Approved by the AUA Board of Directors April 2017

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

American Urological Association (AUA) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO)

CLINICALLY LOCALIZED PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE

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Purpose

Following a prostate cancer diagnosis, patients are faced with a multitude of care options, the advisability of which is influenced by patient factors and by cancer severity or aggressiveness. The ability to categorize patients based on cancer aggressiveness is invaluable for facilitating care decisions. Accordingly, these guidelines for the management of localized prostate cancer are structured first, to provide a clinical framework stratified by cancer severity (or risk group) to facilitate care decisions and second, to guide the specifics of implementing the selected management options, including active surveillance, observation/watchful waiting, prostatectomy, radiotherapy, cryosurgery, high intensity focused ultrasound (HIFU) and focal therapy. Secondary or salvage treatment for localized prostate cancer that persists or recurs after primary definitive intervention, and primary treatment of locally advanced/metastatic disease, are outside the scope of these guidelines. The content of these guidelines is formatted as shown in Table 1.

Methodology

The systematic review utilized in the creation of this guideline was completed in part through the Agency for Healthcare Research and Quality (AHRQ) and through additional supplementation that further addressed additional key questions and more recently published literature. A research librarian experienced in conducting literature searches for comparative effectiveness reviews searched in MEDLINE®, PreMEDLINE, Embase®, the Cochrane Library, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the UK National Health Service Economic Evaluation database to capture literature published from January 1, 2007 through March 7, 2014. Additional supplemental searches were conducted adding additional literature in August 2015 and August 2016. 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). When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

Table 1. Localized Prostate Cancer Guidelines Content		
Section	**Subtopic**	**Guideline Statements**
I. Introduction		NA
	A. Guideline Statements	
	B. Methodology	
	C. Risk Stratification	
II. Shared Decision Making		1-5
III. Care Options by Cancer Severity/ Risk Group		6-27
	A. Very Low / Low Risk	6-14
	B. Intermediate Risk	15-21
	C. High Risk	22-27
IV. Recommended Approaches/Details of Specific Care Options		28-60
	A. Active Surveillance	28-33
	B. Radical Prostatectomy	34-41
	C. Radiotherapy	42-49
	D. Cryosurgery	50-56
	E. HIFU/Focal therapy	57-60
V. Outcome Expectations and Manage-ment		
	A. Side effects and HRQOL	61-65
	B. Post-treatment follow-up	66-68
VI. Future Directions		NA

INTRODUCTION

GUIDELINE STATEMENTS

SHARED DECISION MAKING (SDM)

1. Counseling of patients to select a management strategy for localized prostate cancer should incorporate shared decision making and explicitly consider cancer severity (risk category), patient values and preferences, life expectancy, pre-treatment general functional and genitourinary symptoms, expected post-treatment functional status, and potential for salvage treatment. (Strong Recommendation; Evidence Level: Grade A)
2. Prostate cancer patients should be counseled regarding the importance of modifiable health-related behaviors or risk factors, such as smoking and obesity. (Expert Opinion)
3. Clinicians should encourage patients to meet with different prostate cancer care specialists (e.g., urology and either radiation oncology or medical oncology or both), when possible to promote informed decision making. (Moderate Recommendation; Evidence Level: Grade B)
4. Effective shared decision making in prostate cancer care requires clinicians to inform patients about immediate and long-term morbidity or side effects of proposed treatment or care options. (Clinical Principle)
5. Clinicians should inform patients about suitable clinical trials and encourage patients to consider participation in such trials based on eligibility and access. (Expert Opinion)

CARE OPTIONS BY CANCER SEVERITY/RISK GROUP

Very Low-/Low-Risk Disease

6. Clinicians should not perform abdomino-pelvic CT or routine bone scans in the staging of asymptomatic very low- or low-risk localized prostate cancer patients. (Strong Recommendation; Evidence Level: Grade C)
7. Clinicians should recommend active surveillance as the best available care option for very low-risk localized prostate cancer patients. (Strong Recommendation; Evidence Level: Grade A)
8. Clinicians should recommend active surveillance as the preferable care option for most low-risk localized prostate cancer patients. (Moderate Recommendation; Evidence Level: Grade B)
9. Clinicians may offer definitive treatment (i.e. radical prostatectomy or radiotherapy) to select low-risk localized prostate cancer patients who may have a high probability of progression on active surveillance. (Conditional Recommendation; Evidence Level: Grade B)
10. Clinicians should not add ADT along with radiotherapy for low-risk localized prostate cancer with the exception of reducing the size of the prostate for brachytherapy. (Strong Recommendation; Evidence Level: Grade B)
11. Clinicians should inform low-risk prostate cancer patients considering whole gland cryosurgery that consequent side effects are considerable and survival benefit has not been shown in comparison to active surveillance. (Conditional Recommendation; Evidence Level: Grade C)
12. Clinicians should inform low-risk prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)
13. Clinicians should recommend observation or watchful waiting for men with a life expectancy ≤5 years with low-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade B)
14. Among most low-risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance. (Expert Opinion)

Intermediate-Risk Disease

15. Clinicians should consider staging unfavorable intermediate-risk localized prostate cancer patients with cross sectional imaging (CT or MRI) and bone scan. (Expert Opinion)
16. Clinicians should recommend radical prostatectomy or radiotherapy plus androgen deprivation therapy (ADT) as standard treatment options for patients with intermediate-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)
17. Clinicians should inform patients that favorable intermediate-risk prostate cancer can be treated with radiation

alone, but that the evidence basis is less robust than for combining radiotherapy with ADT. (Moderate Recommendation; Evidence Level: Grade B)

18. In select patients with intermediate-risk localized prostate cancer, clinicians may consider other treatment options such as cryosurgery. (Conditional Recommendation; Evidence Level: Grade C)
19. Active surveillance may be offered to select patients with favorable intermediate-risk localized prostate cancer; however, patients should be informed that this comes with a higher risk of developing metastases compared to definitive treatment. (Conditional Recommendation; Evidence Level: Grade C)
20. Clinicians should recommend observation or watchful waiting for men with a life expectancy ≤5 years with intermediate-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)
21. Clinicians should inform intermediate-risk prostate cancer patients who are considering focal therapy or HIFU that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)

High-Risk Disease

22. Clinicians should stage high-risk localized prostate cancer patients with cross sectional imaging (CT or MRI) and bone scan. (Clinical Principle)
23. Clinicians should recommend radical prostatectomy or radiotherapy plus ADT as standard treatment options for patients with high-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)
24. Clinicians should not recommend active surveillance for patients with high-risk localized prostate cancer. Watchful waiting should only be considered in asymptomatic men with limited life expectancy (≤5 years). (Moderate Recommendation; Evidence Level: Grade C)
25. Cryosurgery, focal therapy and HIFU treatments are not recommended for men with high-risk localized prostate cancer outside of a clinical trial. (Expert Opinion)
26. Clinicians should not recommend primary ADT for patients with high-risk localized prostate cancer unless the patient has both limited life expectancy and local symptoms. (Strong Recommendation; Evidence Level: Grade A)
27. Clinicians may consider referral for genetic counseling for patients (and their families) with high-risk localized prostate cancer and a strong family history of specific cancers (e.g., breast, ovarian, pancreatic, other gastrointestinal tumors, lymphoma). (Expert Opinion)

RECOMMENDED APPROACHES AND DETAILS OF SPECIFIC CARE OPTIONS

Active Surveillance

28. Localized prostate cancer patients who elect active surveillance should have accurate disease staging including systematic biopsy with ultrasound or MRI-guided imaging. (Clinical Principle)
29. Localized prostate cancer patients undergoing active surveillance should have routine surveillance PSA testing and digital rectal exams. (Strong Recommendation; Evidence Level: Grade B)
30. Localized prostate cancer patients undergoing active surveillance should be encouraged to have a confirmatory biopsy within the initial two years and surveillance biopsies thereafter. (Clinical Principle)
31. Clinicians may consider multiparametric prostate MRI as a component of active surveillance for localized prostate cancer patients. (Expert Opinion)
32. Tissue based genomic biomarkers have not shown a clear role in active surveillance for localized prostate cancer and are not necessary for follow up. (Expert Opinion)
33. Clinicians should offer definitive treatment to localized prostate cancer patients undergoing active surveillance who develop adverse reclassification. (Moderate Recommendation; Evidence Level: Grade B)

Prostatectomy

34. Clinicians should inform localized prostate cancer patients that younger or healthier men (e.g., <65 years of age or >10 year life expectancy) are more likely to experience cancer control benefits from prostatectomy than older

men. (Strong Recommendation; Evidence Level: Grade B)

35. Clinicians should inform localized prostate cancer patients that open and robot-assisted radical prostatectomy offer similar cancer control, continence recovery, and sexual recovery outcomes. (Moderate Recommendation; Evidence Level: Grade C)
36. Clinicians should inform localized prostate cancer patients that robotic/laparoscopic or perineal techniques are associated with less blood loss than retropupic prostatectomy. (Strong Recommendation; Evidence Level: Grade B)
37. Clinicians should counsel localized prostate cancer patients that nerve-sparing is associated with better erectile function recovery than non-nerve sparing. (Strong Recommendation; Evidence Level: Grade A)
38. Clinicians should not treat localized prostate cancer patients who have elected to undergo radical prostatectomy with neoadjuvant ADT or other systemic therapy outside of clinical trials. (Strong Recommendation; Evidence Level: Grade A)
39. Clinicians should inform localized prostate cancer patients considering prostatectomy, that older men experience higher rates of permanent erectile dysfunction and urinary incontinence after prostatectomy compared to younger men. (Strong Recommendation; Evidence Level: Grade B)
40. Pelvic lymphadenectomy can be considered for any localized prostate cancer patients undergoing radical prostatectomy and is recommended for those with unfavorable intermediate-risk or high-risk disease. Patients should be counseled regarding the common complications of lymphadenectomy, including lymphocele development and its treatment. (Expert Opinion)
41. Clinicians should inform localized prostate cancer patients with unfavorable intermediate-risk or high-risk prostate cancer about benefits and risks related to the potential option of adjuvant radiotherapy when locally extensive prostate cancer is found at prostatectomy. (Moderate Recommendation; Evidence Level: Grade B)

Radiotherapy

42. Clinicians may offer single modality external beam radiotherapy or brachytherapy for patients who elect radiotherapy for low-risk localized prostate cancer. (Clinical Principle)
43. Clinicians may offer external beam radiotherapy or brachytherapy alone or in combination for favorable intermediate-risk localized prostate cancer. (Clinical Principle)
44. Clinicians should offer 24-36 months of ADT as an adjunct to either external beam radiotherapy alone or external beam radiotherapy combined with brachytherapy to patients electing radiotherapy for high-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)
45. Clinicians should inform localized prostate cancer patients that use of ADT with radiation increases the likelihood and severity of adverse treatment-related events on sexual function in most men and can cause other systemic side effects. (Strong Recommendation; Evidence Level: Grade B)
46. Clinicians should consider moderate hypofractionation when the localized prostate cancer patient (of any risk category) and clinician decide on external beam radiotherapy to the prostate (without nodal radiotherapy). (Moderate Recommendation; Evidence Level: Grade B)
47. For localized prostate cancer patients with obstructive, non-cancer-related lower urinary function, surgical approaches may be preferred. If radiotherapy is used for these patients or those with previous significant transurethral resection of the prostate, low-dose rate brachytherapy should be discouraged. (Moderate Recommendation; Evidence Level: Grade C)
48. Clinicians should inform localized prostate cancer patients who are considering proton beam therapy that it offers no clinical advantage over other forms of definitive treatment. (Moderate Recommendation; Evidence Level: Grade C)
49. Clinicians should inform localized prostate cancer patients considering brachytherapy that it has similar effects as external beam radiotherapy with regard to erectile dysfunction and proctitis but can also exacerbate urinary obstructive symptoms. (Expert Opinion)

Whole Gland Cryosurgery

50. Clinicians may consider whole gland cryosurgery in low- and intermediate-risk localized prostate cancer patients who are not suitable for either radical prostatectomy or radiotherapy due to comorbidities yet have >10 year life expectancy. (Expert Opinion)
51. Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery that cryosurgery has similar progression-free survival as did non-dose escalated external beam radiation (also given with neoadjuvant hormonal therapy) in low- and intermediate-risk disease, but conclusive comparison of cancer mortality is lacking. (Conditional Recommendation; Evidence Level: Grade C)
52. Defects from prior transurethral resection of the prostate are a relative contraindication for whole gland cryosurgery due to the increased risk of urethral sloughing. (Clinical Principle)
53. For whole gland cryosurgery treatment, clinicians should utilize a third or higher generation, argon-based cryosurgical system for whole gland cryosurgery treatment. (Clinical Principle)
54. Clinicians should inform localized prostate cancer patients considering cryosurgery that it is unclear whether or not concurrent ADT improves cancer control, though it can reduce prostate size to facilitate treatment. (Clinical Principle)
55. Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery that erectile dysfunction is an expected outcome. (Clinical Principle)
56. Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery about the adverse events of urinary incontinence, irritative and obstructive urinary problems. (Strong Recommendation; Evidence Level: Grade B)

HIFU and Focal Therapy

57. Clinicians should inform those localized prostate cancer patients considering focal therapy or HIFU that these treatment options lack robust evidence of efficacy. (Expert Opinion)
58. Clinicians should inform localized prostate cancer patients who are considering HIFU that even though HIFU is approved by the FDA for the destruction of prostate tissue, it is not approved explicitly for the treatment of prostate cancer (Expert Opinion).
59. Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)
60. As prostate cancer is often multifocal, clinicians should inform localized prostate cancer patients considering focal therapy that focal therapy may not be curative and that further treatment for prostate cancer may be necessary. (Expert Opinion)

OUTCOME EXPECTATIONS AND MANAGEMENT

Treatment Side Effects and Health Related Quality of Life

61. Clinicians should inform localized prostate cancer patients that erectile dysfunction occurs in many patients following prostatectomy or radiation, and that ejaculate will be lacking despite preserved ability to attain orgasm, whereas observation does not cause such sexual dysfunction. (Strong Recommendation; Evidence Level: Grade B)
62. Clinicians should inform localized prostate cancer patients that long-term obstructive or irritative urinary problems occur in a subset of patients following observation or active surveillance or following radiation, whereas prostatectomy can relieve pre-existing urinary obstruction. (Strong Recommendation; Evidence Level: Grade B)
63. Clinicians should inform localized prostate cancer patients that whole-gland cryosurgery is associated with worse sexual side effects and similar urinary and bowel/rectal side effects as those after radiotherapy. (Strong Recommendation; Evidence Level: Grade B)
64. Clinicians should inform localized prostate cancer patients that temporary urinary incontinence occurs in most patients after prostatectomy and persists long-term in a small but significant subset, more than during

observation or active surveillance or after radiation. (Strong Recommendation; Evidence Level: Grade A

65. Clinicians should inform localized prostate cancer patients that temporary proctitis following radiation persists in some patients long-term in a small but significant subset and is rare during observation or active surveillance or after prostatectomy. (Strong Recommendation; Evidence Level: Grade A)

Post-Treatment Follow Up

66. Clinicians should monitor localized prostate cancer patients post therapy with PSA, even though not all PSA recurrences are associated with metastatic disease and prostate cancer specific death. (Clinical Principle)
67. Clinicians should inform localized prostate cancer patients of their individualized risk-based estimates of post-treatment prostate cancer recurrence. (Clinical Principle)
68. Clinicians should support localized prostate cancer patients who have survivorship or outcomes concerns by facilitating symptom management and encouraging engagement with professional or community-based resources. (Clinical Principle)

INTRODUCTION

METHODOLOGY

Systematic Review. The systematic review utilized in the creation of this guideline was completed in part through the Agency for Healthcare Research and Quality (AHRQ) and through additional supplementation that further addressed additional key questions and more recently published literature. A research librarian experienced in conducting literature searches for comparative effectiveness reviews searched in MEDLINE®, PreMEDLINE, Embase®, the Cochrane Library, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the UK National Health Service Economic Evaluation database to capture literature published from January 1, 2007 through March 7, 2014. Additional supplemental searches were conducted adding additional literature in August 2015 and August 2016.

Assessment of Risk-of-Bias of Individual Studies. Two researchers assessed methodologic risk of bias for each study and resolved discrepancies by consensus. When consensus could not be reached, a third researcher adjudicated. Researchers assessed the risk of bias by following the guidelines in the chapter "Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions" in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[1] This involved evaluating several items, such as randomization, allocation concealment, intention-to-treat-analysis, and completeness of follow-up. Additionally, researchers assessed fidelity to the protocol to address performance bias and blinding of outcome assessors to address detection bias when outcomes were subjective. To be considered as having low risk of bias, the study must have met all the following conditions: randomization or pseudo-randomization (e.g., using instrumental variable analysis) of study participants to treatment groups, concealment of allocation, data analysis based on the intention-to-treat-principle, an outcome that was objective if outcome assessors were not blinded or blinding of outcome assessors was not reported, a difference of 15% or less in the length of follow-up for the comparison groups, data for more than 85% of enrolled patients provided at the time point of interest, and no clear indication of lack of fidelity to the protocol. To be considered as having high risk of bias, the study must have met at least one of the following criteria: trial did not randomly or pseudo-randomly (i.e., using instrumental variables) assign patients to study groups and did not blind outcome assessors, trial had a difference of 15% or more in the length of follow-up for comparison groups, or trial stated that there was not good fidelity to the protocol. To be considered as having medium risk of bias, the study met neither the criteria for low risk of bias nor the criteria for high risk of bias.

