ Bul M, Zhu X, Valdaghi R et al: Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol* 2013; **63**:597.
- ¹⁵² Cooperberg MR, Zheng Y, Faino AV et al: Tailoring intensity of active surveillance for low-risk prostate cancer based on individualized prediction of risk stability. *JAMA Oncol* 2020;**6**: e203187.
- ¹⁵³ Ross AE, Loeb S, Landis P et al: Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *J Clin Oncol* 2010;**28**:2810.
- ¹⁵⁴ Cooperberg MR, Brooks JD, Faino AV et al: Refined analysis of prostate-specific antigen kinetics to predict prostate cancer active surveillance outcomes. *Eur Urol* 2018;**74**:211.
- ¹⁵⁵ Liss MA, Newcomb LF, Zheng Y et al: Magnetic resonance imaging for the detection of high grade cancer in the Canary Prostate Active Surveillance Study. *J Urol* 2020;**204**:701.
- ¹⁵⁶ Tran GN, Leapman MS, Nguyen HG et al: Magnetic resonance imaging-ultrasound fusion biopsy during prostate cancer active surveillance *Eur Urol* 2017;**72**:275.
- ¹⁵⁷ Schoots IG, Petrides N, Giganti F et al: Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol* 2015;**67**:627.
- ¹⁵⁸ Klotz L, Loblaw A, Sugar L et al: Active Surveillance Magnetic Resonance Imaging Study (ASIST): results of a randomized multicenter prospective trial. *Eur Urol* 2019;**75**:300.

- 159 Klotz L, Pond G, Loblaw A et al: Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year postbiopsy follow-up. *Eur Urol* 2020;**77**:311.
- 160 Inoue LYT, Lin DW, Newcomb LF et al: comparative analysis of biopsy upgrading in four prostate cancer active surveillance cohorts. *Ann Intern Med* 2018; **168**: 1.
- 161 Liss MA, Newcomb LF, Zheng Y et al: Magnetic resonance imaging for the detection of high grade cancer in the Canary Prostate Active Surveillance Study. *J Urol* 2020; **204**: 701.
- 162 Chen RC, Rumble RB, Loblaw DA et al: Active surveillance for the management of localized prostate cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2016; **34**: 2182.
- 163 Chu CE, Lonergan PE, Washinton SL et al: Multiparametric magnetic resonance imaging alone is insufficient to detect grade reclassification in active surveillance for prostate cancer. *Eur Urol* 2020;**78**:515.
- 164 Chesnut GT, Vertosick EA, Benfante N et al: Role of changes in magnetic resonance imaging or clinical stage in evaluation of disease progression for men with prostate cancer on active surveillance. *Eur Urol* 2020;**77**:501.
- 165 Rajwa P, Pradere B, Quhal F et al: Reliability of serial prostate magnetic resonance imaging to detect prostate cancer progression during active surveillance: a systematic review and meta-analysis *Eur Urol* 2021; **80**:549.
- 166 Nguyen LN, Head L, Witiuk K et al: The risks and benefits of cavernous neurovascular bundle sparing during radical prostatectomy: a systematic review and meta-analysis. *J Urol* 2017;**198**:760.
- 167 Avulova S, Zhao Z, Lee D et al: The effect of nerve sparing status on sexual and urinary function: 3-year results from the CEASAR study. *J Urol* 2018;**199**:1202.
- 168 Heesakkers J, Farag F, Bauer RM et al: Pathophysiology and contributing factors in postprostatectomy incontinence: a review. *Eur Urol* 2017;**71**:936.
- 169 Ward JF, Zincke H, Bergstralh EJ et al: The impact of surgical approach (nerve bundle preservation versus wide local excision) on surgical margins and biochemical recurrence following radical prostatectomy. *J Urol* 2004;**172**:1328.
- 170 Raskolnikov D, George AK, Rais-Bahrami S et al: The role of magnetic resonance image guided prostate biopsy in stratifying men for risk of extracapsular extension at radical prostatectomy. *J Urol* 2015; **194**: 105.
