Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part II: Recommended Approaches and Details of Specific Care Options

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Abbreviations and Acronyms

ADT = androgen deprivation therapy
DRE = digital rectal examination
EBRT = external beam radiotherapy
HIFU = high intensity focused ultrasound
MRI = magnetic resonance imaging
PIVOT = Prostate Cancer Intervention Versus Observation Trial
PLND = pelvic lymphadenectomy
ProtecT = Prostate Testing for Cancer Treatment Trial
PSA = prostate specific antigen
QoL = quality of life
RCT = randomized clinical trial
SDM = shared decision making
SPCG-4 = Scandinavian Prostate Cancer Group Study Number 4

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Purpose: This guideline is structured to provide a clinical framework stratified by cancer severity to facilitate care decisions and guide the specifics of implementing the selected management options. The summary presented herein represents Part II of the two-part series dedicated to Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline discussing risk stratification and care options by cancer severity. Please refer to Part I for discussion of specific care options and outcome expectations and management.

Materials and Methods: The systematic review utilized in the creation of this guideline was completed by the Agency for Healthcare Research and Quality and through additional supplementation by ECRI Institute. This review included articles published between January 2007 and March 2014 with an update search conducted through August 2016. 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. Additional information is provided as Clinical Principles and Expert Opinions (table 2 in supplementary unabridged guideline, http://jurology.com/).

Results: The AUA (American Urological Association), ASTRO, and SUO (Society of Urologic Oncology) formulated an evidence-based guideline based on a risk stratified clinical framework for the management of localized prostate cancer.

Conclusions: This guideline attempts to improve a clinician's ability to treat patients diagnosed with localized prostate cancer, but higher quality evidence in future trials will be essential to improve the level of care for these patients. In all cases, patient preferences should be considered when choosing a management strategy.

Key Words: prostate, prostatic neoplasms, guideline

RECOMMENDED APPROACHES AND DETAILS OF SPECIFIC CARE OPTIONS

Active Surveillance

For patients who elect active surveillance as a management approach, surveillance should include at least annual prostate specific antigen testing and digital rectal exam as part of the surveillance strategy to help guide considering definitive treatment if the severity of cancer progresses. Periodic re-biopsy to

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monitor cancer grade, and MRI to monitor tumor size or invasiveness, can further inform the surveillance process.

In the Prostate Testing for Cancer Treatment Trial, which showed similar survival with active surveillance versus radiotherapy or radical prostatectomy, trial subjects on active surveillance had only regular PSA testing and DREs performed. While the optimal frequency of PSA and DRE has not been established, ProtecT prescribed PSA testing every 3 months in the first year, then every 6 to 12 months thereafter with DRE performed during urology follow-up visits.[1]

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.[2,3] 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 or invasion on multiparametric MRI and suspicious rises in PSA that may change PSA density.[4] In the Prostate Cancer Intervention Versus Observation Trial and ProtecT studies, approximately 20% and 50%, respectively, of patients who started on active surveillance received treatment within 10 years.[1,5]

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 DRE. (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

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.[6-12] It is, therefore, unlikely that men with short life expectancy will benefit from prostatectomy or other 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 men in the Scandinavian SPCG-4 trial,[13] Even though men > 65 years of age did not experience a significant decrease in mortality in SPCG-4, these older men demonstrated a trend towards longer life and decrease in metastases. In the American PIVOT, prostatectomy was associated with survival advantage over watchful waiting among men having PSA over 10 ng/ml and among those having cancer severity with intermediate or worse risk by clinical criteria.

Population-based observational studies and limited prospective trials have shown that blood loss and transfusion rates are lower when radical prostatectomy is performed using robot-assisted laparoscopic technique as compared to an open retropubic technique. Other outcomes, including cancer control, urinary incontinence, and erectile dysfunction, were found not to be different between robot-assisted laparoscopic and open retropubic approaches in these studies.