Determination of Evidence Strength. The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. 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). By definition, 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.[2]

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 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*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. 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, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[3] 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 is no evidence.

Process. The Localized Prostate Cancer Panel was created in 2012 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair who in turn appointed the Vice Chair. In a collaborative process, additional Panel members, including members of the American Society for Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO), and Society of Urologic Oncology (SUO), with specific expertise in this area were then nominated and approved by the PGC. The AUA conducted a thorough peer review process. The draft guideline document was distributed to peer reviewers. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC and Science and Quality Council (S&Q). Then it was submitted to the AUA, ASTRO, and SUO Board of Directors for final approval. Panel members received no remuneration for their work.

RISK STRATIFICATION

After diagnostic biopsy and appropriate initial staging has demonstrated localized prostate cancer (clinical stage T1-T2, N0 or NX, M0 or MX), risk stratification of prostate cancer severity or aggressiveness should include PSA, clinical stage digital rectal exam (DRE), Grade Group, and amount of cancer on biopsy (i.e. number of cores involved, maximum involvement of any single core) PSA density, and imaging. The Panel agreed that segregating patients into a limited number of risk groups based upon these factors, are simple and easy to use and form the basis for decision making has clinical and practical value. The core of the Panel's risk-grouping is the original low-, intermediate-, and high-risk grouping as proposed by D'Amico et al. in 1998[4] and that has been subsequently adopted by the National Comprehensive Cancer Network (NCCN).[5] We have further augmented the D'Amico criteria by subcategorizing the low-risk group into very low- and low-risk based on criteria analogous to that first proposed by Epstein that have been adapted by the NCCN, and the intermediate-risk group is subcategorized into favorable and unfavorable intermediate risk, based on the contemporary distinction between Grade Group 2 (Gleason score = 3+4) versus Grade Group 3 (Gleason score 4+3), as recently adopted by the World Health Organization, combined with consideration of the criterion of PSA being less than or higher than 10 ng/ml, a criterion that has been validated in discerning outcome differences in numerous clinical trials (Table 3). A practical rationale for care stratification by these core risk groups is that they are broadly used in contemporary practice, and they are based on criteria (PSA, DRE, Gleason score or Grade Group) that have been the cornerstone of eligibility or risk stratification in randomized clinical trials and prospective multicenter studies that constitute the basis of guideline recommendations.

The very low-risk group was adopted based upon the initial identification by Epstein et al.[6] that men at the lowest risk of having significant cancer (defined as 0.2

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 is 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 is no evidence		

cm^3 or larger) were those with 2 or fewer cores positive, no core with >50% involved, Gleason 3+3/ Grade Group 1, and a PSA density <0.15 ng/ml/cc. Multiple studies have since used this definition showing that these men have a very favorable outcome with a low probability of adverse pathology at surgery and low rate of metastatic disease when managed with active surveillance.[7,8] Understanding that these data were derived largely from sextant biopsies, whereas extended core biopsies represent the vast majority of biopsies in clinical practice today, the Panel adopted the concept of no more than two of six cores positive to represent no more than one-third of cores should be positive. This aligns with the Cancer of the Prostate Risk Assessment (CAPRA) score, where patients with 34% or more positive cores are at increased risk.[9] In regards to number of cores, there has been an increased adoption of targeted biopsies in recent years, often using MRI technology. As such, it is not uncommon to have an extended core systematic biopsy plus two or more targeted biopsies. The Panel strongly agreed that the targeted biopsies should not be included in the total percent of cores positive when defining risk group. In other words, if a man undergoes a 12-core systematic biopsy that finds 4 cores positive (1/3 of cores), and a targeted biopsy with 3 cores all of which are positive, the patient should be considered very-low risk (4/12 cores positive, not 7/15 cores positive), assuming he meets all other low-risk criteria and assuming the targeted biopsy was in the same location as one of the systematic biopsies. If the targeted biopsy was outside the location of a systematic biopsy, then it should count as one additional core. In this scenario, the patient would have 5/13 cores positive and be considered low-risk, but not very low-risk. Of note, while the very low-risk grouping was originally designed to detect men with high likelihood of insignificant tumors, defined as <0.2 cc^3, the Panel acknowledges that the definition of an insignificant tumor is difficult to define. As such, an image detected lesion >0.2 cc^3 does not in and of itself mean a patient cannot be very low-risk if the patient otherwise meets very low-risk criteria. As this is a rapidly evolving area, the Panel acknowledges that the definition of very low-risk in the era of highly accurate imaging may need to be revisited in the future.

The intermediate-risk group is defined by the well-established D'Amico criteria for grade and PSA (i.e. Gleason 6 if PSA 10-20; or Gleason 7 if PSA <20), with updating of DRE wherein, consistent with NCCN recommendations, cT2c is categorized as intermediate-risk not high-risk (unless high risk Gleason score is present or PSA is over 20).[10] The Panel determined that to facilitate care decisions, it would be prudent to incorporate contemporary "Grade Group" categorizations (Gleason 6 = Grade Group 1; Gleason 3+4 = Grade Group 2; Gleason 4+3 = Grade Group 3; Gleason score 4+4 = Grade Group 4, and Gleason score 4+5 = Grade Group 5) that were recently validated and endorsed by USCAP and WHO, as a cornerstone of subcategorizing the intermediate-risk group into "favorable" and "unfavorable" intermediate-risk group categories (Table 3).[11-13] Accordingly, the Panel has defined favorable intermediate-risk as those patients having Grade Group 2 cancers and PSA < 10 ng/ml, whereas unfavorable intermediate-risk is comprised of men with either Grade Group 2 cancer with PSA = 10-20, or any Grade Group 3 with PSA <20 (Table 3).

Alternatively, it has been proposed that men with more than one unfavorable risk feature (Grade Group 2, cT2b -c, PSA 10-20 ng/ml, or >50% positive cores) should be considered unfavorable.[10] Evidence that >50% positive cores has consistent prognostic validity is less robust than evidence supporting the distinction between Grade Group 2 and 3, or the evidence of differential outcomes based on PSA less than or greater than 10ng/ml; therefore, the Panel opted not to include percentage positive biopsy core in the subcategorization of intermediate-risk cancers. Similarly, there was concern that in the unusual scenario of a man with cT2b or cT2c and a PSA between 10 and 20 ng/ml, but Grade Group 1, this may not represent unfavorable risk either, though this also requires formal validation in future studies. As such, unfavorable intermediate-risk was defined as Grade Group 3 or Grade Group 2 and either a PSA between 10 and 20 ng/ml and clinical stage cT2b or cT2c.

The Panel did not substratify high-risk patients into high-risk and very high-risk (as has been proposed by the NCCN). The rationale to not further substratify high -risk men is not based upon differences in outcome, but rather the lack of clinical utility as a context for decisions about treatment options is generally similar between high-risk and very high-risk men. However, the Panel did keep the distinction between very low- and low-risk as this does have clinical utility in terms of the optimal management for these men.

Finally, the panel acknowledges that multivariable nomograms can also be used to predict the risk of many clinically relevant outcomes. Of these, the CAPRA score has emerged as a well-validated and often used risk scoring system, though it has yet to be widely

TABLE 3: Risk Stratification for Localized Prostate Cancer	
Very Low Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a AND <34% of biopsy cores positive AND no core with >50% involved, AND PSA density <0.15 ng/ml/cc
Low Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a
Intermediate Risk	PSA 10-<20 ng/ml OR Grade Group 2-3 OR clinical stage T2b-c • Favorable: Grade Group 1 (with PSA 10-<20) OR Grade Group 2 (with PSA<10) • Unfavorable: Grade Group 2 (with either PSA 10-<20 or clinical stage T2b-c) OR Grade Group 3 (with PSA < 20)
High Risk	PSA ≥20 ng/ml OR Grade Group 4-5 OR clinical stage ≥T3*
*Clinical stage T3 cancer is considered locally advanced and, therefore, outside the scope of this guideline.	

incorporated into clinical trial design.[9,14] While the Panel acknowledges that nomograms have advantages in terms of accuracy, there is lack of consensus regarding the best nomogram and what outcome should be measured.

II. SHARED DECISION MAKING (SDM)

1. **Counseling of patients to select a management strategy for localized prostate cancer should incorporate shared decision making and explicitly consider cancer severity (risk category), patient values and preferences, life expectancy, pre-treatment general functional and genitourinary symptoms, expected post-treatment functional status, and potential for salvage treatment. (Strong Recommendation; Evidence Level: Grade A)**

Prostate cancer treatment is a complex medical decision. In almost all cases, there is not a single best treatment choice with regard to oncologic outcomes or side effects. Treatment selection should consider patient, tumor, and treatment-related factors. However, men undergoing treatment for prostate cancer are often not presented with a complete description of all treatment options and treatment-related side effects; up to a quarter of men are not asked about their treatment preferences.[15] It is the consensus of the Panel that clinicians should fully engage in shared decision making (SDM), allowing patient values to drive this decision.

SDM is a collaborative decision making process between patients and their clinicians. SDM is especially relevant in discussion of prostate cancer treatment because such decisions involve multiple clinically accepted options, and the ratio of benefits to harms is uncertain, equivalent, or "preference sensitive" (i.e. dependent on the value that an individual patient may place on them).[16,17] 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.[18-21] 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.[17,18] 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.[22,23]

2. **Prostate cancer patients should be counseled regarding the importance of modifiable health-related behaviors or risk factors, such as smoking and obesity. (Expert Opinion)**

While age is a well-established risk factor for prostate cancer, there are now clear data showing that other patient-related factors such as smoking and excess body weight, typically assessed as a high body mass index (BMI), are correlated with prostate cancer death.[24,25] Moreover, these factors are also risk factors for death from any cause. As such, clinicians are strongly encouraged to use the time of prostate cancer diagnosis as a "teachable moment" to counsel patients about weight loss and smoking cessation. In regards to surgically treated patients, in general, smoking, older age, and obesity increase the risk of perioperative complications, including bleeding, infections, and deep venous thromboses in non-prostate surgeries.[26-28] As similar results have been seen elsewhere in the urological literature, there is no reason to believe these factors do not contribute to perioperative morbidity from prostate cancer.[29] Another factor linked with poor

outcomes is frailty. Two recent studies using patients undergoing urological surgery both found that higher frailty index was associated with a significantly higher risk of complications.[29,30] Similarly, another study found lower functional status (i.e. partially or totally dependent versus independent) was associated with increased risk of complications, particularly Clavien Grade IV or V complications.[31] Therefore, life-expectancy should be assessed on all men prior to deciding on appropriate treatment for prostate cancer.

However, while these factors increase the risk of general surgical complications, the degree to which these factors impact prostate cancer treatment-related morbidity is less clear. A prospective multicenter study of 1,201 prostate cancer survivors treated with radical prostatectomy or radiotherapy reported an independent association of obesity with reduced vitality or androgen function but not other aspects of health-related quality of life (QoL), such as urinary or sexual function.[32] As obesity is correlated with more aggressive prostate cancer, whether this worse androgen function is related independently to obesity or mediated by a greater need for hormonal therapy in obese men due to their more aggressive disease is not known. Similarly, another prospective study found obesity was associated with worse pretreatment vitality,[33] which had a negative impact on posttreatment health-related QoL. In regards to smoking, there are limited data linking smoking with treatment-specific outcomes. However, as smoking is in general associated with poor erectile function and urinary problems, it stands to reason that smoking may make recovery of these factors post-treatment more problematic.

In summary, there is strong circumstantial evidence that smoking and obesity may adversely impact treatment outcomes in men undergoing treatment for prostate cancer. Given these concerns, the Panel felt that patients should be informed of the risks. Moreover, the Panel agreed that most patients should be offered the opportunity to delay therapy for a few months to allow them time to lose weight or stop smoking to reduce these perioperative risks as long as doing so does not significantly impair cancer control.

3. **Clinicians should encourage patients to meet with different prostate cancer care specialists (e.g., urology and either radiation oncology or medical oncology or both), when possible to promote informed decision making. (Moderate Recommendation; Evidence Level: Grade B)**

A patient deciding on treatment for localized prostate cancer often has many options. Even choosing among common treatment options can be overwhelming for a newly diagnosed patient. The various and evolving options also make it less likely that any individual clinician will have personal experience and current knowledge of all therapeutic modalities. Moreover, studies suggest that practitioners may have biases (conscious and subconscious, financial and non-financial) for and against certain management strategies.[34] Both urologists and radiation oncologists have been observed to recommend whichever therapy they deliver in their practice.[35,36] Such observations are troubling, since prostate cancer treatment decisions should be concordant with patients' preferences. Providers can combat the effects of such biases on treatment selection by engaging the patient in SDM. Additionally, patients may better understand the available treatment options by consulting with multiple practitioners skilled in the specific treatment modalities relevant to the patient's particular case. Consultation with multiple providers, especially in teams including a medical oncologist, in one location on the same day, may benefit the patient by encouraging SDM and mitigating the possible effects of physician bias.[37-39] Additionally, including primary care providers in the treatment discussion may help patients make a preference-concordant decision.[40]

4. **Effective shared decision making in prostate cancer care requires clinicians to inform patients about immediate and long-term morbidity or side effects of proposed treatment or care options. (Clinical Principle)**

Each of the initial localized prostate cancer management strategies has a typical pattern of side effects, frequently different from those of other treatments. For properly counseled patient, these side effect profiles may determine treatment selection. However, patients are often not informed of these side effects in sufficient detail, which precludes effective SDM and may lead to a preference-discordant treatment choice.[23]

Active surveillance has no immediate effect on urinary, bowel, or sexual function. Indeed, over time, active surveillance preserves QoL compared to surgical and radiation treatments until such time as one of those treatments may become necessary.[41] However, patients who elect active surveillance as an initial management strategy may expect to see declines in urinary, bowel, and sexual function over time, and select men may experience anxiety over deferring definitive management.[42-44] Changes in urinary and sexual function come as a normal part of aging in these men.

Conflicting data exist regarding the possibility that serial biopsies may be associated with accelerated declines in these domains.[45,46] However, prediagnosis obstructive urinary symptoms are known to be worse in active surveillance patients in comparison to those who elect surgery.[47] All in all, between 50-73% of men who elect active surveillance as an initial management strategy have discontinued it by year 10.[7,48,49]

Patients electing definitive therapy are more likely to have immediate side effects. Surgery patients may experience bleeding, infection, and pain in the immediate term and then experience erectile dysfunction, urinary incontinence, urethral stricture and (very rarely) bowel problems. The risk of perioperative death from prostate cancer surgery is <0.1% in most series.[32,50,51] The same side effects observed after surgery are possible with radiotherapy approaches, though bowel problems are more common, and sexual and continence side effects take much longer to develop. In general, radical prostatectomy causes more early erectile dysfunction (nerve-sparing better than non-nerve sparing) and urinary incontinence than radiation treatment,[32,52] though erectile dysfunction and urinary bother beyond two to five years may be similar between surgery and radiation.[43,44,53] Radiation treatment causes more urinary irritation (brachytherapy more than external beam radiation)[32] and modestly more gastrointestinal side effects than radical prostatectomy.[44,52]

Radiation treatment may be associated with a very small but increased risk for secondary cancer, specifically bladder cancer and rectal cancer. The suspected incidence of radiation-induced second primary cancers is reported to affect between 1-3% of patients in the years following treatment.[54,55] However, the absolute increase in risk is likely small, and published studies are difficult to interpret due to uncontrolled confounders. External beam radiotherapy is associated with secondary rectal cancers (30 cases per 100,000 person-years of follow-up; or 0.03% of patients followed for 10 years). Brachytherapy may have a slightly lower risk of secondary rectal cancers than external beam radiation (6 cases per 100,000 person-years).

5. **Clinicians should inform patients about suitable clinical trials and encourage patients to consider participation in such trials based on eligibility and access. (Expert Opinion)**

Treatment options can be characterized as standard and as investigational (clinical trial). In general standard therapies have proven efficacy and risks determined by prospective trials. There are many types of clinical trials including trials evaluating novel systemic, surgical or radiation therapies, new approaches to approved therapies, device trials and trials focusing on QoL and other patient outcomes. All clinical trials include specified aim(s) with a predetermined statistical plan. Institutional Review Boards (IRB) approve all clinical trials and patient consent forms, and all patients must sign consent for trial participation.

In appropriate patients (i.e., good performance status, no active medical issues), clinical trial options should be considered, and trial options should be discussed with patients as part of the SDM process. Clinical trials are listed by diagnosis and stage on the Clinicaltrials.gov website.