- 171 Fossati N, Willemse P-PM, Van den Broeck T et al: The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. *Eur Urol* 2017;**72**:84.
- 172 Chen J, Wang Z, Zhao J et al: Pelvic lymph node dissection and its extent on survival benefit in prostate cancer patients with a risk of lymph node invasion >5%: a propensity score matching analysis from SEER database. *Sci Rep* 2019;**9**:17985.
- 173 Berglund RK, Sadetsky N, DuChane J: Limited pelvic lymph node dissection at the time of radical prostatectomy does not affect 5-year failure rates for low, intermediate and high risk prostate cancer: results from CaPSURE. *J Urol* 2007;**177**:526.
- 174 Bhatta-Dhar N, Reuther AM, Zippe C et al: No difference in six-year biochemical failure rates with or without pelvic lymph node dissection during radical prostatectomy in low-risk patients with localized prostate cancer. *Urology* 2004;**63**:528.
- 175 Weight CJ, Reuther AM, Gunn PW et al: Limited pelvic lymph node dissection does not improve biochemical relapse-free survival at 10 years after radical prostatectomy in patients with low-risk prostate cancer. *Urology* 2008;**71**:141.
- 176 Fergany A, Kupelian PA, Levin HS et al: No difference in biochemical failure rates with or without pelvic lymph node dissection during radical prostatectomy in low-risk patients. *Urology* 2000;**56**:92.
- 177 Lestingi JFP, Guglielmetti GB, Trinh QD et al: Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: early oncological outcomes from a randomized phase 3 trial. *Eur Urol* 2021;**79**:595.
- 178 Touijer KA, Sjoberg DD, Benfante N et al: Limited versus extended pelvic lymph node dissection for prostate cancer: a randomized clinical trial. *Eur Urol Oncol* 2021;**4**:532.
- 179 Clark T, Parekh DJ, Cookson MS et al: Randomized prospective evaluation of extended versus limited lymph node dissection in patients with clinically localized prostate cancer. *J Urol* 2003;**169**:145.

- ¹⁸⁰ Masterson TA, Bianco FJ, Jr., Vickers AJ et al: The association between total and positive lymph node counts, and disease progression in clinically localized prostate cancer. *J Urol* 2006; **175**:1320.
- ¹⁸¹ Messing EM, Manola J, Yao J et al: Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006; **7**: 472.
- ¹⁸² Abdollah F, Karnes RJ, Suardi N et al: Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol* 2014; **32**: 3939.
- ¹⁸³ Briganti A, Larcher A, Abdollah F et al: Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol* 2012; **61**:480.
- ¹⁸⁴ Gandaglia G, Soligo M, Battaglia A et al: Which patients with clinically node-positive prostate cancer should be considered for radical prostatectomy as part of multimodal treatment? the impact of nodal burden on long-term outcomes. *Eur Urol* 2019; **75**: 817.
- ¹⁸⁵ Cagiannos I, Karakiewicz P, Eastham JA et al: A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. *J Urol* 2003; **170**:1798.
- ¹⁸⁶ Lestingi JF, Pontes Jr J, Borges LL et al: PD43-06 extended vs limited pelvic lymphadenectomy during radical prostatectomy for intermediate-and high-risk prostate cancer: a prospective randomized trial. *J Urol* 2015; **193**:e893.
- ¹⁸⁷ Engel J, Bastian PJ, Baur H et al: Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. *Eur Urol* 2010; **57**:754.
- ¹⁸⁸ Jeong W, Sukumar S, Petros F et al: Intraoperative finding of gross lymph node metastasis during robot-assisted prostatectomy. *J Robot Surg* 2012; **6**:329.
- ¹⁸⁹ Steuber T, Budaus L, Walz J et al: Radical prostatectomy improves progression-free and cancer-specific survival in men with lymph node positive prostate cancer in the prostate-specific antigen era: a confirmatory study. *BJU Int* 2011; **107**:1755.
- ¹⁹⁰ Bhindi B, Rangel LJ, Mason RJ et al: Impact of radical prostatectomy on long-term oncologic outcomes in a matched cohort of men with pathological node positive prostate cancer managed by castration. *J Urol* 2017; **198**:86.