Pelvic lymphadenectomy is the most effective means of detecting regional nodal metastases.[14] However, evidence is lacking as to whether or not the removal of lymph nodes containing metastatic prostate cancer has therapeutic benefit. This, coupled with knowledge that PLND carries specific risks, such as lymphocele, has tempered enthusiasm for routine pelvic lymphadenectomy, and supports the option of recommending PLND based on cancer severity.[15-21]

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 neo-adjuvant androgen deprivation therapy (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. **PLND 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

Various radiotherapy options exist with unique treatment and technical issues related to each modality.[22,23] Options for treatment include intensity modulated radiotherapy, stereotactic body radiotherapy, low dose rate brachytherapy, and high-dose rate brachytherapy.[24-27]

Intensity modulated radiotherapy is a form of external beam radiotherapy that uses multiple radiation beams 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. Stereotactic body radiotherapy generally utilizes photon-based intensity modulated radiotherapy 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 on 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.

Additionally, combination therapy of EBRT combined with brachytherapy can also be delivered using various combinations (intensity modulated radiotherapy 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.[28] High-level prospective clinical trials to define the most appropriate radiation treatment to optimize clinical outcomes continues to emerge in the literature.

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

43. **Clinicians may offer EBRT 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 EBRT alone or EBRT 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 EBRT 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 EBRT with regard to erectile dysfunction and proctitis but can also exacerbate urinary obstructive symptoms. (Expert Opinion)**

Whole Gland Cryosurgery

Cryosurgery can be an appropriate treatment option for men with low or 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),[29] or who have relative contraindications to radiotherapy (i.e. previous pelvic radiation, inflammatory bowel disease, or rectal disorders).[28] The paucity of randomized controlled trials evaluating cryosurgery limits knowledge regarding its comparative efficacy: only two RCTs 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 RCT 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 of follow-up.[30] Actuarial five-year overall survival and disease-specific survival were also similar. Notably, cryosurgery showed a lower rate of persistent primary cancer on study mandated prostate biopsy at 36 months (8% after cryotherapy versus 29% for EBRT). However, sample size and duration of follow-up were 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 (33% Gleason score 6, 55% Gleason score 7, median PSA 9), constituting the basis for the Panel's recommendation of this modality for low and intermediate risk disease.

Prostate gland volume is a factor in patient selection in that it can be difficult to achieve uniform cold temperatures throughout the organ.[31,32] Most investigators have not recommended treating glands that exceed 60 g with 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 EBRT (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. (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, and irritative and obstructive urinary problems. (Strong Recommendation; Evidence Level: Grade B)**

High Intensity Focused Ultrasound 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.[33]

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 with focused biopsy or a three-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.[34,35]

The Panel acknowledges that focal ablative therapy is of significant interest to patients and clinicians as it may offer benefits in terms of quality of life for selected patients with a solitary well-defined index lesion. Initial studies with short-term follow-up suggest that effective disease eradication in the treated volume can be attained.[34,36] 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.[36] However, it should be noted that long-term follow-up data are 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)**

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 QoL

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.

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 preexisting 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)**

Posttreatment Follow-Up

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. The natural history of relapsed prostate cancer is extremely variable. The important clinical metrics include time to metastasis and death from prostate cancer. An accurate assessment of the risks of failure and success for prostate cancer treatment are essential to good patient counseling and shared decision making.

Prostate cancer patients and survivors should also be offered available survivorship programs to help improve functional outcomes, psychological and other health needs.

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 outcome concerns by facilitating symptom management and encouraging engagement with professional or community-based resources. (Clinical Principle)**

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.

Emerging evidence is anticipated from follow-up analyses of ProtecT comparing active surveillance, prostatectomy, and radiotherapy. Such subsequent analyses 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 EBRT, and the relative risk/benefit of extended compared to standard PLND 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, to evaluate risk/benefit of ablative techniques, and to characterize the impact that even limited intervals of ADT may have on long-term health related QoL.

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.

Please refer to Part I of the guideline for discussion of risk stratification and care options by cancer severity.

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.

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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 intended 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.

CONFLICT OF INTEREST (COI) DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic and non-topic related relationships. Any author not listed had nothing to disclose.

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