III. CARE OPTIONS BY CANCER SEVERITY/RISK GROUP

Management options for localized prostate cancer stratified by cancer severity risk group, are summarized in Table 4 based on level of evidence and strength of recommendation. Specific guidelines for selecting management options for each localized prostate cancer risk group and the evidence basis for these recommendations follow:

VERY LOW-/LOW-RISK DISEASE

Very Low Risk: PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a AND <34% of biopsy cores positive AND no core with >50% involved, AND PSA density <0.15 ng/ml/cc

Low Risk: PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a

6. **Clinicians should not perform abdomino-pelvic CT or routine bone scans in the staging of asymptomatic very low- or low-risk localized prostate cancer patients. (Strong Recommendation; Evidence Level: Grade C)**

Evidence does not support the use of these scans for staging of newly diagnosed very low- and low-risk prostate cancer. CT scan is very unlikely to provide actionable information in men with very low/low-risk prostate cancer. Likewise, bone scans are generally unnecessary in patients with favorable risk, newly diagnosed prostate cancer (PSA <20.0 ng/mL and a Grade Group =1; or PSA<10ng/ml and Grade Group 2, Table 3); unless the patient's history or clinical examination suggests bony involvement.[56,57]

Table 4. Care Options for Localized Prostate Cancer by Level of Evidence and Strength of Recommendation[1]

Evidence Level/ Recommendation Strength	Prostate Cancer Severity/Aggressiveness				
	Low Risk		Intermediate Risk		High Risk
	Very Low Risk	Low Risk	Favorable	Unfavorable	
A / Strong	Active Surveillance	NA	Radical Prostatectomy OR Radiotherapy[2] with Androgen Deprivation Therapy	Radical Prostatectomy OR Radiotherapy[2] with Androgen Deprivation Therapy	Radical Prostatectomy OR Radiotherapy[2] with Androgen Deprivation Therapy
B / Moderate	NA	Active Surveillance	Radiotherapy[2] without Androgen Deprivation Therapy	NA	NA
B / Conditional	NA	Radical Prostatectomy OR Radiotherapy[2]	NA	NA	NA
C / Conditional	NA	Cryosurgery (whole gland)	Active Surveillance OR Cryosurgery (whole gland)	Cryosurgery (whole gland)	NA
No evidence / clinical principle or expert opinion	NA	Focal Ablative Therapy OR High Intensity Focused Ultrasound	Focal Ablative Therapy OR High Intensity Focused Ultrasound	Focal Ablative Therapy OR High Intensity Focused Ultrasound	NA

[1]Multicenter Randomized Clinical Trials that constitute the basis for evidence:
EORTC-Bolla (XRT+ADT vs XRT): Evidence supporting XRT+ADT (intermediate-risk, high-risk)
SPCG4 (RP vs WW): Evidence supporting RP (intermediate-risk, high-risk)
RTOG 9408 (XRT+ADT vs XRT): Evidence supporting XRT+ADT (intermediate risk)
PIVOT (RP vs WW): Evidence supporting AS (very low-risk, low-risk); RP (intermediate-risk, high-risk)
EORTC (Widmark XRT+ADT vs ADT alone): Evidence supporting XRT+ADT (intermediate-risk, high-risk)
PROTECT (AS vs RP vs XRT+ADT): Evidence supporting AS (very low-risk, low-risk, favorable intermediate-risk); RP or XRT+ADT (low-risk, favorable intermediate-risk)
Single-center RCT: Donnelly et al. (Cryo+ADT vs XRT+ADT): Evidence supporting whole gland cryotherapy (low-risk, intermediate-risk)

[2]Radiotherapy includes a range of various forms of radiotherapy delivery (e.g., IMRT, brachytherapy, other) for which details of evidence and recommendation strength are presented in statements 42-49 of the guideline text

7. Clinicians should recommend active surveillance as the best available care option for very low-risk localized prostate cancer patients. (Strong Recommendation; Evidence Level: Grade A)

Multiple studies have shown that overall and prostate specific mortality appears higher for men with higher baseline Gleason scores.[58-61] While Gleason 6 disease may have genetic and genomic abnormalities of disease with metastatic potential (though unclear if clinically significant), substantial evidence indicates that the majority of Gleason 6 prostate cancer has limited or no metastatic potential and does not pose a threat to the patient's life.[62,63] Most Gleason pattern 3 cancers lack the characteristic genetic aberrations associated with malignancy. Very low-risk patients have a lower risk of harboring occult high-grade cancer than those with higher volume Gleason 6. Low PSA density and low number of cores involved are all associated with a lower risk of contemporaneous high-risk disease.

Long-term follow up studies of very low-risk patients initially managed with active surveillance have shown a metastatic progression rate of <1% at 15 years.[7,64,65] Studies indicate that the QoL of men managed with surveillance is superior to those who are treated with surgery or radiotherapy.[52] Continence and erectile function is better in men on surveillance compared to those who undergo treatment, though both decline as a natural part of aging.

Aside from disease progression, a major risk of active surveillance is that entailed by serial biopsies. These are recommended at between three and five year intervals after the initial confirmatory biopsy.[7,66] Biopsies are associated with risks of infection and bleeding as well as increased rates of erectile dysfunction. The risks of serial prostate biopsies on health and QoL, particularly if performed at infrequent intervals, are considerably less than the long-term risks of surgery and radiotherapy.

There is a small subset of men who find the prospect of living with untreated prostate cancer severely anxiety-provoking and are unwilling to remain on surveillance.[42]

Thus patients with very low-risk prostate cancer in most cases require no treatment and should have active surveillance as their recommended care option.

8. Clinicians should recommend active surveillance as the preferable care option for most low-risk localized prostate cancer patients. (Moderate Recommendation; Evidence Level: Grade B)

There is now sufficient evidence that the majority of men with low-risk localized prostate cancer should initially be managed by active surveillance regardless of life expectancy. Such men with lower-risk disease have a lower risk of both overall mortality and disease progression.[58-61] While the natural history of active surveillance is uncertain and continues to be better defined, there is evidence that the risk of ultimate death from prostate cancer for low-risk men managed with active surveillance is low. Likewise, the risk of metastases is low, though the very long-term outcomes of active surveillance are not yet known. Moreover, while it is unlikely that active surveillance can lead to better oncological outcomes versus active treatment, it is clear that all treatments for prostate cancer have potential side effects. This is in sharp contrast with active surveillance, wherein the risks are related to repeat biopsies and missed occult higher-risk disease, not the treatment itself. Thus, given the low risk of progression to metastatic disease on surveillance coupled with QoL benefits, active surveillance is the preferred management for most low-risk men. The natural history of active surveillance for low-risk men (as opposed to very low-risk men) is less clear in part due to inherent limitations in biopsy sampling and current imaging approaches, though still appears quite favorable. The Panel acknowledges that men with higher volume disease (i.e. greater >50% of cores positive or those larger lesions seen on imaging), albeit still low-risk, may be better served with active treatment. However, as with all treatment decisions in prostate cancer, SDM is paramount.

9. Clinicians may offer definitive treatment (i.e. radical prostatectomy or radiotherapy) to select low-risk localized prostate cancer patients who may have a high probability of progression on active surveillance. (Conditional Recommendation; Evidence Level: Grade B)

Active surveillance for low-risk disease reduces over-treatment in prostate cancer. However, some men with low-risk disease may have a higher risk of clinical progression on active surveillance and may benefit from definitive treatment at the time of diagnosis. Definitive treatment may be in the form of radical prostatectomy or radiotherapy with equivalent outcomes as discussed elsewhere in this guideline. Surgical and radiation treatments do not improve survival within 10 years of follow-up compared to active surveillance for patients with early disease, but has been found to reduce disease progression and development of metastatic disease as shown in the Prostate Cancer Intervention

Versus Observation Trial (PIVOT) (10% versus 5%) and the Prostate Testing for Cancer Treatment trial (ProtecT) (6% versus 2%).[50,51] The rationale for electing definitive treatment in low-risk men is based on the fact that even men with low-risk disease face a small chance of metastasis or prostate cancer specific mortality on active surveillance with data from long term studies finding this occurrence to be roughly 3%.[66] While this number is based on a combination of low- and intermediate-risk patients, it should be noted that metastasis occurs even in low-risk patients, as evidenced by the data from the PIVOT and ProtecT trials, although at a low rate. Patients should be informed of the potential tradeoffs between immediate treatment versus active surveillance. In the PIVOT and ProtecT studies, 20% and 50%, respectively, of patients who started on active surveillance received treatment within 10 years.[50,51] These patients likely harbored higher grade disease at the time of diagnosis, and identifying variables associated with progression may decrease the likelihood of these men missing their window for cure. Clinical predictors for an increased risk of higher grade disease or reclassification of subsequent biopsy include PSA density > 0.15, obesity as measured by BMI, African American race, and extensive Gleason 6 cancer on systematic biopsy cores.[67-72] Men with a family history of aggressive prostate cancer characterized by early metastasis may not be ideal candidates for active surveillance even when presenting with low-risk disease and should be counseled carefully regarding the diagnostic uncertainty of biopsy and progression. A recent analysis of the Canary Prostate Cancer Active Surveillance cohort identified patients with BMI>35kg/m as having a three-fold increased risk of reclassification to higher risk disease on first surveillance biopsy. Men with PSA density >0.15ng/ml have a two-fold risk of reclassification on first biopsy.[67]

African American men have a higher rate of reclassification than Caucasian men on active surveillance as well as a higher rate of adverse pathology on radical prostatectomy when this is chosen as definitive treatment.[73,74] This is true among low-risk patients, and this unique risk should be carefully weighed when deciding among treatment options.

While reclassification does not always indicate that definitive treatment is required, the likelihood of short term progression must be discussed with all men considering active surveillance. The use of multiparametric MRI (mpMRI) has increased diagnostic specificity and should be considered at some point in the evaluation of men considering active surveillance.

10. **Clinicians should not add ADT along with radiotherapy for low-risk localized prostate cancer with the exception of reducing the size of the prostate for brachytherapy. (Strong Recommendation; Evidence Level: Grade B)**

In RTOG 9408, which randomized 1,979 patients to EBRT with four months of ADT versus without ADT and had 9.1 years of median follow-up, overall survival was not improved with ADT in subgroup analysis of 685 low-risk patients.[75] There is no randomized trial supporting a survival benefit from adding ADT to radiotherapy for low-risk cancer. ADT can be used to reduce the size of the prostate to allow for improved dosimetry brachytherapy, but can cause short-term sexual dysfunction and other associated side effects.

11. **Clinicians should inform low-risk prostate cancer patients considering whole gland cryosurgery that consequent side effects are considerable and survival benefit has not been shown in comparison to active surveillance. (Conditional Recommendation; Evidence Level: Grade C)**

As most men with low-risk disease have favorable outcomes with active surveillance, it is unclear whether cryosurgery improves survival outcomes. One randomized trial of EBRT versus cryosurgery with primarily intermediate- and high-risk prostate cancer patients reported similar actuarial five-year overall and disease–specific survival.[76] Both utilized six months of perioperative ADT for both treatment arms. Prospective randomized or comparative trials of cryosurgery with active surveillance in a low-risk cohort are lacking.

It is unlikely that whole gland cryosurgery can provide comparable QoL as the preferred management for most low-risk men. Erectile dysfunction should be an expected outcome for potent patients. A 2009 review of the literature concluded that most patients (80-90%) should expect erectile dysfunction after whole gland cryosurgery and that it should not be offered to patients who desire preservation of potency.[77]

As with all treatments, patients considering cryosurgery should also be informed about the risks of adverse urinary and bowel function outcomes. Urinary retention after cryosurgery can persist for a few weeks and is best managed with a urethral or suprapubic catheter. Urethral sloughing at the verumontanum where the urethral warming catheter may not fully contact the mucosa apposition can result in temporary bothersome irritative symptoms in the early recovery period.

12. **Clinicians should inform low-risk prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)**

As most men with low-risk disease have favorable outcomes with active surveillance, it is unclear whether focal therapy or HIFU improve survival outcomes or provide comparable QoL as the preferred management for most low-risk men. Prospective randomized or comparative trials of HIFU with active surveillance or other treatment modalities are lacking. Published five year oncologic outcomes are variable and attributable to the lack of consensus on objective response criteria.[78] The Panel awaits the results of well-designed comparative clinical trials in order to define the appropriate role of this technology in the management of low-risk prostate cancer. The Panel also recognizes there is a growing interested in partial prostate treatment (i.e. focal therapy) by both patients and clinicians. Theoretical advantages include less morbidity versus whole gland treatment. However, this is at the potential expense of leaving undetected and untreated cancer. In a group of men at high risk for overtreatment and coupled with the lack of long-term oncological data of focal therapy, the Panel felt it was premature at this point to consider partial prostate treatment outside of a clinical trial.

13. **Clinicians should recommend observation or watchful waiting for men with a life expectancy ≤5 years with low-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade B)**

Men with a life expectancy of ≤5 years do not benefit from prostate cancer screening,[79] diagnosis, or treatment. Prostate cancer treatment does not improve survival within five years of follow-up.[51] Patients diagnosed with low-risk disease and a limited life expectancy should pursue watchful waiting. Unlike active surveillance, watchful waiting carries a palliative, non-aggressive intent, and does not involve routine cancer monitoring including biopsies. With watchful waiting, patients who develop symptomatic progression from prostate cancer are offered treatments to palliate these symptoms.

An accurate determination of a man's life expectancy based on age and comorbidities is difficult.[80] 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 man's primary care physician to determine a shared decision regarding surveillance.

Clinicians should include the life expectancy estimate in a discussion with patient and family to develop rational individual patient treatment plans.

14. **Among most low-risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance. (Expert Opinion)**

Prospective active surveillance cohorts now comprise >10,000 patients, thousands of whom have been followed for >10 years. Clinical parameters (e.g., PSA, PSA density, extent of disease on biopsy, race, T-stage) allow for stratification for risk of co-existent higher-grade disease. Monitoring low-risk patients on surveillance is associated with a low risk of prostate cancer-specific mortality. Therefore, the benefit to most patients of a biomarker to further stratify patients according to the risk of progression is modest.

However, selected patients, particularly those whose risk factors suggest they are at above average risk for higher-grade disease, may benefit from genomic testing. There are two potential benefits: reassurance for those patients with a favorable genomic risk score that conservative management is likely to be safe, and earlier identification of those at risk for disease progression on active surveillance who could benefit from treatment.

As of the publication of this document, the three genetic tissue assays summarized below have been approved by the FDA for men with prostate cancer. None of these tests have yet been validated as providing substantial benefit in the active surveillance population.

Genomic Classifier (GC) This is a 22-marker genomic classifier (GC), based on RNA expression. GC had independent predictive value on multivariable analysis for predicting metastasis following prostatectomy, with a hazard ration (HR) of 1.5 for each 10 percent increase in score,[81] and these results were validated in two separate prostatectomy cohorts.[82,83] A high score on biopsy is associated with an increased risk of metastasis (HR 1.7 for each 10% increase in score).[84,85]

Genomic Prostate Score (GPS): This assay incorporates 12 cancer genes that represent four biological pathways of prostate cancer oncogenesis: the

androgen receptor pathway, cellular organization, stromal response, and proliferation. A 20-point increase in the genomic prostate score (GPS) is associated with a statistically significantly increased risk of high-grade and/or non-organ-confined disease (odds ratio [OR] 1.9, 95% CI 1.3-2.9).[86-88]

Cell Cycle Progression (CCP): This analyzes 31 cell cycle related genes and 15 housekeeping genes by quantitative RT-PCR.

The Transatlantic Prostate Group examined cell cycle progression (CCP) scores using needle biopsies of a conservatively managed prostate cancer cohort from Great Britain.[89] In this cohort, of 349 men managed without primary treatment, the cumulative incidence of death was increased among those with CCP scores >2 (19% of the population) compared with those with lower CCP scores. Patient outcomes could not be differentiated in those with lower CCP scores. The HR of prostate cancer death was 1.7 per unit increase in CCP score to 10 or CAPRA high-risk disease.[90]

INTERMEDIATE-RISK DISEASE

Intermediate Risk: PSA 10-<20 ng/ml OR Grade Group 2-3 OR clinical stage T2b-c

- *Favorable: Grade Group 1 (with PSA 10-<20) OR Grade Group 2 (with PSA<10)*
- *Unfavorable: Grade Group 2 (with either PSA 10-<20 or clinical stage T2b-c) OR Grade Group 3 (with PSA < 20)*

15. Clinicians should consider staging unfavorable intermediate-risk localized prostate cancer patients with cross sectional imaging (CT or MRI) and bone scan. (Expert Opinion)

The probability for metastasis at diagnosis of localized prostate cancer associates with risk classification.[91] The presence of metastasis increases with tumor stage and influences treatment options. Baseline staging recommendations are guides with the goal of reducing or eliminating routine imaging in men at low risk for metastasis and performing imaging of common metastatic sites in men at most risk for metastasis. The most common sites are pelvic/retroperitoneal lymph nodes and bones. Less common metastatic sites include lung and liver; however, metastasis to lung and liver are often seen at late disease stage or with uncommon variants, such as small cell. For men with intermediate-risk prostate cancer, the Panel does not recommend routine imaging at diagnosis in all patients. The Panel recommends metastasis staging for men with two or more of the following features – palpable nodule on DRE (stage T2b/c), Gleason 7 (3+4 or 4+3) or PSA >10.