- ¹⁹¹ Gandaglia G, Bravi CA, Dell'Oglio P et al: The impact of implementation of the European Association of Urology guidelines panel recommendations on reporting and grading complications on perioperative outcomes after robot-assisted radical prostatectomy. *Eur Urol* 2018; **74**:4.
- ¹⁹² Palapattu G, Allaf ME, Trock BJ et al: Prostate specific antigen progression in men with lymph node metastases following radical prostatectomy: results of long-term followup. *J Urol* 2004; **172**: 1860.
- ¹⁹³ Touijer K, Mazzola CR, Sjoberg DD et al: Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. *Eur Urol* 2014; **65**: 20.
- ¹⁹⁴ Studer UE, Whelan P, Wimpissinger F et al: Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. *Eur Urol* 2014; **66**: 829.
- ¹⁹⁵ Boorjian SA, Thompson RH, Siddiqui S et al: Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. *J Urol* 2007; **178**: 864.
- ¹⁹⁶ Park S, Kim SC, Kim W et al: Impact of adjuvant androgen-deprivation therapy on disease progression in patients with node-positive prostate cancer. *Korean J Urol* 2011; **52**:741.
- ¹⁹⁷ Tilki D, Preisser F, Tennstedt P et al: Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. *BJU Int* 2017; **119**:717.
- ¹⁹⁸ Wong YN, Freedland S, Egleston B et al: Role of androgen deprivation therapy for node-positive prostate cancer. *J Clin Oncol* 2009; **27**:100.
- ¹⁹⁹ Seay TM, Blute ML, Zincke H: Long-term outcome in patients with pTxN+ adenocarcinoma of prostate treated with radical prostatectomy and early androgen ablation. *J Urol* 1998; **159**:357.
- ²⁰⁰ Touijer K, Karnes RJ, Passoni N et al: Survival outcomes of men with lymph node-positive prostate cancer after radical prostatectomy: A comparative analysis of different postoperative management strategies. *Eur Urol* 2018; **73**:890.
- ²⁰¹ Wiegand LR, Hernandez M, Pisters LL et al: Surgical management of lymph-node-positive prostate cancer: improves symptomatic control. *BJU Int* 2011; **107**:1238.

- 202 Abdollah F, Karnes RJ, Suardi N et al: Predicting survival of patients with node-positive prostate cancer following multimodal treatment. *Eur Urol* 2014;**65**:554.
- 203 Abdollah F, Dalela D, Sood A et al: Impact of adjuvant radiotherapy in node-positive prostate cancer patients: the importance of patient selection. *Eur Urol* 2018;**74**:253.
- 204 Briganti A, Karnes RJ, Da Pozzo LF et al: Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. *Eur Urol* 2011;**59**:832.
- 205 Da Pozzo LF, Cozzarini C, Briganti A et al: Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol* 2009;**55**:1003.
- 206 Bravi CA, Tin A, Vertosick E et al: Androgen deprivation therapy in men with node-positive prostate cancer treated with postoperative radiotherapy. *Urol Oncol* 2020;**38**:204.
- 207 Kneebone A, Fraser-Browne C, Duchesne GM et al: Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol* 2020;**21**:1331.
- 208 Parker CC, Clarke NW, Cook AD et al: Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet* 2020; **396**:1413.
- 209 Sargos P, Chabaud S, Latorzeff I et al: Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol* 2020;**21**:1341.
- 210 Vale CL, Fisher D, Kneebone A et al: Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet* 2020;**396**:1422.
- 211 Tilki D, Chen MH, Wu J et al: Adjuvant versus early salvage radiation therapy for men at high risk for recurrence following radical prostatectomy for prostate cancer and the risk of death. *J Clin Oncol* 2021;**39**:2284.
- 212 Mariados N, Sylvester J, Shah D et al: Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2015;**92**:971.
- 213 Hamstra DA, Mariados N, Sylvester J et al: Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. *Int J Radiat Oncol Biol Phys* 2017; **97**:976.
