LOCALIZED PROSTATE CANCER

INITIAL EVALUATION AND MANAGEMENT OPTIONS

Needs Assessment

In 2016, the Prostate Cancer Advisory Council released the guidelines for the evaluation and detection of prostate cancer in Florida men. The guidelines provide clarity to Florida men at risk for prostate cancer. This is in an environment of widespread contradictory and confusing information about the overall value of prostate cancer screening. PSA-based screening resulted in a powerful 60% reduction in metastasis at the time of diagnosis and a 40% reduction in prostate cancer mortality compared to the pre-screening era. However, concerns for over-diagnosis and ensuing over-treatment, generated by several population studies, suggested a small overall survival benefit to treatment. As a result, widely accepted guidelines not to screen reduced the nationwide prostate cancer incidence by 30% including 23% less diagnosis of high-risk prostate cancer in 2013. The over-riding concern, of course, is that prostate cancer true incidence is unchanged or rising and that detection rates from lack of discovery account for the decline.

The Florida Cancer Data System identified 11,395 new prostate cancer diagnoses in 2013 and 2,110 deaths from prostate cancer the same year. 63% of Florida men were screened for prostate cancer. There were disparities between race, age, education, income status and health insurance coverage as to screening rates. 60% of blacks were screened as opposed to 64% of whites. The FCDS is currently making increased efforts to correct the possible under reporting of prostate cancer related to VA and private practice diagnosis and management.

The risk for prostate cancer diagnosis, subsequent risk of mortality related to disease as well as treatment side effects are pertinent questions for the Florida male. Not all Florida men diagnosed with prostate cancer need treatment. There is growing clinical evidence that active surveillance may be appropriate for up to 40% of patients. Not all Florida men diagnosed with prostate cancer get the treatment they need. The Florida Cancer Atlas noted regional as well as county to county differences in prostate cancer diagnosis, treatment and mortality. Disease related factors certainly play a role in the observed differences. However, non-clinical factors such as access to health care and health literacy factor into the delivery and decisions for treatment. Variation in care may also be a result of geographic and demographic diversity within the state. Regardless, standards of care and management will narrow disparities, lessen variation and target at-risk populations, which may result in reduction of prostate cancer mortality in the state.

Men with prostate cancer receive incomplete information regarding the appropriate evaluation when newly diagnosed with prostate cancer. Many men undergo unnecessary tests leading to over-utilization of resources. They also receive conflicting information regarding management options for localized prostate cancer.

The focus of this document is to serve as a primary resource for Florida patients and providers involved in treatment decisions regarding the initial management of localized prostate cancer. The report does not address treatment decisions related to advanced, refractory or relapsing prostate cancer management.

Risk Stratification

Risk stratification at the time of diagnosis of prostate cancer is recommended to enhance treatment selection, predict presence of metastatic disease, and provide prognostic information following treatment. The key elements included in risk stratification include the findings from digital rectal examination, pre biopsy serum PSA results, and prostate biopsy findings. Table 1 lists the components included in standard risk stratification. The most commonly employed risk stratification model utilized is based upon outcomes of patients undergoing definitive radiation therapy or radical prostatectomy. The best use of the risk stratification system will occur when all components have been evaluated and included. The findings obtained from the digital rectal exam should be used to assign a clinical T stage to the cancer. The clinical T stage is based upon the tumor size, location, and involvement of adjacent organs as detailed in Table 1. The pre biopsy PSA value is important in differentiating between low, intermediate and high risk groups. PSA density is calculated based upon the pre biopsy PSA and prostate volume noted on prostate ultrasound. In the presented risk stratification system, PSA density is only utilized in assigning very low risk disease.

Once prostate cancer has been noted in the biopsy specimens the pathologist will report the number of cores involved, the percentage of cancer noted in each biopsy core, and the grade of prostate cancer within each involved core. It is important to ensure that the prostate biopsy performed has included at least 12 cores evaluating all regions of the prostate. In patients with less than 12 cores sampled or limited sampling of all regions of the prostate, the biopsy data may not accurately represent the true volume or grade of the cancer. Repeat biopsy in patients with less than 12 cores may be recommended, especially in patients considering active surveillance. The number of cores involved and the percentage of each core involved with cancer has an impact on the assigned risk categories as listed in Table 2. As with other cancers, a higher grade is indicative of having a more aggressive cancer. For years the Gleason scoring system has been utilized to assign the grade of prostate cancers. The Gleason score is calculated by adding the two most prominent grades noted within tumor and can range from 2-10. In contemporary series it is rare for a Gleason score to be less than 3+3=6, which is considered low risk. In order to simplify the Gleason scoring system a grade grouping system has been proposed. This grade grouping system will report a grade as I (3+3=6), II (3+4=7), III (4+3=7), IV (Gleason score 8), and V (Gleason score 9-10). It is becoming more common for the pathologist to report both the Gleason score and the corresponding grade grouping.