The type of imaging performed may vary by physician preference and availability, but testing should evaluate the pelvic/retroperitoneal lymph nodes by cross sectional imaging and bones by bone scintigraphy (^{99m}Tc-MDP).[92] The recommended cross sectional imaging is either MRI of the prostate or pelvis or CT scan of the abdomen/pelvis. There are relative advantages and disadvantages associated with MRI and CT. Prostate MRI provides more accurate imaging of the prostate gland and has no associated radiation exposure compared to CT; however, high-quality prostate MRI may not be available at all sites.[93] Technetium bone scans have been a longstanding assessment tool in prostate cancer. More sensitive bone imaging is becoming available, including 18F-sodium fluoride PET/CT bone scans, PSMA-PET imaging, and whole body MRI.[94,95] Currently, only 18F-sodium fluoride PET/CT is FDA approved. While these next generation scans are routinely used outside the United States, because of development and reimbursement issues, they are not routinely available in the United States and are not routinely recommended for staging at this time herein.

For intermediate-risk prostate cancer, the Panel's recommendations for baseline imaging vary somewhat from NCCN and American College of Radiology (ACR) recommendations. NCCN qualifies staging recommendations for men with life expectancy > 5 years or symptomatic disease and recommends bone scan for T2 and PSA >10 and CT if T2 and have a nomogram probability for nodal involvement >10%. ACR uses descriptive language, and for intermediate-risk prostate cancer recommends that pelvic MRI "usually" be done and CT and bone scan "may" be done.[92] This Panel's recommendation, based on expert opinion, is that imaging be considered if two or more risk factors are present and does not include nomogram calculations.

16. Clinicians should recommend radical prostatectomy or radiotherapy plus androgen deprivation therapy (ADT) as standard treatment options for patients with intermediate-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)

Two RCTs have evaluated overall survival and prostate cancer-specific survival among men undergoing radical prostatectomy compared to watchful waiting or

observation: the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4)[96] and PIVOT.[51] The SPCG-4 trial provided evidence supporting the setting of intermediate-risk disease, because even though subset analyses focusing on the intermediate-risk subgroup defined for the guidelines herein were not pre-specified, most trial participants had intermediate-risk cancer as evidenced by a) Gleason score 7 on biopsy, or b) clinical stage of T2, or c) PSA >10ng/ml at enrollment. SPCG-4 showed higher overall survival and prostate cancer-specific survival among patients randomized to radical prostatectomy at 10 year's follow-up. In the trial, the relative risk of dying after surgery was observed to be reduced at 0.62 (95% CI 0.44 to 0.87, p=0.01) with a reduction of cumulative incidence of death from prostate cancer from 20.7% to 14.6% at fifteen years.

The PIVOT trial is the only RCT to have included pre-specified analyses for evaluating survival differences stratified by prostate cancer risk categories and by PSA at initial diagnosis. Subject participants in PIVOT had predominantly low-risk disease, and the trial was underpowered to conclusively demonstrate non-inferiority. Accordingly, there was no difference in overall survival among the entire trial cohort (including low- and intermediate-risk subjects combined). However, pre-specified subset analyses showed reduction in prostate cancer mortality among PIVOT participants who had either intermediate-risk cancer or baseline PSA greater than 10ng/ml and underwent radical prostatectomy. In the trial, men who were randomized to surgery were found to have a lower risk of death from prostate cancer or treatment (hazard ratio 0.63, 95% CI 0.36 to 1.09, p=0.09) with an absolute risk reduction estimated at 2.6%. Surgery was associated with an improvement in all-cause mortality primarily in patients with PSA levels greater than 10 ng/ml (p=0.04) and possibly with intermediate- and high-risk cancers (p=0.07).

Notably, the watchful waiting and observation arms of SPCG-4 and PIVOT, respectively, did *not* include monitoring or surveillance with intent to use delayed definitive intervention for specific progression criteria, as is the fundamental principle that discerns contemporary *active* surveillance/management (in contrast to watchful waiting or observation). Such *active* surveillance/management was compared to radical prostatectomy in the ProtecT trial, which randomized subjects to surveillance, external beam radiotherapy combined with hormonal therapy, or radical prostatectomy.[50] However, ProtecT had an even greater preponderance of low-risk prostate cancer among participants than was present in PIVOT. Among patients randomized to surveillance, nearly half underwent definitive intervention at some point during the first 10 years of follow-up. A non-significant difference in overall survival or prostate cancer specific survival was seen at 10 years follow-up in ProtecT, but subset analysis of intermediate-risk patients was not performed, limiting the relevance of ProtecT with regard to possible survival benefit of radical prostatectomy in intermediate-risk cancer. Of interest, despite the preponderance of low-risk disease in ProtecT, prostate cancer clinical progression and metastases were significantly lower among subjects randomized to either prostatectomy or radiation with hormonal therapy compared to those randomized to surveillance.

Additionally, an early underpowered RCT enrolling 97 men compared radical prostatectomy to radiotherapy but found no difference in death or metastatic rate after five years of follow-up.[97]

A series of comparative outcome results based on retrospective information using propensity adjustment or instrumental analysis comparing radical prostatectomy versus external beam radiotherapy, and radical prostatectomy versus prostate brachytherapy, have suggested a mortality reduction in patients treated with surgery compared to external beam radiation and brachytherapy.[59,60,98-107] In follow-up to these individual investigations, Wallis et al. have published a meta-analysis of nineteen pooled studies with 118,830 patients.[108] This study reported that overall survival and prostate cancer specific survival were higher for the surgical patients. In particular, the observed benefit was seen irrespective of risk category, radiation regimen, time period, and follow-up length. This study, although large, utilizes retrospective data and can be subject to significant bias. The magnitude of this potential clinical benefit, if any, has not been prospectively validated or demonstrated in any large RCT, including the ProtecT study.

17. Clinicians should inform patients that favorable intermediate-risk prostate cancer can be treated with radiation alone, but that the evidence basis is less robust than for combining radiotherapy with ADT. (Moderate Recommendation; Evidence Level: Grade B)

Two randomized trials support the addition of ADT to EBRT for intermediate-risk prostate cancer. RTOG 9408 randomized 1,979 patients to EBRT (66.6 Gy) with versus without four months of ADT and had 9.1 years of median follow-up.[75] Ten year overall survival improved with ADT for the intermediate-risk subgroup

of 1,068 patients from 54% to 61% (p=.03). A smaller trial randomized 206 patients to 70 Gy of radiation with versus without 6 months of ADT.[109] In patients with little or no comorbidity, 15-year overall survival was improved with ADT (31% versus 44%, p=.04).

A caveat to these trials was the use of lower radiation doses no longer considered standard today. At least four randomized trials have compared lower radiation doses (68-70 Gy) to modern higher radiation doses (74 -80 Gy), and all demonstrated improved cancer control with higher radiation doses.[110-113] These trials have led to the adoption of higher radiation doses as the modern standard of care, and the benefit of adding ADT to modern higher doses of radiation is the subject of continued investigation. EORTC 22991 randomized 819 patients (75% intermediate risk) to RT (doses ranged from 70 to 78 Gy) versus RT with ADT;[114] ADT improved clinical progression-free survival even among patients who received 78 Gy of RT, but overall survival data are not yet mature.

There are no randomized trials demonstrating a survival benefit from adding ADT to low-dose rate or high-dose rate brachytherapy monotherapy, so ADT should not be added to brachytherapy except to reduce the size of the prostate to allow the dosimetry to be optimized.

There is emerging recognition that intermediate-risk prostate cancer represents a broad group of patients with varying prognoses, and a new classification system separates intermediate-risk into unfavorable and favorable groups (as defined in the Introduction).[11] Patients with unfavorable intermediate risk disease should be especially considered for the addition of ADT to EBRT.

18. **In select patients with intermediate-risk localized prostate cancer, clinicians may consider other treatment options such as cryosurgery. (Conditional Recommendation; Evidence Level: Grade C**)

Treatment options routinely employed for the treatment of intermediate-risk prostate cancer include radical prostatectomy, and external-beam radiotherapy. However, cryosurgery, may be appropriate depending on patient-specific factors, including preferences, comorbidities, and life expectancy. Comparative effectiveness research evaluating cryosurgery for localized prostate cancer has been limited to one RCT and several non-randomized prospective or comparative studies.[115-117]

Whole gland ablative therapies such as cryosurgery may be appropriate for patients with contraindications to more traditional therapies, such as prostatectomy or radiotherapy (e.g. medically inoperable patients with either previous pelvic radiotherapy or autoimmune disorders). All of these management approaches (observation/watchful waiting, active surveillance, cryosurgery) do not currently have sufficient published prospective comparative evidence for their routine application for the management of intermediate-risk prostate cancer, and patients should be informed of this lack of comparative evidence during SDM discussions.

19. **Active surveillance may be offered to select patients with favorable intermediate-risk localized prostate cancer; however, patients should be informed that this comes with a higher risk of developing metastases compared to definitive treatment. (Conditional Recommendation; Evidence Level: Grade C)**

Active surveillance may be appropriate in selected patients with intermediate-risk disease who have selected deferred primary treatment to delay treatment -related toxicities until tumor progression. Patients who are considering surveillance may benefit from an MRI and targeted biopsy. If the MRI is negative, or targeted biopsy shows only Gleason 6 disease, they are likely to have a favorable prognosis, and surveillance is a reasonable strategy. However, patients who elect active surveillance should be informed that this comes with a risk of developing metastases as shown in the PIVOT and ProtecT trials.[50,51]

There are, several groups of Gleason 7 patients who may be favorable candidates.[118] Patients with small volume cancer on biopsy who have < 10% Gleason pattern 4 may reflect artifactual upgrading due to tangential cut of a Gleason 3 acinus, in which case the lumen is not seen and the pathologist's impression is of a solid clump of cells (i.e. higher grade).[119,120]

20. **Clinicians should recommend observation or watchful waiting for men with a life expectancy ≤5 years with intermediate-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)**

Observation/watchful waiting is an approach to prostate cancer that does not include active surveillance with PSA/MRI/repeat prostate biopsy and by definition also does not include prostate cancer therapies such as surgery/radiation/androgen deprivation. Randomized trials have been done comparing prostatectomy to observation.[51,52,96] The SPCG-4 trial was composed of non-screen detected tumors and demonstrated benefit

for prostatectomy; the survival benefit was primarily in men < 65 years of age.[96] The PIVOT trial (40% low-, 34% intermediate-, 25% high-risk) did not show a benefit for prostatectomy for the total group; however, a subset analysis of the intermediate-risk patients did show benefit (HR 0.69).[51] At four years the mortality was identical in both cohorts. Thus patients with life expectancy <5 years are unlikely to derive survival benefit from prostatectomy.

When choosing an initial therapy for localized prostate cancer, it is important to consider the patients psychological state (competency, anxiety, depression). A SEER-Medicare analysis demonstrated that men with depression were less likely to have definitive therapy (surgery or radiation) and that depressed men also had worse overall (not prostate cancer specific) mortality across prostate cancer risk classifications.[121] Clinicians should be aware of mental health issues as a possible cause of treatment disparity and seek multidisciplinary input when appropriate.

21. **Clinicians should inform intermediate-risk prostate cancer patients who are considering focal therapy or HIFU that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)**

The Panel recognizes that novel therapies including HIFU and focal prostate ablation may provide QoL advantages for patients in comparison to surgery and radiotherapy. However, there are no prospective randomized or comparative effectiveness data versus traditional treatments available. Published five year oncologic outcomes for HIFU are variable and attributable to the lack of consensus on objective response criteria.[78] The Panel awaits the results of well-designed comparative clinical trials of HIFU in order to define the appropriate role of this technology in the management of intermediate risk prostate cancer.

The Panel also recognizes there is a growing interested in partial prostate treatment (i.e. focal therapy) by both patients and clinicians. Theoretical advantages include less morbidity versus whole gland treatment though this is at the potential expense of leaving undetected and untreated cancer. Initial focal therapy reports with short term follow-up suggest effective disease eradication in the treated area of appropriately selected patients. Studies where TRUS biopsy of the treated volume or side was performed per protocol, clinically significant cancer was identified in a minority (<14%) of patients.[122-124] However, comparative data comparing focal therapy to other treatment approaches, such as prostatectomy, radiotherapy, observation, or active surveillance, are lacking in the literature.[118,125] The Panel recommends that if focal therapy or HIFU is offered as an alternative treatment modality for intermediate risk prostate cancer, it should preferably be offered within the context of a clinical trial.

HIGH-RISK DISEASE

High Risk: PSA >20 ng/ml OR Grade Group 4-5 OR clinical stage >T3

22. **Clinicians should stage high-risk localized prostate cancer patients with cross sectional imaging (CT or MRI) and bone scan. (Clinical Principle)**

Before widespread adoption of PSA screening, most incident prostate cancers were only diagnosed at an advanced stage. Treatment options such as surgery or radiation were believed only to benefit patients with localized disease, which necessitated an imaging evaluation to stage almost every patient prior to treatment. In the modern era, however, over 90% of prostate cancers are localized, making the need for routine imaging to detect metastases with CT, MRI, or bone scan obsolete.[126]

Prior studies demonstrate that PSA <10 ng/ml has a negative predictive value of 99.5% for significant findings on bone scan, and <1% of patients with PSA < 20ng/ml have positive bone scans or CTs.[127-131] In spite of these data and longstanding guidelines to curb imaging overuse, many patients still undergo improper imaging.[126] Data is limited for other tests to detect distant metastases such as fluciclovine PET, total body MRI, NaF PET, choline/acetate PET, PSMA PET.[132] Further research may establish the utility of these modalities, but likely only for high-risk patients. Standard FDG-PET is generally not a useful test in this setting.[133]

23. **Clinicians should recommend radical prostatectomy or radiotherapy plus androgen deprivation therapy as standard treatment options for patients with high-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)**

Men with high-risk disease are most likely to develop metastases and die from prostate cancer. There are two randomized prospective studies that support radical prostatectomy as treatment of high-risk disease. The SPCG-4 trial compared radical prostatectomy and watchful waiting.[96] At 15 years, all-cause mortality favored radical prostatectomy (46.1% versus 52.7%,

RR, 0.75; 95% CI, 0.61 to 0.92), and prostate cancer-specific mortality favored radical prostatectomy (14.6% versus 20.7%, RR, 0.62; 95% CI, 0.44 to 0.87). Although the PIVOT trial did not demonstrate an overall survival advantage with surgery, there was a significant difference in the rate of bone metastases at both the 10 -year and 12-year follow-up favoring radical prostatectomy treated patients.[51] Furthermore, in men with high-risk disease undergoing surgery, the rates of prostate cancer-specific death was significantly lower, 9.1% compared to 17.5% for the observation arm.

For radiotherapy and ADT, there are two types of studies that show efficacy. First, ADT and radiotherapy are superior to radiotherapy alone, and long term ADT is superior to short term ADT although the duration of long term ADT remains under investigation.[134-136] Second, ADT and radiotherapy are superior to ADT alone and thus suggest that local therapy is important even among patients at high risk for subclinical metastatic disease.[137,138] For high-risk prostate cancer patients receiving external beam radiotherapy and ADT, brachytherapy boost (low-dose rate or high-dose rate) should be offered to eligible patients.

24. Clinicians should not recommend active surveillance for patients with high-risk localized prostate cancer. Watchful waiting should only be considered in asymptomatic men with limited life expectancy (≤5 years). (Moderate Recommendation; Evidence Level: Grade C)

Localized high-risk prostate cancer should be considered a life threatening disease. Albertsen et al. analyzed Connecticut Tumor Registry data of men with localized prostate cancer who were either not treated or treated with delayed ADT.[139] Men with Gleason 8-10 tumors had a 60-87% chance of dying from prostate cancer within 15 years of diagnosis (age dependent). Thus watchful waiting for high-risk prostate cancer should only be considered for asymptomatic men with limited life expectancy (<5 years).

RCTs are of high quality, but results differ likely based on baseline patient characteristics.[51,52,96] The PIVOT trial randomly assigned men with localized prostate cancer to prostatectomy or observation (21% were high -risk).[51] For the total cohort at four years, there was no difference in death from prostate cancer. Prostate cancer mortality was lower for high-risk patients in the prostatectomy cohort compared to observation (9.1% versus 17.5%, p=0.04). In the SPCG-4 trial (25% high-risk) prostatectomy was associated with reduced mortality in all groups with the most benefit in the younger men (<65 years, relative risk 0.38). While randomized data is lacking comparing radiation to observation, in a population based cohort, prostate cancer specific mortality was higher with observation compared to radiation in the subset of men with high-risk disease.[140] Available data supports active intervention (rather than surveillance) in men with high -risk disease unless a patient is expected to die from competing causes within five years.