- 214 Jackson A, Marks LB, Bentzen SM et al: The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. *Int J Radiat Oncol Biol Phys* 2010; **76 (3 Suppl)**: S155.
- 215 Beasley M, Driver D, Dobbs HJ: Complications of radiotherapy: improving the therapeutic index. *Cancer Imaging* 2005; **5**: 78.
- 216 Al-Mamgani A, van Putten WL, Heemsbergen WD et al: Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**72**:980.
- 217 Beckendorf V, Guerif S, Le Prise E et al: 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011;**80**:1056.
- 218 Creak A, Hall E, Horwich A et al: Randomised pilot study of dose escalation using conformal radiotherapy in prostate cancer: long-term follow-up. *Br J Cancer* 2013;**109**:651.
- 219 Dearnaley D, Syndikus I, Mossop H et al: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;**17**:1047.
- 220 Dearnaley DP, Hall E, Lawrence D et al: Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005;**92**:488.
- 221 Dearnaley DP, Jovic G, Syndikus I et al: Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014;**15**:464.
- 222 Dearnaley DP, Sydes MR, Graham JD et al: Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;**8**:475.

- 223 Heemsbergen WD, Al-Mamgani A, Slot A et al: Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother Oncol* 2014;**110**:104.
- 224 Kuban DA, Tucker SL, Dong L et al: Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**:67.
- 225 Pasalic D, Kuban DA, Allen PK et al: Dose escalation for prostate adenocarcinoma: a long-term update on the outcomes of a phase 3, single institution randomized clinical trial. *Int J Radiat Oncol Biol Phys* 2019;**104**:790.
- 226 Peeters ST, Heemsbergen WD, Koper PC et al: Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;**24**:1990.
- 227 Pollack A, Zagars GK, Starkschall G et al: Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;**53**:1097.
- 228 Zietman AL, Bae K, Slater JD et al: Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/American College of Radiology 95-09. *J Clin Oncol* 2010;**28**:1106.
- 229 Zietman AL, DeSilvio ML, Slater JD et al: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;**294**:1233.
- 230 Michalski JM, Moughan J, Purdy J et al: effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer. *JAMA Oncol* 2018; **4**: e180039.
- 231 Michalski JM, Yan Y, Watkins-Bruner D et al: Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. *Int J Radiation Oncol Biol Phys* 2013; **87**: 932.
- 232 Cella L, Lomax A, Miralbell R et al: Potential role of intensity modulated proton beams in prostate cancer radiotherapy. *Int J Radiation Oncology Biol Phys* 2001; **49**:217.
- 233 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**: e201.
- 234 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**: 1076.
- 235 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**: 25.
- 236 Hickey BE, James ML, Daly T et al: Hypofractionation for clinically localized prostate cancer. *Cochrane Database Syst Rev.* 2019.
- 237 Alexidis P, Dragoumis D, Karatzoglou S et al: The role of hypofractionated radiotherapy for the definitive treatment of localized prostate cancer: early results of a randomized trial. *J Cancer* 2019;**10**:6217.
- 238 Alexidis P, Karatzoglou S, Dragoumis D et al: Late results of a randomized trial on the role of mild hypofractionated radiotherapy for the treatment of localized prostate cancer. *J Cancer* 2020;**11**:1008.
- 239 Avkshol V, Ruth KJ, Ross EA et al: Ten-year update of a randomized, prospective trial of conventional fractionated versus moderate hypofractionated radiation therapy for localized prostate cancer. *J. Clin. Oncol* 2020; **38**: 1676.
- 240 Zhong QZ, Xia X, Gao H et al: Hypofractionated versus conventionally fractionated image-guided volumetric-modulated arc radiotherapy for localized prostate cancer: a phase II randomized trial from China. *Aging (Albany NY)* 2021;**13**:6936.
- 241 Widmark A, Gunnlaugsson A, Beckman L et al: Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* 2019;**394**:385.
- 242 Fransson P, Nilsson P, Gunnlaugsson A et al: Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. *Lancet Oncol* 2021;**22**:235.