Table 1

Clinical and Pathologic Features used for risk stratification

Digital rectal exam
• T1
  o No palpable tumor or not visible on imaging
• T2
  o T2a tumor involves one half or less than one lobe
  o T2b tumor involves more than one half of one lobe but not both lobes
  o T2c tumor involves both lobes
• T3
  o T3a extracapsular extension (unilateral or bilateral)
  o T3b tumor involves seminal vesicle(s)
• T4
  o Tumor is fixed or invades adjacent structures other than seminal vesicles
PSA
PSA Density
• Calculated based upon pre biopsy PSA value and prostate volume measured by ultrasound performed at the time of biopsy
Prostate Biopsy
• Gleason score/grade group
• Number of cores involved
• % of cancer within individual cores

While it is very common for patients to undergo imaging studies for the staging of other malignancies, radiographic staging is only recommended prostate cancer patients classified as having high risk disease at the time of diagnosis. Additional radiographic staging is not recommended in patients with low and intermediate risk disease due to the reported rates of metastatic disease being less than 5% in these patient populations. Approximately 15% of newly diagnosed patients will be classified as having high risk disease and are recommended to undergo additional radiographic staging to rule out the presence of metastatic disease prior to initiating definitive therapy. Ruling out metastatic disease in this population is important due to the associated increased rate of metastatic disease and the dramatic change in recommended treatments in patients with documented metastatic disease. The risk of having metastatic disease ranges from 7-90% in high risk patients, depending on individual risk factors. Standard radiographic evaluation for patients with high risk disease prior to treatment should include cross sectional imaging of the abdomen and pelvis and a whole body bone scan. CT and MRI imaging are performed primarily to assess nodal staging and evaluation of nodal metastasis is based on radiographic node size. While these imaging modalities have a specificity approaching 100% their sensitivity remains low, <10%, due to the poor detection of metastatic lymphatic invasion. Whole body bone scan is utilized for detecting bone metastasis which will be present in 7-39% of patients with PSA values between 20-50 ng/ml, 19-90% of patients with T3 disease, and 17-30% of patients with Gleason 8 disease. The specificity of bone scans is low due to the common findings of non-cancer related abnormalities, however the negative predictive value is >85% in patients with normal bone scans. At this time PET CT scan is not considered a routine component of staging prostate cancer at the time of initial diagnosis.

Table 2

Risk Category	Clinical and Pathologic Features
Very Low	cT1c Gleason score ≤6/grade group I PSA < 10 ng/ml Fewer than 3 positive biopsy cores, ≤50% cancer in each core PSA density <0.15 ng/ml/g
Low	T1-T2a Gleason score ≤6/grade group I PSA < 10
Intermediate	T2b-T2c or Gleason 3+4=7/grade group II or Gleason 4+3=7/grade group III or PSA 10-20 ng/ml
High	T3a or Gleason score 8/grade group IV or Gleason score 9-10/grade group V PSA >20 ng/ml
Very High	T3b-T4 or Primary Gleason pattern 5/grade group 5 or Greater than 4 cores with Gleason score 8-10/grade group IV or V

With the proper data in place a risk category can be assigned as presented in Table 2. The presented risk stratification system is endorsed by the National Comprehensive Cancer Network and is considered when recommending treatment approaches. In addition to the risk stratification system based upon clinical and pathologic tumor features, a patient's other medical conditions and life expectancy must be taken into consideration when making treatment decisions. It is important to note that if a patient is asymptomatic and has a less that 5-year life expectancy that no additional evaluation or treatment of their prostate cancer is recommended. Table 3 outlines recommended treatment options based upon patient life expectancy and tumor risk stratification.

Table 3 (Adapted from NCCN guidelines)

Risk Stratification Group	Treatment Options
Very Low	Life Expectancy ≥ 20 years • Active Surveillance • Radiation Therapy • Radical Prostatectomy Life Expectancy 10-20 years • Active Surveillance Life Expectancy <10 years • Observation
Low	Life Expectancy ≥10 years • Active Surveillance • Radiation Therapy • Radical Prostatectomy Life Expectancy <10 years • Observation
Intermediate	Life Expectancy ≥10 years • Radiation Therapy • Radical Prostatectomy Life Expectancy <10 years • Radiation Therapy • Observation
High	Radiation Therapy plus Androgen Deprivation Therapy Radical Prostatectomy with Lymph node dissection
Very High	Radiation Therapy plus Androgen Deprivation Therapy Radical Prostatectomy with Lymph node dissection Androgen Deprivation Therapy alone

Management options

- Active Surveillance
- Surgery
- Radiation Therapy
- Alternative Modalities
  - Cryotherapy
  - HIFU
  - RFA

Active Surveillance

Rationale:

Active Surveillance for men with prostate cancer involves scheduled and careful monitoring and results in the avoidance or postponement of immediate treatment. Low risk prostate cancer may never require treatment. Additionally, postponing treatment may not significantly reduce the chance for cure. Patients on active surveillance, therefore, can be spared the potential side effects of treatment as well as the cost. With appropriate surveillance, patients can subsequently be reclassified to higher risk for progression and receive definitive treatment at that time.