25. Cryosurgery, focal therapy and HIFU treatments are not recommended for men with high-risk localized prostate cancer outside of a clinical trial. (Expert Opinion)

A randomized clinical trial evaluating the efficacy of cryosurgery in comparison to radiotherapy or radical prostatectomy for high-risk localized prostate cancer is lacking. One randomized clinical trial demonstrating similar short-term oncologic outcomes for EBRT versus cryosurgery has been reported for primarily intermediate- risk disease patients.[76] A small percentage had high-risk features (9% Gleason score ≥8, 18% ≥ T3a, none with PSA > 20) but a subset analysis was not provided to support cryosurgery for high-risk localized prostate cancer patients. Another randomized trial comparing outcomes of EBRT versus cryosurgery for primarily high-risk or locally advance disease patients terminated early for lack of accrual and demonstrated inferior 8-year biochemical disease-free recurrence rate for the cryosurgery (17% versus 59%).[141] Long-term prospective randomized data of cryosurgery for men with high-risk localized prostate cancer is lacking.

There are no prospective randomized or comparative effectiveness data for HIFU versus traditional treatments available. Published five year oncologic outcomes for HIFU are variable and attributable to the lack of consensus on objective response criteria.[78] The Panel awaits the results of well-designed comparative clinical trials of HIFU in order to define the appropriate role of this technology in the management of high-risk prostate cancer.

There is no agreement defining the ideal patient for focal therapy. Consensus statements identify patients with low-risk prostate cancer and an unequivocal solitary primary tumor who desire intervention as the ideal candidate for this investigational approach.[118,124] Some investigators have expanded criteria to patients with intermediate-risk disease and rarely high- risk. However, comparative data comparing focal therapy to other treatment approaches for high-risk prostate cancer, such as prostatectomy or radiotherapy, are

lacking in the literature. The Panel recommends that if cryosurgery, focal therapy or HIFU is offered as an alternative treatment modality for high-risk prostate cancer, it should only be done within the context of a clinical trial.

26. Clinicians should not recommend primary ADT for patients with high-risk localized prostate cancer unless the patient has both limited life expectancy and local symptoms. (Strong Recommendation; Evidence Level: Grade A)

A randomized prospective study comparing the androgen receptor inhibitor bicalutamide 150 mg to placebo found no significant difference in overall survival or prostate cancer specific survival in men with localized prostate cancer.[142] Several large retrospective studies comparing primary ADT to no ADT failed to demonstrate improved long-term overall or disease-specific survival for men with localized prostate cancer.[143-145] In one study, there was a slightly reduced risk of all-cause mortality in a high-risk subgroup treated with primary ADT,[143] but in another study the small benefit was limited to prostate cancer-specific survival and not overall survival in men with poorly differentiated cancer.[144] The risks of serious adverse events associated with ADT and the high costs associated with its use outweigh the limited benefits, if any. Therefore, primary ADT should be used only to palliate symptoms of disease or prevent imminent symptoms associated with disease progression.

27. Clinicians may consider referral for genetic counseling for patients (and their families) with high-risk localized prostate cancer and a strong family history of specific cancers (e.g., breast, ovarian, pancreatic, other gastrointestinal tumors, lymphoma). (Expert Opinion)

The incidence of germline mutation in DNA repair genes in localized prostate cancer is low with estimates of BRCA2 in 1-2%,[146,147] and there have not been standard recommendations for genetic screening/ counseling for prostate cancer patients. Recently it was reported that the incidence of somatic mutation of DNA repair genes (e.g., BRCA2, ATM) in metastatic castration-resistant prostate cancer (mCRPC) is 25%.[148] The incidence of germ-line mutation of DNA repair genes in men with mCRPC is approximately 10%.[149] The mutations seen were BRCA2 (44%), ATM (13%), CHEK2 (12%), BRCA1 (7%) and others (1-4%). High Gleason score (8-10) and family history of cancer (breast, ovarian, pancreatic, other gastrointestinal, lymphoma) in first-degree relatives was associated with germline DNA repair mutations in mCRPC patients. Young age and family history of prostate cancer was not associated with germline DNA repair mutations in the seven cohorts analyzed.

Patients with localized prostate cancer who are at highest risk for developing mCRPC, may have a higher incidence of germline DNA repair mutations than expected from published reports: the incidence is to be determined but may approach 5-8%. The presence of germline DNA repair gene mutations has important implications for the prostate cancer patient in terms of general cancer screening and possible future prostate cancer treatment decisions. Additionally the presence of germline DNA repair mutations is of utmost relevance to the patient's first-degree family members due to increased cancer risk and screening implications. The Panel recommends that clinicians take detailed family history of cancers and give consideration to patient referral for genetic screening and counseling for men with localized high-risk prostate cancer, particularly in the setting of family history of first degree relatives with cancers of breast, ovary, pancreas, other gastrointestinal cancers, and lymphoma.

IV. RECOMMENDED APPROACHES AND DETAILS OF SPECIFIC CARE OPTIONS

ACTIVE SURVEILLANCE

28. Localized prostate cancer patients who elect active surveillance should have accurate disease staging including systematic biopsy with ultrasound or MRI-guided imaging. (Clinical Principle)

The accuracy of initial prostate biopsy schemes depends on several factors. Sampling accuracy decreases progressively with increasing prostate volume.[150] Furthermore, PSA, free/total PSA ratio (% fPSA), and DRE influence the detection rate.

Substantial modifications from the original sextant approach have resulted in an extended biopsy scheme (defined as the traditional sextant template plus at least four and up to eight laterally directed samplings from the peripheral zone) as an initial diagnostic biopsy strategy.[150-152] The 12-core biopsy scheme (sextant template plus laterally directed sampling from each sextant template) has become the most widely accepted method. Some practitioners also take a core from the anterior transition zone on each side since this is a common site for missed cancers.[153]

Extended biopsy has a significantly superior detection rate compared to sextant biopsy.[154,155] The Vienna

nomogram suggested a minimum number of cores (range: 8–18) based on patient age and gland volume in the PSA 2–10 ng/ml range to ensure 90% certainty of cancer detection.[156] Most initial biopsy studies have shown that more than 12-15 cores is not beneficial.[157,158] Current consensus supports a 10- to 12 -core extended biopsy scheme, with additional cores from areas suspected by DRE, transrectal ultrasonography (TRUS), or MRI.

Template Transperineal Saturation Biopsy: In an attempt to improve the detection of clinically significant cancers, transperineal template mapping techniques have been developed using an external 5-mm grid.[159,160] In one study, 3D mapping biopsy was positive for cancer in only 80% (144 of 180) of patients with previously proven cancer. Bilateral disease was demonstrated in 61%, and 19% were confirmed to have only unilateral disease. The false negative rate was 20%, even with an aggressive transperineal technique in men who were known to be positive for cancer at initial biopsy. Detection of anterior cancer is enhanced using this technique.[160] However, template-based biopsy is significantly more resource intensive and invasive. Template biopsy also risks biopsy-related morbidity, including a 10% rate of urinary retention. Oversampling also increases the potential for diagnosing clinically insignificant cancer. Conformational changes occur during multiple needle passes, and template-based biopsy can still involve real -time sampling errors. It requires anesthesia and more pathology resources Therefore, the indications for a transperineal saturation template biopsy remain limited, but there may be a role.

MRI targeted biopsy: The recent development of MRI imaging of prostate cancer promises to enhance the early identification of aggressive disease in men diagnosed with low-risk prostate cancer who are candidates for surveillance. These men may benefit from an MRI and targeted biopsy; about 30% can be expected to be upgraded. In several recent publications comparing targeted to template biopsies, about 10% of men with a negative MRI had clinically significant cancer.[161-163] The need for confirmatory biopsies in surveillance candidates with a negative MRI is controversial. This should likely depend on other risk factors, including PSA density, race, and the known volume of Gleason 6 cancer.

Targeted biopsy can be performed using cognitive co-registration, fusion targeted biopsy systems, or in-bore MRI guided biopsies. Each of these has pros and cons. All three techniques are acceptable.

Several small series have suggested that stable findings on mpMRI are associated with Gleason score stability.[164] The appeal of serial MRI in men on surveillance is that it may allow a safe reduction in the frequency and number of follow up biopsies. However, the role of serial MRI for monitoring patients during surveillance has yet to be validated. An interval of wo years between MRIs in men on surveillance has been suggested by several authors.[165]

Value of DRE:[166] In a prostate cancer screening study of 36,000 men, many cancers detected by DRE were clinically important in those with a PSA level <4.0 ng/ ml. Six percent (n = 2,233) underwent radical prostatectomy, and 303 (14%) were diagnosed by DRE alone. Of the cancers detected by DRE alone, 60 (20%) were non–organ confined, and 56 (20%) had a Gleason score ≥7. Gleason score ≥7 cancers detected at PSA levels <1.0, 1.0–2.0, 2.0–3.0, and 3.0–4.0 ng/ml were present in 10%, 22%, 14%, and 35% of cases, respectively.

In surveillance series, 3-5% of patients are identified as having progression based on DRE. While limited by the subjective nature of the examination, annual DRE remains an important part of the assessment of men on surveillance.

29. Localized prostate cancer patients undergoing active surveillance should have routine surveillance PSA testing and digital rectal exams. (Strong Recommendation; Evidence Level: Grade B)

For patients who elect active surveillance as a management approach, surveillance should include PSA testing and DRE in order to help identify patients who may consider active treatment. In the ProtecT trial, which showed similar survival with active surveillance versus radiotherapy or radical prostatectomy, trial subjects had regular PSA testing and DREs performed. While the optimal frequency of PSA and DRE has not been established, in ProtecT PSA testing was recommended every three months in year one, then three to six month subsequently with DRE performed during urology follow-up visits.[50]

30. Localized prostate cancer patients undergoing active surveillance should be encouraged to have a confirmatory biopsy within the initial two years and surveillance biopsies thereafter. (Clinical Principle)

The published active surveillance literature includes 23 prospective studies. The largest 11 studies with extended follow-up encompass approximately 5,000

men and are summarized in Table 5.[7,66,167-175]

The studies contain varying eligibility criteria. While each was designed to identify patients with favorable prognoses, and thus good candidates for active surveillance, the clinical criteria applied at different sites and in different studies vary. They each include early clinical stage, low serum PSA, and Gleason score consistent with well- or moderately-differentiated tumors. Beyond these three core components, many incorporate number and percentage of positive cores, extent of tumor involvement within a biopsy core, PSA density, and kinetics. PSA density has been recognized by many groups as a biomarker for higher-risk disease. A PSA density of <0.15 is an indicator of a more benign phenotype and low volume disease.

Although not universally accepted, several sites recommend repeat prostate biopsy before committing to active surveillance in order to identify patients where initial biopsies may have missed higher-risk features. In most patients, delaying this biopsy for six months to a year is unlikely to have an impact on long term outcome, even if higher-grade disease is later identified.

Eligibility criteria heterogeneity reflects a different risk tolerance between investigators. For those centers with more inclusive criteria, the potential advantages of surveillance outweigh what is believed to be a small increased risk of metastasis occurring while being surveilled. In the ProtecT trial, in whom 25% of randomized patients had intermediate- or high-risk cancer, there was a small increase in metastatic progression in the expectant management arm compared to those treated radically, but no difference in prostate cancer mortality. The increased progression rate likely reflected the inclusion of higher-risk patients in the cohort.[50] In contrast, other centers only include very low-risk patients by NCCN guidelines (1-2 cores positive, < 50% of core involvement, and PSA density <0.15). Several decision analyses suggest that it would require a substantial increase in prostate cancer mortality under surveillance compared to radical intervention before surveillance would lose the net benefit for low and intermediate risk groups.[176] However, these analyses are limited by the uncertainty inherent in these models.

Surveillance follow up strategies differ depending on study center. Although the key parameters available for monitoring include PSA, DRE, and repeat prostate biopsy, no group has defined the appropriate criteria to trigger active intervention or testing intervals. The probability that higher-grade disease will be diagnosed on biopsy during active surveillance is 8- 28%.[177] This usually represents a higher-grade component of the original tumor that was not originally sampled rather than evolution to higher-grade disease. Biopsy intervals vary from one to five years. In the large scale PRIAS trial, men are prospectively followed on active surveillance and repeat prostate biopsies are scheduled at one, four, and seven years after the diagnostic biopsy.[167] Current Cancer Care Ontario Guidelines,[178] which have also been adopted by ASCO,[179] are for PSA every 3-6 months, DRE each year, and systematic biopsies within 6-12 months after the diagnostic biopsy, and then every 3-5 years until the patient is 'switched' to watchful waiting.

31. Clinicians may consider multiparametric prostate MRI as a component of active surveillance for localized prostate cancer patients. (Expert Opinion)

mpMRI of the prostate is a promising diagnostic test that may improve both selection of patients for and monitoring of patients on active surveillance.[180] The literature reports a high negative predictive value (82-95%) for the detection of clinically significant prostate cancer using mpMRI.[181] A negative MRI thus may improve enrollment and long term outcomes for active surveillance candidates by ruling out the presence of occult lesions and confirming that presumed low-risk disease is truly low-risk. mpMRI may also improve retention of men in active surveillance programs by obviating the need for frequent repeat biopsies. Finally, MRI appears to be useful in detecting occult clinically significant disease among active surveillance candidates whose initial biopsy demonstrates only Gleason 6 disease. If it is employed, mpMRI should be performed on at minimum a 1.5 Tesla magnet MRI and include diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC), T2-weighted (T2W) imaging, and dynamic intravenous contrast-enhanced (DCE) imaging.[93,181,182] The interpretation and reporting of mpMRI information should be performed by a radiologist experienced in the interpretation of prostate mpMRI and conform to the the guidelines described in the Prostate Imaging Reporting and Data System (PI-RADS) v2.[183] It should be noted that MRI as a single modality is not able to detect all Gleason 7 or higher tumors, potentially exposing a small subset of men to delayed treatment of clinically significant cancer. The Panel does not recommend the use of mpMRI in place of prostate biopsy at this time.

TABLE 5: Active Surveillance

Reference	*n*	Median follow-up (months)	% treated overall; % treatment free	Overall/disease specific survival (%)	% BCR post deferred treatment
Klotz (2015) Canada[66]	993	92	30; 72 at 5 years	79/ 97 at 10 years	25 (6 overall)
Tosoian (2015) United States[7]	1298	60	50 at 10 years 57 at 15 years	69/99.9 at 15 years	NR
Bul (2013) Multicenter, Europe[167]	2500 2494	20	21	77/100 at 10 years	20
Dall'Era (2008) United States[168]	328 321	43	24; 67 at 5 years	100 (disease-specific)	NR
Kakehi (2008) Multicentre, Japan[169]	118	36	51; 49 at 3 years	NR	NR
Roemeling (2007) Netherlands[170]	273	41	29; 71 at 5 years	89/100 at 5 years	NR
Barayan (2014) Canada[171]	155 155	65	20	100/100	NR
Rubio-Briones (2014) Spain[172]	232	36	27	93 at 5 years/99.5	NR
Godtman (2014)[173]	439		63	81/99.8	14
Thomsen (2013) Denmark[174]	167	40	35; 60 at 5 years	NR	NR
Selvadurai (2014) United Kingdom[175]	471	67	30	98/99.7	12

32. Tissue based genomic biomarkers have not shown a clear role in active surveillance for localized prostate cancer and are not necessary for follow up. (Expert Opinion)

The lethal potential of prostate cancer is difficult to predict with precision based on stage, grade, and PSA level. The presence of only Gleason pattern 3 predicts for a favorable clinical outcome. However, the limitation of systematic biopsies is the pathologic miss of higher-grade cancer in 25-30% of patients.[184,185]

Earlier identification of patients with co-existent higher-grade cancer is a major unmet need in the field. The challenge for tissue-based genetic tests is to provide more accurate risk stratification than currently available optimally used clinical tools and predictive modeling in a way that is reasonably cost effective.

The role of tissue based genomic biomarkers for patients on active surveillance during follow up remains uncertain. RNA expression profiles of selected gene panels can be performed on small samples of cancer in biopsy specimens to predict prognosis more accurately. Genomic analyses of prostate cancer reveal distinct patterns of alterations in the genotype that may predict prognosis more accurately.

While such assays have sufficient analytic and clinical validity, their clinical utility in active surveillance remains to be established. In particular, these assays were validated in the pre-MRI era. Their incremental value in the context of men who have had a mpMRI is unclear. An additional concern regarding the use of biopsy-based molecular biomarkers is the sampling error inherent in prostate biopsy given known tumor heterogeneity.

The proportion of men whose clinical risk category is substantially altered by molecular tests, particularly in men with low-risk disease, is relatively minor. However, in the future these assays may have the greatest incremental value at the time of diagnosis in reassuring selected men who have 'low-risk' (versus very low-risk) disease (for example, men with extensive Gleason 6 cancer and/or high PSA density, or a strong family history of early death from prostate cancer); and in those in whom clinical findings are discordant with the pathological findings on follow up (for example, men with a PI-RADS 4-5 lesion on MRI whose targeted

biopsy is negative or shows only Gleason 6 cancer).