- 243 Morgan SC, Hoffman K, Loblaw DA et al: Hypofractionated radiation therapy for localized prostate cancer: an ASTRO, ASCO, and AUA evidence-based guideline. *J Clin Oncol* 2018;**36**:JCO1801097.

- 244 Hathout L, Mahmoud O, Wang Y et al: A Phase 2 randomized pilot study comparing high-dose-rate brachytherapy and low-dose-rate brachytherapy as monotherapy in localized prostate cancer. *Adv Radiat Oncol* 2019;**4**:631.
- 245 Goy BW, Burchette R, Soper MS et al: Ten-year treatment outcomes of radical prostatectomy vs external beam radiation therapy vs brachytherapy for 1503 patients with intermediate-risk prostate cancer. *Urology* 2020;**136**:180.
- 246 Morton G, McGuffin M, Chung HT et al: Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. *Radiother Oncol* 2020; **146**: 90
- 247 Corkum M, Loblaw A, Hasan Y et al: Prostate high dose-rate brachytherapy as monotherapy for prostate cancer: Late toxicity and patient reported outcomes from a randomized phase II clinical trial. *Radiother Oncol* 2021; **156**:160.
- 248 Pommier P, Chabaud S, Lagrange JL et al: Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007;**25**:5366.
- 249 Pommier P, Chabaud S, Lagrange JL et al: Is there a role for pelvic irradiation in localized prostate adenocarcinoma? update of the long-term survival results of the GETUG-01 randomized study *Int J Radiat Oncol* 2016;**96**:759.
- 250 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**:1904.
- 251 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**:1504.
- 252 Lawton CA, DeSilvio M, Roach 3rd M et al: An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007; **69**:646.
- 253 Keating NL, O'Malley AJ, Smith MR: Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006; **24**: 4448.
- 254 Sanda MG, Dunn RL, Michalski J et al: Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008; **358**:1250.
- 255 Nguyen PL, Alibhai SM, Basaria S et al: Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015;**67**:825.
- 256 Ataman F, Zurlo A, Artignan X et al: Late toxicity following conventional radiotherapy for prostate cancer: analysis of the EORTC trial 22863. *Eur J Cancer* 2004;**40**:167481.
- 257 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**:103.
- 258 Bolla M, Maingon P, Carrie C et al: Short androgen suppression and radiation dose escalation for intermediate- and high-risk localized prostate cancer: results of EORTC Trial 22991. *J Clin Oncol* 2016;**34**:1748.
- 259 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**:1066.
- 260 D'Amico AV, Chen MH, Renshaw AA et al: Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008;**299**:289.
- 261 D'Amico AV, Manola J, Loffredo M et al: 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004;**292**:821.
- 262 Denham JW, Steigler A, Lamb DS et al: Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol*.2011;**12**:451.
- 263 Giacalone NJ, Wu J, Chen MH et al: Prostate-specific antigen failure and risk of death within comorbidity subgroups among men with unfavorable-risk prostate cancer treated in a randomized trial. *J Clin Oncol* 2016;**34**:3781.
- 264 Jones CU, Hunt D, McGowan DG et al: Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011;**365**:107.
- 265 McPartlin AJ, Glicksman R, Pintilie M et al: PMH 9907: Long-term outcomes of a randomized phase 3 study of

- short-term bicalutamide hormone therapy and dose-escalated external-beam radiation therapy for localized prostate cancer. *Cancer* 2016;**122**:2595.
- ²⁶⁶ Pilepich MV, Krall JM, al-Sarraf M et al: Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. *Urology* 1995;**45**:616.
- ²⁶⁷ Pilepich MV, Winter K, John MJ et al: Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;**50**:1243.
- ²⁶⁸ Roach M, 3rd, Bae K, Speight J et al: Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008;**26**:585.
- ²⁶⁹ Vargas CE, Alam NB, Terk M et al: Initial results of a randomized phase III trial of high dose image guided radiation with or without androgen deprivation therapy for intermediate-risk prostate cancer. *Cancer Treat Res Commun* 2019;**19**:100119.