33. Clinicians should offer definitive treatment to localized prostate cancer patients undergoing active surveillance who develop adverse reclassification. (Moderate Recommendation; Evidence Level: Grade B)

For patients who elect active surveillance as a management approach (versus watchful waiting) there is an assumption that active treatment should be initiated upon the detection of adverse features that may change the patient's risk category. This may be due either to an incorrect original classification or to true progression from a lower-risk to a higher-risk category.[67,186] Thus, if there is adverse reclassification due to the detection of a higher Gleason score than was present at the initiation of surveillance, definitive treatment should be considered. Other factors that may lead to adverse reclassification include growth of lesion on mpMRI and suspicious rises in PSA that may change PSA density.[187] In the PIVOT and ProtecT studies, 20% and 50%, respectively, of patients who started on active surveillance received treatment within 10 years.[50,51]

PROSTATECTOMY

34. Clinicians should inform localized prostate cancer patients that younger or healthier men (e.g., <65 years of age or >10 year life expectancy) are more likely to experience cancer control benefits from prostatectomy than older men. (Strong Recommendation; Evidence Level: Grade B)

Compared to other cancers, prostate cancer is typically a slowly evolving disease. Numerous studies exploring its natural history have suggested that, even if high-grade and left untreated, disease specific survival is a median of 8-10 years after diagnosis.[139,188-193] It is, therefore, unlikely that men with short life expectancy will benefit from treatment. It is also unlikely that clinical trials following patients for a shorter interval than 8-10 years will be able to demonstrate a survival advantage attributable to the intervention being studied. In comparison to watchful waiting, the survival benefit from radical prostatectomy was observed predominantly in the <65 year old age group.[96] While the older group did not experience a statistically significant decrease in mortality, these older men nonetheless demonstrated a trend towards longer life and a significant decrease in metastases. Two other studies with short follow up failed to demonstrate that age was significantly associated with survival after radical prostatectomy.[50,51] However, even at 10 years follow up, one of them did find an increased risk of metastases among younger men, a finding highly suggestive of future risk of prostate cancer mortality.

35. Clinicians should inform localized prostate cancer patients that open and robot-assisted radical prostatectomy offer similar cancer control, continence recovery, and sexual recovery outcomes. (Moderate Recommendation; Evidence Level: Grade C)

Data from a prospective RCT in Australia found no difference in margin status between open and robotic approaches. Ten percent of patient in the open and 15% of patients in the robotic group had a positive surgical margin (p=0.21). Follow up was very limited in these patients, so long term outcomes are not known.[194] The Health Professionals Follow up study also found no difference in oncologic outcomes between the two surgical approaches, including no difference in positive surgical margin rates, and no difference in recurrence-free survival at three and five years of follow up, odds ratios 0.98 [95%CI, 0.46-2.08] and 0.75[95%CI, 0.18-3.11], respectively.[195] A matched comparison study of open and robotic radical prostatectomy found no significant difference in biochemical progression free survival at three years. While these data are limited, all indicate that the surgical approach does not impact cancer control in the immediate term.

Urinary incontinence is one of the most distressing side effects of radical prostatectomy, even when limited in duration and severity. Multiple studies have found no statistical difference in the rates of continence after open, robotic, or perineal radical prostatectomy.[194-197]

All surgical approaches confer a risk of erectile dysfunction after radical prostatectomy, and this must be discussed with patients preoperatively. There is no statistically significant difference in retrospective, prospective non-randomized, and prospective randomized trials in the rate and recovery of erectile function if an open, laparoscopic, or robotic assisted laparoscopic approach is used.

36. Clinicians should inform localized prostate cancer patients that robotic/laparoscopic or perineal techniques are associated with less blood loss than retropupic prostatectomy. (Strong Recommendation; Evidence Level: Grade B)

Radical prostatectomy has a risk of bleeding requiring transfusion whether it is performed open or via a

minimally invasive approach, such as pure laparoscopic or robotic assisted laparoscopic surgery. Patients must be informed prior to surgery of this risk, and patient preferences regarding transfusion must be considered accordingly. Two randomized trials found a lower rate of transfusion with minimally invasive approaches compared to open surgery.[194,197] In a prospective randomized trial of open radical retropubic prostatectomy versus robotic assisted laparoscopic prostatectomy from Australia, there was a mean estimated blood loss of 1,338ml for open surgery compared to 443ml for robotic surgery, p<0.001. There were no intraoperative transfusions due to use of cell saver, but six patients in the open group had postoperative transfusions compared to one in the robotic group. This difference was not statistically significant p=0.12.[194,197] A prospective non-randomized trial in Sweden also found statistically less perioperative bleeding with a robotic approach, 185ml, versus an open approach, 683cc p<0.001. The Health Professionals follow up study similarly found a lower estimated blood loss (207ml versus 852ml) and a lower transfusion rate (4.3% versus 30%) associated with robotic assisted laparoscopic radical prostatectomy compared to open radical retropubic prostatectomy (P<0.0001).

37. **Clinicians should counsel localized prostate cancer patients that nerve-sparing is associated with better erectile function recovery than non-nerve sparing. (Strong Recommendation; Evidence Level: Grade A)**

Early experience with radical prostatectomy was marked by large intraoperative blood loss and near-certain postoperative erectile dysfunction. Advances in anatomic understanding of pelvic anatomy and advances in surgical technique allowed for the preservation of the neurovascular bundles containing the cavernous nerves responsible for penile tumescence. Preservation of the neurovascular bundles during radical prostatectomy allowed for the possibility of erections in 50-95% of men, a strong proof of principle. Prospective registries have demonstrated that nerve-sparing prostatectomy improved post-operative sexual function as well as overall QoL.[32,198] This benefit appears to exist irrespective of surgical approach, as no difference has been observed in erectile dysfunction between robotic assisted laparoscopic radical prostatectomy as compared to open radical prostatectomy, where nerve sparing techniques are possible; however, erectile dysfunction was less in retropubic radical prostatectomy as compared to perineal prostatectomy, where nerve sparing is typically not possible.

38. **Clinicians should not treat localized prostate cancer patients who have elected to undergo radical prostatectomy with neoadjuvant ADT or other systemic therapy outside of clinical trials. (Strong Recommendation; Evidence Level: Grade A)**

Four randomized prospective studies compared three months of neoadjuvant ADT followed by radical retropubic prostatectomy to radical prostatectomy alone.[199-202] In all four studies, at up to seven years of follow-up, there was no significant difference in biochemical (PSA) recurrence between the groups. Therefore, there is no long-term oncologic benefit to adding neoadjuvant ADT to radical prostatectomy for localized prostate cancer. A randomized, prospective study of neoadjuvant docetaxel combined with ADT followed by radical prostatectomy compared to radical prostatectomy alone for high risk prostate cancer is ongoing, so this combination is still considered investigational.[203]

39. **Clinicians should inform localized prostate cancer patients considering prostatectomy, that older men experience higher rates of permanent erectile dysfunction and urinary incontinence after prostatectomy compared to younger men. (Strong Recommendation; Evidence Level: Grade B)**

Patient age has been recognized to be a key determinant of post-prostatectomy sexual recovery since the earliest studies of nerve-sparing prostatectomy by Walsh, and the pivotal role of patient age as an indicator of erectile function recovery has been validated in two multicenter prospective cohorts (CaPSURE and PROSTQA).[32,204-207] Predictive models indicate approximately 15-20% reduction in probability for recovery of erections firm enough for intercourse for each decade of life from age 50 to 70.[204,208-210] It commonly takes one to two years to achieve maximal recovery of erectile function. Patients considering prostatectomy should be counseled accordingly.

Older age has also been shown to reduce the pace and extent of post-prostatectomy urinary continence recovery.[32,205,211] For example, studies evaluating patient-reported pad-use, as a measure of urinary incontinence, showed that the relative risk of incontinence increases 2 fold for men 70 years of age compared to men at 60 years of age (14% versus 7% incontinence at 1 year, when defined as use of more than one pad daily).[212,213]

40. Pelvic lymphadenectomy can be considered for any localized prostate cancer patients undergoing radical prostatectomy and is recommended for those with unfavorable intermediate-risk or high-risk disease. Patients should be counseled regarding the common complications of lymphadenectomy, including lymphocele development and its treatment. (Expert Opinion)

Pelvic lymphadenectomy (PLND) is the most effective means of detecting nodal metastases. Variability in the reported rates of nodal metastases reflects both primary tumor characteristics and the extent of PLND. Several reports have clearly shown that extended PLND is associated with a higher lymph node detection rate as compared with limited PLND, regardless of prostate cancer aggressiveness.[214] The primary lymph nodes draining the prostate are extensive, as high as the aorta and inferior vena cava in the retroperitoneum.[215] About 40% of the primary lymph nodes are contained within a standard dissection limited to the obturator fossa; about two-thirds of the primary nodes are contained within an extended template that includes the obturator fossa and the tissue medial and lateral to the internal iliac vessels.[216]

Evidence is lacking as to whether or not the removal of lymph nodes containing metastatic prostate cancer has therapeutic benefit. Several studies suggest an extended PLND improves biochemical relapse-free survival,[217-219] but this finding has not been consistently observed, particularly with more limited dissections.[220-223] Even if improved biochemical-free survival translates to improved prostate cancer-specific survival, removal of all primary nodes is not feasible.[216] There is no curative benefit from having negative lymph nodes removed, although one study demonstrated a modest (0.8%) improved prostate cancer-specific and overall survival compared to patients who did not undergo a lymph node dissection at the time of radical prostatectomy. Nomograms have been developed to predict the likelihood of having histologically positive nodes.[214,225]

Lymphocele is the most common complication of PLND occurring in up to 60% of cases.[226] Most lymphoceles are asymptomatic and require no treatment.[227] Symptomatic lymphoceles occur in 0.4% to 16% of patients,[226] and can be managed by placing a percutaneous drain and instilling sclerosing agents with resolution between 70–100 % depending on the study and type of sclerosing agent being used. In lymphoceles refractory to percutaneous drainage and sclerosis, minimally invasive marsupialization of the lymphocele is recommended.[226]

41. Clinicians should inform localized prostate cancer patients with unfavorable intermediate -risk or high-risk prostate cancer about benefits and risks related to the potential option of adjuvant radiotherapy when locally extensive prostate cancer is found at prostatectomy. (Moderate Recommendation; Evidence Level: Grade B)

SWOG 8794 randomized subjects to adjuvant radiotherapy or no adjuvant after prostatectomy and showed that adjuvant radiotherapy was associated with temporary or early gastrointestinal (Grade 1-2 in 59% in adjuvant group versus 7% in controls) and urinary (37% in adjuvant versus 18% in controls) toxicity at 6 weeks after treatment. These side effects subsided to no difference between the treatment arms at five years.[228] Although a single non-randomized prospective study has implicated late Grade 2 urinary toxicity in 10% of subjects receiving adjuvant radiotherapy,[229] a single-institution RCT showed no difference in urinary continence at one year.[230] These RCT's are flawed in that they relied on clinician report, which is prone to underestimate morbidity, and did not measure treatment-specific morbidity by contemporary patient-report methodology.

RADIOTHERAPY

42. Clinicians may offer single modality external beam radiotherapy or brachytherapy for patients who elect radiotherapy for low-risk localized prostate cancer. (Clinical Principle)

While active surveillance is the preferred management strategy, radiotherapy can be considered as an alternative for low-risk prostate cancer in patients who select treatment at diagnosis or during follow-up.[50,231] Various radiotherapy options exist with unique treatment and technical issues related to each modality.[232,233] Options for treatment include intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), low-dose rate brachytherapy, and high-dose rate brachytherapy.[234-237]

IMRT is a form of external beam photon therapy that uses multiple radiation beam and/or arcs to provide a highly conformal treatment of the prostate with normal tissue sparing of adjacent organs, such as the rectum and bladder. SBRT generally utilizes photon-based IMRT treatment to deliver hypofractionated radiation

treatment usually in five or fewer fractions of treatment. Low-dose rate brachytherapy utilizes radioactive seeds that are implanted based of pretreatment and intraoperative image-guidance according to a computer plan. High-dose rate brachytherapy uses temporary catheters implanted in the prostate to allow for the delivery of a high-activity radiation source. All allow for the delivery of highly conformal radiotherapy. There is no evidence that combinations of therapies are required for the treatment of low-risk prostate cancer given the low-risk of extra capsular disease extension and the favorable biochemical control rates associated with the use of monotherapy.

43. Clinicians may offer external beam radiotherapy or brachytherapy alone or in combination for favorable intermediate-risk localized prostate cancer. (Clinical Principle)

Radiotherapy can be considered as an appropriate option for intermediate-risk prostate cancer.[50,231] Various radiotherapy options exist with unique treatment and technical issues related to each modality.[232,233] Options for treatment include IMRT, SBRT, low-dose rate brachytherapy, and high-dose rate brachytherapy.[234-237]Additionally, combination therapy of external beam combined with brachytherapy can be also be delivered using various combinations (IMRT combined with either low-dose or high-dose rate brachytherapy). The rationale of combination therapy can be either for the improved coverage of the periprostatic space and/or planned coverage of the pelvic lymph nodes in patients with unfavorable intermediate risk disease.[238] High-level prospective clinical trials to define the most appropriate radiation treatment to optimize clinical outcomes for intermediate-risk prostate cancer continues to emerge in the literature. Results of the RTOG 0232 trial assessing low-dose brachytherapy with and without EBRT have been reported and published in abstract form while complete findings are awaited.

44. Clinicians should offer 24-36 months of ADT as an adjunct to either external beam radiotherapy alone or external beam radiotherapy combined with brachytherapy to patients electing radiotherapy for high-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade A)

Two randomized trials have compared EBRT with short-term versus long-term ADT. EORTC 22961 randomized 1,113 men with high-risk prostate cancer to EBRT plus 6 versus 36 months of ADT.[135] Five-year overall mortality was 19% for short-term ADT and 15% for long-term ADT. RTOG 9202 randomized patients to EBRT plus 4 versus 28 months of ADT.[239] In the subgroup of patients with Gleason 8-10 disease, 5-year overall survival was 71% for short-term ADT and 81% for long-term ADT. Based on these trials, acceptable ADT durations for radiotherapy patients with high-risk prostate cancer range from 24-36 months. A randomized trial that compared radiotherapy plus 18 versus 36 months ADT in high-risk patients has not been published with mature data; at this time it is unknown if 18 months of ADT is an acceptable duration.

Radiation treatment options for high-risk prostate cancer include IMRT, and IMRT plus brachytherapy (low - or high-dose rate). There are little data of long-term efficacy of SBRT in high-risk prostate cancer, and this modality is not recommended.

In high-risk patients without evidence of nodal metastasis based on imaging, radiation treatment may electively include pelvic nodal areas because published nomograms demonstrate that these patients have a risk of harboring micrometastatic nodal disease. Whether pelvic radiotherapy improves survival is the subject of a current randomized trial. Prior randomized trials comparing prostate-only versus prostate and pelvic radiation treatment have not demonstrated improved survival from electively adding pelvic radiation.[240-242]

45. Clinicians should inform localized prostate cancer patients that use of ADT with radiation increases the likelihood and severity of adverse treatment-related events on sexual function in most men and can cause other systemic side effects. (Strong Recommendation; Evidence Level: Grade B)

ADT can cause sexual side effects, hot flashes, decreased bone mineral density, gynecomastia, depression, fatigue, and weight gain. A variety of strategies have been studied to help mitigate these effects.[243] Patient-reported sexual dysfunction of radiotherapy plus short-term ADT versus radical prostatectomy was compared in a randomized trial, with the latter associated with more sexual dysfunction through six years of follow-up.[52] Patients who receive long-term ADT versus short-term ADT experience these symptoms for a longer period of time. However, in the EORTC 22961 trial, long-term overall QoL was similar in the two arms, likely suggesting patient adaptation to the ADT-associated symptoms over time.[135]

There is a risk of non-recovery of testosterone in a

subset of patients after ADT. In a published study of patients who received 2 years of ADT, 93% recovered to supracastrate testosterone levels while 72% recovered to baseline or normal testosterone levels.[244] Younger patients are more likely to have testosterone recovery.

46. Clinicians should consider moderate hypofractionation when the localized prostate cancer patient (of any risk category) and clinician decide on external beam radiotherapy to the prostate (without nodal radiotherapy). (Moderate Recommendation; Evidence Level: Grade B)

Traditionally, radical EBRT is usually delivered with standard daily fractionation schedules with about 1.8-2.0Gy per day.[245] The rationale for this approach is that most tumors are thought to have rapid proliferation and are best treated with standard fractionation schedules to best take advantage of the high alpha-beta ratio associated with such situations.[245] Alpha-beta values describe the curvature of a cell survival curve after exposure to various doses of radiotherapy. The alpha-beta ratio is the dose where cell killing due to the linear and quadratic components are equal. There is mounting evidence that certain tumors (e.g., prostate, sarcoma, and melanoma) may be associated with lower proliferation and hence with an associated lower alpha-beta ratio.

Recently, a series of RCTs have been published to inform the potential of moderate hypofractionation given with modern radiation technology as well as what is considered by many to be adequate doses to optimize biochemical control in both the standard (1.8-2.0Gy/day) and experimental (hypofractionation) arms for these studies. The CHHiP trial randomized 3,216 men to one of three treatment arms (74Gy standard fractionation, 60Gy hypofractionation at 3 Gy/fraction, and 57Gy hypofractionation at 3 Gy/fraction).[246-248] Sixty Gy in 20 fractions was found to be non-inferior to 74Gy in 37 fractions (HR 0.84 (90% CI 0.68-1.03) in terms of biochemical and/or clinical failure. No differences in side effects were noted between the study groups.

The short-term non-inferiority of modern moderate hypofractionated external beam radiotherapy have been replicated in two other non-published RCTs; however, the main limitation of these studies is the lack of long-term follow-up in terms of clinically important cancer control and toxicity outcomes. Patients at risk for late effects of radiotherapy (including but not limited to pre-existing lower urinary tract symptoms [LUTS], transurethral resection of the prostate [TURP], and anticoagulant usage) may be better served with conventional fractionation (1.8-2.0 Gy/day).

47. For localized prostate cancer patients with obstructive, non-cancer-related lower urinary function, surgical approaches may be preferred. If radiotherapy is used for these patients or those with previous significant transurethral resection of the prostate, low-dose rate brachytherapy should be discouraged. (Moderate Recommendation; Evidence Level: Grade C)

Because EBRT and brachytherapy, especially the latter, can cause acute urinary obstructive and irritative symptoms,[32] patients with significant baseline urinary obstructive symptoms may prefer radical prostatectomy. Another relative contraindication for brachytherapy is large prostate size >60 cc because of increased risk of urinary side effects.[249] A prior TURP is an absolute contraindication for brachytherapy if the defect precludes adequate placement of seeds.[21]

Relative contraindications to EBRT and brachytherapy include inflammatory bowel disease and history of prior pelvic radiotherapy due to increased risk for treatment-related morbidity.[250] Ataxia telangiectasia is an absolute contraindication to both EBRTand brachytherapy because these patients have a severe response to ionizing radiation.[250]

48. Clinicians should inform localized prostate cancer patients who are considering proton beam therapy that it offers no clinical advantage over other forms of definitive treatment. (Moderate Recommendation; Evidence Level: Grade C)

The predominant forms of EBRT are delivered by photon therapy (either generated by a machine such as a linear accelerator or by a radioactive source such as a cobalt-60 unit) or electrons (usually used for superficial tumors/targets).[251] Proton therapy utilizes proton charged particles with superior dosimetric advantages over photons and electrons as they stop depositing dose at an energy-dependent distance from the treatment source; therefore, sparing of tissue beyond this distance can be accomplished.[251] In situations where targets are in close proximity to normal tissue organs, the proton approach may lead to dosimetric advantages to other radiation techniques.

In the specific context of prostate cancer, very limited information exists in relation to the comparative effectiveness of proton therapy compared to other

radiation techniques or other modalities of treatment.[251] In a 2012 SEER Medicare retrospective population-based analysis, photon-based IMRT was compared to proton therapy in terms of various clinical endpoints.[252] No difference was found in terms of most treatment-related morbidities except for a lower rate of gastrointestinal toxicity associated with IMRT when compared to proton therapy.[252]

The lack of evidence demonstrating clinical advantages of proton therapy over other forms of radiation and non-radiation treatment has led to the ABIM Foundation Choosing Wisely statement endorsed by ASTRO: "Don't routinely recommend proton beam therapy for prostate cancer outside a prospective clinical trial or registry."[253] It is advised that prospective clinical trials are necessary to establish the potential advantage(s) of this treatment over other therapies prior to wider adoption of this form of treatment.[253] A National Cancer Institute randomized phase III trial is underway comparing proton versus photon beam radiotherapy for low- and low-intermediate-risk prostate cancer with a health-related QoL primary endpoint.

49. Clinicians should inform localized prostate cancer patients considering brachytherapy that it has similar effects as external beam radiotherapy with regard to erectile dysfunction and proctitis but can also exacerbate urinary obstructive symptoms. (Expert Opinion)

Prospective QoL research showed that both EBRT and brachytherapy led to modest rates of bloody stools, rectal pain, and overall bowel problems.[32] In addition, EBRT and brachytherapy resulted in similar rates of erectile dysfunction symptoms and overall sexuality problems.[32]

WHOLE GLAND CRYOSURGERY

50. Clinicians may consider whole gland cryosurgery in low- and intermediate-risk localized prostate cancer patients who are not suitable for either radical prostatectomy or radiotherapy due to comorbidities yet have >10 year life expectancy. (Expert Opinion)

Cryosurgery can be an appropriate treatment option for men with intermediate-risk prostate cancer who are not suitable candidates for prostatectomy (i.e. due to comorbidities, such as morbid obesity or a prior history of pelvic surgery),[115] or who have relative contra-indications to radiotherapy (i.e. due to including previous pelvic radiation, inflammatory bowel disease, or rectal disorders).[115] The paucity of RCT's evaluating cryosurgery limits knowledge regarding its comparative efficacy: only two RCT's of cryosurgery have been reported; both included neoadjuvant ADT (whose benefit with cryosurgery has not been formally shown) in a comparison to EBRT; the multicenter RCT was aborted before half of the target accrual goal had been reached, whereas the only study that completed target accrual was a single center study. Neither RCT was powered to evaluate comparative cancer-specific or overall mortality. The one completed (albeit single-center) randomized trial of EBRT (with adjuvant ADT) versus cryosurgery (also with adjuvant ADT) for clinically localized disease demonstrated comparable biochemical recurrence-free survival at three, five, and seven years' follow-up.[76] Actuarial five-year overall survival and disease-specific survival were also similar. Notably, cryosurgery showed lower rate of persistent primary cancer on study-mandated prostate biopsy at 36 months (8% after cryotherapy vs 29% for EBRT). However, sample size and duration of follow-up was insufficient to determine whether or not cryosurgery has long-term cancer-specific or overall survival efficacy comparable to EBRT. The trial population was comprised principally of patients who would be categorized as intermediate risk based on Gleason score and PSA criteria (35% Gleason score =6, 55% Gleason score =7, median PSA= 9; DRE not reported), constituting the basis for the Panel's recommendation of this modality for low and intermediate risk disease.

The second randomized trial comparing cryosurgery versus EBRT was predominantly comprised of men with locally advanced disease, but also included patients with high risk localized (T2c) prostate cancer, and demonstrated long-term biochemical recurrence-free survival for cryosurgery to be remarkably inferior to that following EBRT (17% versus 59%, respectively, at 8 years median follow-up).[141]Based on the inferior efficacy of cryosurgery compared to EBRT in this limited trial, it is the Panel's judgment that high-risk patients are less suited for this treatment. Moreover, high risk patients may require multimodal/salvage therapy, and clinicians should consider lymph node dissection prior to or in conjunction with cryosurgery.[115-117]

Prostate gland volume is a factor in patient selection in that it can be difficult to achieve uniform cold temperatures throughout the organ.[77,115,117] Most investigators have not recommended treating glands that exceed 60 g with cyrosurgery.

51. Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery that cryosurgery has similar progression-free survival as did non-dose escalated external beam radiation (also given with neoadjuvant hormonal therapy) in low- and intermediate-risk disease, but conclusive comparison of cancer mortality is lacking. (Conditional Recommendation; Evidence Level: Grade C)

One randomized clinical trial of non-dose escalated EBRT versus cryosurgery has been reported for localized prostate cancer with primarily intermediate- and high-risk disease patients (114 and 117 in each arm respectively). Fifty eight patients in the EBRT arm received <70 Gy. The primary endpoint of short-term (36 months) biochemical recurrence-free survival (PSA nadir + 2 ng/ml) was comparable for cryosurgery and EBRT (17% and 13% respectively).[76] Cryosurgery and radiotherapy patients alike received 6 months of neoadjuvant ADT, and secondary endpoints of actuarial 5-year overall survival (88.5% versus 89.7%) and disease-specific survival (96% in both groups) were also similar. Cryosurgery showed lower rate of persistent primary cancer on study-mandated prostate biopsy at 36 months (8% after cryotherapy versus 29% after EBRT). However, the study was not powered to compare cancer survival or overall survival, and long-term data beyond 10 years are also lacking. Of note, even though neoadjuvant ADT was consistently given with cryosurgery in the two trials that compared cryosurgery to radiotherapy, neoadjuvant ADT in cryosurgery has not been demonstrated to improve oncologic outcomes compared to cryotherapy alone. Conversely, multicenter trials comparing cryosurgery *without* neoadjuvant ADT to other prostate cancer treatment modalities are lacking. At three years, the cryosurgery patients reported slightly lower sexual function, slightly better urinary function, and comparable bowel function outcomes in comparison to the EBRT patients.[254]

52. Defects from prior transurethral resection of the prostate are a relative contraindication for whole gland cryosurgery due to the increased risk of urethral sloughing. (Clinical Principle)

The urethral warming catheter may fail to fully contact the urethral mucosa in patients with a TURP defect increasing the likelihood for urethral necrosis, sloughing, dysuria, and urinary retention.[115] Cryosurgery is contraindicated in patients who cannot have transrectal ultrasound guidance and monitoring of probe placement and the ablation cycle, such as surgical absence of the rectum from a previous abdominal perineal resection.

53. For whole gland cryosurgery treatment, clinicians should utilize a third or higher generation, argon-based cryosurgical system for whole gland cryosurgery treatment. (Clinical Principle)

Optimal oncologic and QoL outcomes of whole gland cryosurgery are achieved with a third generation, argon -based cryosurgical system. In addition to a urethral warming catheter, real-time ultrasound monitoring of the advancing ice ball is recommended.[115] A double freeze-thaw cycle is standard protocol as numerous studies have demonstrated greater likelihood of complete cell kill and treatment zone devascularization.[115,255] The advancing hyperechoic margin identified on TRUS is approximately 0°C with the inner edge representing the point of intracellular ice formation at approximately -15°C to -20°C.[256] The desired nadir temperature at the prostate capsule to ensure complete cell kill is -40°C.[115,256]

54. Clinicians should inform localized prostate cancer patients considering cryosurgery that it is unclear whether or not concurrent ADT improves cancer control, though it can reduce prostate size to facilitate treatment. (Clinical Principle)

The Panel is unaware of any conclusive studies evaluating whether or how the use of concurrent ADT enhances or mitigates the oncologic efficacy of cryosurgery. Nevertheless, the addition of ADT to cryosurgery is common. Two randomized trials of EBRT versus cryosurgery have been reported with primarily intermediate-risk, high-risk, or locally advanced disease patients. Both utilized 6 months of perioperative ADT for both treatment arms. One study of primarily localized prostate cancer reported similar actuarial 5-year overall and disease –specific survival.[76] The other study, terminated early for lack of accrual and consisting of primarily high-risk or locally advance disease patients demonstrate an inferior 8-year biochemical disease-free recurrence rate for the cryosurgery and ADT arm (17% vs. 59%).[141] For glands greater than 40 g, neoadjuvant ADT (3-6 months) should be considered due to the potential technical challenges from pubic arch interference and increased difficulty in achieving uniform temperatures.[115]

55. Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery that erectile dysfunction is an expected outcome. (Clinical Principle)

Available evidence has shown that erectile dysfunction should be expected the usual outcome for potent patients undergoing whole gland ablation. In a 2009 review of the literature, Langenhuijsen and colleagues concluded that most patients (80-90%) should expect erectile dysfunction after whole gland cryosurgery and that it should not be offered to patients who desire preservation of potency.[77] In one RCT sexual function outcomes for cryosurgery were inferior to EBRT.[76] In non-randomized cohort studies, sexual function outcomes for cryosurgery were also inferior to brachytherapy[257,258] and comparable to radical prostatectomy.[258] To improve the likelihood of erectile function recovery, nerve-sparing and focal prostate cryosurgery has been reported.[259] However, focal ablation cryosurgery lacks robust long-term oncologic data.

56. Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery about the adverse events of urinary incontinence, irritative and obstructive urinary problems. (Strong Recommendation; Evidence Level: Grade B)

As with all treatments, in addition to the high risk of erectile dysfunction, patients considering cryosurgery should be informed about the risks of adverse urinary and bowel quality of life outcomes. Urinary retention after cryosurgery can persist for a few weeks and is best managed with a urethral or suprapubic catheter. Urethral sloughing at the verumontanum where the urethral warming catheter may not fully contact the mucosa apposition can result in temporary bothersome irritative symptoms in the early recovery period. Urethral fistula with third generation cryosurgical systems and thermocouple monitoring is very rare (0.5%) in primary treatment cases. [77,115] Permanent urinary incontinence can be expected in less than 10% of patients. [77,115] In the only completed RCT comparing cryosurgery to EBRT, cryosurgery patients reported modestly better urinary function outcomes three years after treatment.[254] In the only other randomized trial comparing cryosurgery to EBRT (which was comprised predominantly of patients with locally advanced disease, but also included patients with high risk localized disease and was aborted before reaching half of the accrual goal), cryosurgery patients reported less gastrointestinal toxicity and comparable genitourinary complaints than those who received EBRT.[260] In non-randomized cohort comparisons to brachytherapy, cryosurgery patients reported slightly less incontinence (11.3% versus 18.2% respectively)[257] but comparable urinary function and urinary bother outcomes.[258] In a non-randomized comparison to radical prostatectomy, cryosurgery patients showed modestly better urinary function and bother outcomes.[258]

HIFU AND FOCAL THERAPY

The Panel recommends that if HIFU is offered as an alternative treatment modality for localized prostate cancer, it should be done within the context of a clinical trial. Prospective randomized or comparative trials with other treatment modalities are lacking. Published five year oncologic outcomes are variable and attributable to the lack of consensus on objective response criteria.[78] However, it has been recognized that the PSA nadir level after whole gland HIFU is predictive of biochemical recurrence.[261] The Panel awaits the results of well-designed comparative clinical trials in order to define the appropriate role of this technology in the management of localized prostate cancer. Whole prostate ablation utilizing HIFU with or without short term neoadjuvant ADT has been associated with a comparable incidence of post-treatment incontinence, bladder neck/urethral stricture, and rectourethral fistulae.[262]

Focal therapy is based on the concept that, although prostate cancer can present as multifocal disease within the prostate gland, some patients may have a significant single index intraprostatic lesion. This index lesion may be associated with the most aggressive nidus of cancer within the gland and may be the most appropriate target for treatment. A prerequisite for focal therapy involves advanced mapping of lesions within the prostate. This can be done with a saturation biopsy or, more commonly, with MRI imaging with focused biopsy or a 3-dimensional transperineal mapping biopsy to identify appropriate patients with clinically significant disease, to provide an appropriate index target, and to provide an appropriate target for follow-up scanning and biopsies.[118,125]

Focal therapy involves subtotal or zonal destruction of the prostate with cryosurgery, HIFU or other focally ablative techniques with the aim to minimize treatment toxicity. The Panel acknowledges that focal ablative therapy is of significant interest to patients and clinicians as it may offer benefits in terms of QoL for selected patients with a solitary well-defined index lesion. However, the Panel recommends that if focal therapy is offered as an alternative treatment modality

for localized prostate cancer, it should only be done within the context of a clinical trial. Initial studies with short term follow up suggest that effective disease eradication in the treated volume can be attained.[118,124] A systematic review of focal therapy has been published to provide some information regarding the clinical outcomes that can be expected with the application of focal therapy.[124] However, it should be noted that long-term follow up data is lacking. The Panel recognizes that concern exists about the potential for undetected and, therefore, occult untreated clinically-significant multifocal disease. Confirmation of oncologic effectiveness is currently lacking and will require prospective studies with long-term follow up.

57. Clinicians should inform those localized prostate cancer patients considering focal therapy or HIFU that these treatment options lack robust evidence of efficacy. (Expert Opinion)

The Panel recognizes that novel therapies including HIFU and focal prostate ablation may provide QoL advantages for patients in comparison to surgery and radiotherapy. However, there is a lack of consensus on objective response criteria, very limited long-term oncologic data, and, importantly, no comparative effectiveness data versus traditional treatments available. For patients with intermediate- and high-risk disease treated with HIFU, neoadjuvant ADT has been demonstrated to reduce PSA recurrence, but long-term oncologic effectiveness is unknown.[262] For focal therapy, initial reports with short term follow-up suggest effective disease eradication in the treated area of appropriately selected patients. Studies where TRUS biopsy of the treated volume or side was performed per protocol, clinically significant cancer was identified in a minority (<14%) of patients.[122-124] A recent consensus conference acknowledge that with increasing experience, prostate volume may not be a primary determinant for denying focal therapy.[263] However, given the concern about the potential for undetected and untreated occult multifocal disease, agreement on robust endpoints and confirmation of oncologic effectiveness in larger series with longer follow-up is currently lacking. When discussing such novel therapies as HIFU and focal therapy, clinicians should inform patients of the lack of robust long term oncologic data and how this relates to the patient's own life expectancy and the significant potential for recurrence and/or new prostate cancer development. Patients should also be informed that the appropriate treatment for disease progression and the risk of metastatic progression remain undefined.