- ²⁷⁰ Kishan AU, Sun Y, Hartman H et al: Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. *Lancet Oncol* 2022;**23**:304.
- ²⁷¹ Bolla M, de Reijke TM, Van Tienhoven G et al: Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;**360**:2516.
- ²⁷² Denham JW, Joseph D, Lamb DS et al: Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. *Lancet Oncol.* 2019;**20**:267.
- ²⁷³ Denham JW, Wilcox C, Joseph D et al: Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial. *Lancet Oncol* 2012;**13**:1260.
- ²⁷⁴ Denham JW, Wilcox C, Lamb DS et al: Rectal and urinary dysfunction in the TROG 03.04 RADAR trial for locally advanced prostate cancer. *Radiother Oncol* 2012;**105**:184.
- ²⁷⁵ Hanks GE, Pajak TF, Porter A et al: Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003;**21**:3972.
- ²⁷⁶ Horwitz EM, Mitra RK, Uzzo RG et al: Impact of target volume coverage with Radiation Therapy Oncology Group (RTOG) 98-05 guidelines for transrectal ultrasound guided permanent Iodine-125 prostate implants. *Radiother Oncol* 2003;**66**:173.
- ²⁷⁷ Pisansky TM, Hunt D, Gomella LG et al: Duration of androgen suppression before radiotherapy for localized prostate cancer: Radiation Therapy Oncology Group randomized clinical trial 9910. *J Clin Oncol* 2015;**33**:332.
- ²⁷⁸ Zapatero A, Guerrero A, Maldonado X et al: High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2015;**16**:320.
- ²⁷⁹ Zapatero A, Guerrero A, Maldonado X et al: Late radiation and cardiovascular adverse effects after androgen deprivation and high-dose radiation therapy in prostate cancer: results from the DART 01/05 randomized phase 3 trial. *Int J Radiat Oncol Biol Phys* 2016;**96**:341.
- ²⁸⁰ Nabid A, Carrier N, Martin AG et al: Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. *Eur Urol* 2018;**74**:432.
- ²⁸¹ Arcangeli S, Strigari L, Gomellini S et al: Updated results and patterns of failure in a randomized hypofractionated trial for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**84**:1172.
- ²⁸² Dearnaley D, Sydikus I, Mossop H et al: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-Year outcomes of the randomized, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;**17**:1047.
- ²⁸³ Musunuru HB, Cheung P, Loblaw A: Evolution of hypofractionated accelerated radiotherapy for prostate cancer- The Sunnybrook experience. *Front Oncol* 2014;**4**:313.
- ²⁸⁴ Hoskin PJ, Rojas AM, Bownes PJ et al: Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;**103**:217.
- ²⁸⁵ Hoskin PJ, Rojas AM, Ostler PJ et al: Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: mature 12-year results. *Radiother Oncol* 2021;**154**:214.

- ²⁸⁶ Sathya JR, Davis IR, Julian JA et al: Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;**23**:1192.
- ²⁸⁷ Morris WJ, Tyldesley S, Rodda S et al: Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;**98**:275.
- ²⁸⁸ Rodda S, Morris WJ, Hamm J et al: ASCENDE-RT: an analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;**98**:581.
- ²⁸⁹ Rodda S, Tyldesley S, Morris WJ et al: ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;**98**:286.
- ²⁹⁰ Murthy V, Maitre P, Kannan S et al: Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. *J Clin Oncol* 2021;**39**:1234.
- ²⁹¹ 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**:593.
- ²⁹² 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**:136.
- ²⁹³ Weller MA, Kupelian PA, Reddy CA et al: Adjuvant versus neoadjuvant androgen deprivation with radiotherapy for prostate cancer: does sequencing matter? *Clin Genitourin Cancer* 2015;**13**:e183.
- ²⁹⁴ 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**:845.
- ²⁹⁵ 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 Radiation Oncology Biol Phys* 2021; **11**:S50.
- ²⁹⁶ 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**:208.
- ²⁹⁷ 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 18F-DCFPyL in prostate cancer patients (OSPReY). *J Urol* 2021; **206**: 52.