58. Clinicians should inform localized prostate cancer patients who are considering HIFU that even though HIFU is approved by the FDA for the destruction of prostate tissue, it is not approved explicitly for the treatment of prostate cancer. (Expert Opinion)

Most treatments for prostate cancer, such as surgery, radiation, and cryosurgery, predate mandated regulation by the FDA. Thus, by the time the FDA started to control what treatments could be delivered, all three of these treatments were grandfathered as approved for prostate cancer. However, this was not the case for HIFU. Initial attempts were made to get HIFU approved for treatment of prostate cancer. To accomplish this, the FDA mandated a clinical trial of HIFU versus another similar treatment, and cryosurgery was chosen. However, due to poor accrual, this trial never completed. In further discussion with the FDA, it was felt that the FDA may accept an alternative indication for HIFU – destruction of prostate tissue. Thus, after submitting a revised application, ultimately, on October 9th, 2015 the FDA approved HIFU for destruction of prostate tissue. To date, HIFU is still not approved for treatment of prostate cancer.

As noted, no other modern treatment for prostate cancer had to obtain similar regulatory approvals. Thus, the fact that HIFU is not FDA approved for treating prostate cancer does not necessarily mean it is inferior to other treatments. However, the fact that it is not approved has implications for patients. While discussion of costs of care is beyond the purview of the Panel, the Panel did agree that patients should be informed of the lack of FDA approval for treating prostate cancer and the potential implications of this ruling.

59. Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)

Physicians may have difficulty fully ablating anterior tumors in patients with prostate volumes greater than 40 g due to the limited focal length of the HIFU technology. Post-treatment MRI has demonstrated a margin of untreated anterior tissue in such patients.[264] In addition, to minimize possible thermal injury to the external urethral sphincter and risk incontinence, it is common practice to initiate HIFU several millimeters proximal to the apical capsule and rely on heat diffusion to ablate the apical margin. However this can increase

the risk of incomplete treatment in patients with apical tumors. Employing a 6 mm apical safety margin Boutier et al. reported on 99 patients (mean prostate volume of 24 g) who underwent systematic prostate biopsies 3-6 months after treatment.[265] Of patients with residual cancer, 60% were in the apical sextants, 24% in the mid gland, and 16% in the base.

Limited data suggest whole gland HIFU ablation is not optimally suited for men with a prostate >40 g due to limited focal length of technology and higher rates of urinary retention. The mean prostate volume in virtually all HIFU series is less than 40 g. This is due to the limited focal length of the technology preventing the ability to treat anterior tumor extension, increase in procedure time, and higher rates of urinary retention.[78,262] TURP or neoadjuvant ADT prior to HIFU for patients with large prostates can prevent post-procedure urinary retention and reduce prostate volume.[78,266]

60. As prostate cancer is often multifocal, clinicians should inform localized prostate cancer patients considering focal therapy that focal therapy may not be curative and that further treatment for prostate cancer may be necessary. (Expert Opinion)

The hypothesis of treating only the dominant lesion to minimize toxicity is attractive to the patient and clinician.[118,267] However, the Panel agrees that patients should be counseled that a subset of non-index cancers in the prostate may have a higher grade and, if untreated, pose a risk.[118] In addition, patients should be informed that there is no consensus on objective response criteria. The prevailing opinion is that patients should undergo a targeted and template post-treatment biopsy approximately one year after treatment to assess for residual viable cancer. A rising PSA or suspicious areas on mpMRI should also trigger biopsy.[263] Residual clinically significant cancer may be detected in targeted biopsies in a small but significant percentage of patients requiring additional therapy.[123,263] Men should also be informed that after any focal or ablative treatment, follow up biopsies will still be required.

V. OUTCOME EXPECTATIONS AND MANAGEMENT

TREATMENT SIDE EFFECTS AND HEALTH RELATED QUALITY OF LIFE

61. Clinicians should inform localized prostate cancer patients that erectile dysfunction occurs in many patients following prostatectomy or radiation, and that ejaculate will be lacking despite preserved ability to attain orgasm, whereas observation does not cause such sexual dysfunction. (Strong Recommendation; Evidence Level: Grade B)

In counseling patients about potential QoL effects after different treatment options, it is important to provide data based on modern treatment technologies. Because surgical and radiation technologies have evolved significantly over time, QoL results from patients treated in an older era likely do not represent the results of patients treated today.

In a prospective QoL study, poor erections increased from 14% of patients (pre-treatment) to 58% at 2 years after radical prostatectomy (increase of 44%), 37% to 60% after EBRT (increase of 23%), and 30% to 51% after brachytherapy (increase of 21%).[32] While patients after surgical or radiation treatments may lack ejaculate, many preserve the ability to attain orgasm.[32] The proportions of patients who reported difficulty with orgasm from before to 2 years after treatment were 12% to 42% (radical prostatectomy), 32% to 50% (external beam radiotherapy), and 24% to 45% (brachytherapy). In addition, climacturia can occur in 30% of patients after radical prostatectomy.[268]

Time course of sexual dysfunction differs between radical prostatectomy and radiation treatment (both EBRT and brachytherapy). Radical prostatectomy causes an immediate worsening of sexual function, with recovery over two years of time afterwards.[32,52] EBRT and brachytherapy cause a more modest acute decline of sexual function after treatment, also with partial recovery thereafter.[32,52] Adding ADT to prostatectomy or radiotherapy adds to the sexual dysfunction.[32] Erectile dysfunction of radiotherapy plus three to six months of ADT versus radical prostatectomy was compared in a randomized trial.[52] Approximately 67% of men reported erections firm enough for intercourse at baseline, which declined to 17% at 6 years after radical prostatectomy, 27% after radiotherapy with ADT, and 30% in the active monitoring group. A study of patients diagnosed in 1994-95 and assessed long-term patient-reported QoL showed that sexual function was similar after radical prostatectomy and EBRT from 5 to 15 years after treatment.[53]

Non-treatment (active surveillance or watchful waiting) does not directly cause sexual dysfunction except for worsening of function and symptoms related to aging.

62. Clinicians should inform localized prostate cancer patients that long-term obstructive or irritative urinary problems occur in a subset of

patients following observation or active surveillance or following radiation, whereas prostatectomy can relieve pre-existing urinary obstruction. (Strong Recommendation; Evidence Level: Grade B)

A small but significant subset (10-20%) of men with localized prostate cancer, have problematic obstructive LUTS at the time of cancer diagnosis, and a similar number will develop obstructive symptoms *de novo* while on observation or surveillance, or after radiotherapeutic or ablative treatment.[47,51,269-271] Pre-existing obstructive LUTS can be mitigated by prostatectomy, representing a notable clinical scenario wherein prostatectomy for localized prostate cancer can result in *improvement* rather than *impairment* of health related QoL. [269,271]

63. Clinicians should inform localized prostate cancer patients that whole-gland cryosurgery is associated with worse sexual side effects and similar urinary and bowel/rectal side effects as those after radiotherapy. (Strong Recommendation; Evidence Level: Grade B)

In the single randomized clinical trial comparing EBRT and cryosurgery,[76] the short-term sexual function was worse for cryosurgery than EBRT.[254] At 3 years, men in the cryosurgery group experienced lower sexual function scores compared with EBRT (16.0 versus 36.7, $p<0.001$), there was no difference in bowel function scores, and men in the EBRT group had slightly lower urinary function scores compared to cryosurgery (88.6 versus 93.0, $p=0.049$), but this difference is of questionable clinical significance. Longer-term data comparing these side effects of cryosurgery and EBRT from this study are lacking.

Three nonrandomized studies of lower quality compared cryosurgery to brachytherapy for urinary, bowel and sexual outcomes.[257,258,272] The findings were not consistent. In one study patients treated with brachytherapy had significantly more incontinence and sexual dysfunction, but less bowel events, than patients treated with cryosurgery.[257] In another study, patients treated with cryosurgery had more incontinence than those treated with brachytherapy (10 year rate brachytherapy 0.61 versus cryosurgery 2.44).[272] In the third study, the authors did not perform a test of statistical significance for this comparison, so the results are inconclusive for bowel, urine and sexual outcomes.[258]

64. Clinicians should inform localized prostate cancer patients that temporary urinary incontinence occurs in most patients after prostatectomy and persists long-term in a small but significant subset, more than during observation or active surveillance or after radiation. (Strong Recommendation; Evidence Level: Grade A)

Urinary incontinence is a well-known side effect of radical prostatectomy. The magnitude of urinary incontinence is most profound in the first few months after prostatectomy, when incontinence is commonplace, during which time QoL in the urinary domain is significantly worse after prostatectomy then it is among patients who undergo radiotherapy or surveillance (which are not associated with early incontinence). Notably, urinary incontinence subsides to be small to no bother for most men by one year post-prostatectomy. Beyond one year after treatment, urinary continence is moderately (or more) bothersome for 5-25% of men, whereas urinary obstructive or irritative symptoms are similarly bothersome for 5-15% of men after radiotherapy or during active surveillance. This pattern of urinary incontinence and recovery following prostatectomy, contrasted to the pattern of obstructive and irritative symptoms during surveillance or after radiotherapy, has been demonstrated in multiple RCTs and prospective, multi-center cohorts alike. [32,51,52,64,271,273]

65. Clinicians should inform localized prostate cancer patients that temporary proctitis following radiation persists in some patients long-term in a small but significant subset and is rare during observation or active surveillance or after prostatectomy. (Strong Recommendation; Evidence Level: Grade A)

In counseling patients about potential QoL effects after different treatment options, it is important to provide data based on modern treatment technologies. Because surgical and radiation treatment technologies have evolved significantly over time, QoL results from patients treated in an older era likely do not represent the results of patients treated today.

A prospective randomized trial comparing active surveillance, radical prostatectomy, and 3D-conformal radiotherapy reported QoL outcomes in these three groups of patients.[52] The proportion of patients who reported loose stools increased after radiotherapy (15.6% at baseline to 25.1% at 6 months, absolute increase 9.5%), but subsequently declined to baseline levels (15.5%) at 72 month follow-up. Bloody stools also increased modestly after radiotherapy, from 1.6% at baseline to 5.6% at 72 months (absolute increase

4.0%). Another study published in 2008 of patients who received IMRT demonstrated the absolute increase of bloody stools from baseline to 2 years to be 4%, rectal pain 2%, bowel urgency 13%, frequency 8%, and incontinence 1%.[32] Increases in symptoms are similar after brachytherapy.[32]

These data show that radiation treatment causes proctitis affecting <10% of patients for most symptoms. It is possible that with more modern radiation technology (image guided radiotherapy), risk of proctitis could be less. Proctitis is not expected after radical prostatectomy or in patients who receive no treatment.[52]

POST-TREATMENT FOLLOW UP

66. Clinicians should monitor localized prostate cancer patients post therapy with PSA, even though not all PSA recurrences are associated with metastatic disease and prostate cancer specific death. (Clinical Principle)

Initial therapy for localized prostate cancer is intended to cure the cancer. Remission/possible cure is variably defined; however, a reasonable definition of long-term remission and likely cure is no evidence of PSA or radiographic progression 10 years after initial localized therapy. Remission after prostatectomy is defined as nadir PSA $\leq$ 0.2 ng/ml and in the context of radiation +/- ADT nadir PSA <2.0 ng/ml with testosterone recovered if previous ADT. PSA surveillance after local therapy is recommended for at least 10 years with PSA frequency determined by risk of relapse and patient preferences for monitoring. PSA monitoring beyond 10 years can be considered in men with high risk of relapse and long life expectancy.

Patients should be informed that salvage therapies with potential for cure are available. Salvage therapy after prostatectomy includes radiation with or without ADT. The cure rates for salvage radiation vary according to patient risk factors, such as Gleason score, time to PSA failure after prostatectomy, and PSA doubling time. Salvage therapies after radiation are heterogeneous and include prostatectomy, HIFU, cryosurgery, and repeat radiation. Many of the post-radiation salvage approaches have either high potential for toxicity or low or unclear rates for cure and the pros and cons of localized salvage therapy after radiation should be carefully considered with the patient.

It is recommended that the treating physician carefully explain the goals of therapy and probability for cure. In addition the definitions of relapse after curative therapy should be outlined. It is important to educate the patient of the kinetics of testosterone recovery after ADT and expected concomitant rise in PSA. The natural history of relapsed prostate cancer is extremely variable. The important clinical metrics include time to metastasis and death from prostate cancer. The definition of metastatic prostate cancer and a clear differentiation of the difference between PSA relapse, metastasis and death from prostate cancer should be explained to the patient.[274] With indolent PSA relapse or in men with competing morbidities, no additional therapy for prostate cancer may ever be needed. Patients are often focused on PSA levels and can't differentiate between PSA relapse and death from prostate cancer. In the setting of indolent PSA relapse it is paramount that the treating physician relieve patient stress and anxiety by educating the patient and family of the long natural history of relapsed marker only prostate cancer and in most cases the low chance of death from prostate cancer within 10 years of local therapy.

67. Clinicians should inform localized prostate cancer patients of their individualized risk-based estimates of post-treatment prostate cancer recurrence. (Clinical Principle)

An accurate assessment of the risks of failure and success for prostate cancer treatment are essential to good patient counseling and SDM. While the 5-year relative survival for prostate cancers diagnosed in 2005 to 2011 (most recent data) are 99% for localized disease; many factors, such as tumor grade and stage as well as patient race, family history and age, play an important role in determining a personalized prognosis.[275] In order to synthesize all of an individual's personal and cancer-specific characteristics, there are a number of published predictive models and nomograms offering prognosis of pathologic stage, biochemical recurrence after treatment, as well as development of metastatic disease and likelihood of survival after treatment.[276-278] For the most part, these prognostic tools focus on the most common, evidence-based treatment modalities, such as surgery and radiotherapy, while some attempt to predict outcomes such as biochemical recurrence and positive follow up biopsies after treatment with therapies such as cryosurgery.[279,280] Genomic testing can add to risk stratification of men with adverse pathological features or biochemical recurrence following initial treatment.[281-283]

68. Clinicians should support localized prostate cancer patients who have survivorship or outcomes concerns by facilitating symptom management and encouraging engagement with professional or community-based resources. (Clinical Principle)

Potential resources to consider include psychosocial support (referral to social worker for patients experiencing distress), local prostate cancer support groups, and national/international prostate cancer patient advocacy groups that can provide information and further support (e.g., the Urology Care Foundation, the Prostate Health Education Network, Us TOO, and ZERO – the End of Prostate Cancer). Prostate cancer patients and survivors should also be offered available survivorship programs to help improve functional outcomes, psychological and other health needs.

VI. FUTURE DIRECTIONS

The extended time course between prostate cancer diagnosis and its eventual outcome poses challenges to the timeliness of ascertaining the efficacy of newer approaches to cancer risk ascertainment or therapeutic intervention. The maturation of evidence to provide robust guidance for optimizing care consequently lags the development of new technology. Nevertheless, emerging evidence is anticipated in several key areas, while well-designed, multi-center studies are urgently needed in others.

Emerging evidence is anticipated from follow up analyses of the ProtecT randomized trial comparing active surveillance, prostatectomy, and radiotherapy. Data maturation may elucidate longer term outcomes (i.e. whether or not differences seen in clinical metastases between arms at 10 years will lead to differences in subsequent mortality). Subsequent analyses of ProtecT also have the potential to further clarify the role of surveillance versus treatment between low and intermediate risk cancers. Emerging evidence is also anticipated from clinical trials evaluating the risk benefit of brachytherapy compared to external radiotherapy (RTOG 0232), and the relative risk/benefit of extended compared to standard lymphadenectomy during radical prostatectomy for patients with intermediate and high risk disease.

Well-designed prospective studies are needed to optimize the utility of new imaging modalities (e.g., multiparametric MRI or PET with prostate-specific radiotracers), to evaluate risk/benefit of ablative techniques (e.g., HIFU or focal ablative treatment), and to characterize the impact that even limited intervals of androgen-deprivation may have on long-term HRQOL. The need to better characterize long-term HRQOL effects of ADT warrants special emphasis, as this treatment modality is part of the standard recommended radiotherapy care options for intermediate and high risk disease and is already broadly utilized. We need better evidence to council patients regarding the impact of adjuvant androgen deprivation on long-term HRQOL, despite recognition that effects on vitality, libido, and cognitive status can be substantial among patients undergoing ADT monotherapy.

To enable progress in prostate cancer care that is informed by the best evidence we must continue to prospectively evaluate new technologies as they are developed.

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All panel members completed COI disclosures. Disclosures listed include both topic– and non-topic-related relationships.

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DISCLAIMER

This document was written by the Clinically Localized Prostate Cancer Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2014. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology/ medical oncology/radiation oncology with specific expertise on this disorder. The mission of the Panel was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of clinically localized prostate cancer.

Funding of the Panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the Panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.