Patient selection:

The critical issue in the choice of active surveillance is the identification of patients at low or very low risk for prostate cancer progression over an extended time-period. Inclusion criteria include:

1. Low pathological grade (Gleason 6)
2. Low stage (clinically localized T1 or T2a)
3. Low volume (no more than 2 cores positive and no more than 50% positive of any core based on an at least 10 core biopsy)
4. PSA less than 10 ng/mL, PSAD less than 0.15 ng/mL

Additional inclusion/exclusion criteria for AS may include assessment of risk factors related to age, life expectancy, race, family history and patient preference. For patients with a life expectancy less than 5 years and low-grade prostate cancer, watchful waiting (WW) without repeated prostate biopsy may be more appropriate. On the other hand, patients with a life expectancy greater than 20 years will potentially be subjected to decades of invasive surveillance testing and may need to be considered for treatment at diagnosis. Other diagnostic tests for assessment of progression risk include mpMRI to optimize patient selection for active surveillance and subsequent monitoring as well as molecular prognostic tests.

From the standpoint of race-related risk, African American ethnicity is associated with an increased incidence of prostate cancer, which includes earlier age of onset, higher PSA levels, higher Gleason scores and more advanced disease at presentation. These associations are multifactorial and may, in part, reflect issues related to access to health care as well as genetic and environmental factors. There is data to reflect an increased risk for progression of disease for African American men on active surveillance.

Surveillance Strategy:

The primary parameters for monitoring AS patients for potential progression of disease include PSA, DRE and repeat prostate biopsy. No clinical studies have defined the appropriate testing intervals or criteria to trigger active treatment intervention. The JOP Prostate Cancer Clinical Guidelines from 11/2014 suggest a PSA at six-month intervals, annual DRE and confirmatory biopsy at 12-18 months. The JOP recommended subsequent biopsies at every 12-24 month intervals. Variable guidelines exist for the interval of subsequent prostate biopsies and range from one year (NCCN) to as high as 5 years (Cancer Care Ontario).

PSA parameters that may trigger a re-assessment include a doubling time of less than 3 years or a rise of PSA value greater than 10 to 15.

The initial confirmatory prostate biopsy is intended to detect higher-grade disease that may have been missed on the original positive biopsy. Subsequent biopsies and/or MRI are intended to detect biological progression.

Outcomes:

In the PRIAS study of 5302 patients with low-risk prostate cancer, 52% of men at 5 years and 73% of men at 10 years had discontinued active surveillance. 62% did so because of biopsy reclassification to higher risk disease. In the Johns Hopkins experience, 1298 men were followed for a median of 5 years with annual prostate biopsy. The cumulative incidences of up-grading were 26% at 10 years and 31% at 15 years. The 10 and 15-year rates of curative intervention were 50 and 57% respectively. The 15-year prostate-cancer-mortality was only 0.4% and emphasized the extremely low risk of active surveillance as a management strategy. Quality of life analyses suggest that AS is associated with a higher quality-adjusted life expectancy than initial treatment with external beam radiation therapy or radical prostatectomy.

Summary:

Active surveillance plays a significant role in the management of low-risk prostate cancer and may be appropriate in up to 40% of patients initially diagnosed. All treatment choices depend on the informed patient decision with full knowledge of advantages and disadvantages associated with treatment and non-treatment approaches.

Surgery

The goals of surgical therapy for prostate cancer are to remove all of the cancer while limiting urinary and sexual side effects. During the surgery the entire prostate and seminal vesicles are removed, a pelvic lymph node dissection will be performed in select patients. Following removal of the prostate the remaining bladder is sutured to the urethra. A catheter will be left in place for 7-14 days while the patient heals from surgery. Patient selection for surgery is very important, consideration must be given to a patient's life expectancy, competing health conditions, risk of disease recurrence, and patient tolerance of potential treatment related side effects. Many of the potential complications of prostatectomy are not unique to this surgery including bleeding requiring blood transfusion, infection, and injury to adjacent organs. The occurrences of these complications are low, occurring in less than 5% of patients. Specific complications associated with prostatectomy include: urinary incontinence, erectile dysfunction, bladder neck contracture and urine leak.

Prior to surgery, careful discussions must occur regarding impact on sexual function, urinary function, and potential for positive surgical margins. Controlled urination should be achieved in over 80% of men within 12 months of surgery. Recovery of erectile function can be noted in 25-80% within 12 months of surgery. Critical components for recovery of erectile function following surgery are the quality of erections prior to surgery, patient age, and the extent of nerve sparing that can be performed at the time of surgery. Unfortunately, nerve sparing surgery cannot be offered to all patients due to extent of disease which may necessitate excision the nerves at the time of surgery.

The surgery can be accomplished with a standard open approach or a laparoscopic (with or without robotic assistance) approach. Less often employed approaches include perineal prostatectomy or a pure laparoscopic prostatectomy. A lymph node dissection may be omitted in low risk patients due to the low, <5%, risk of lymph node metastasis in this patient population. The cure rates achieved with prostatectomy are closely associated with pathologic tumor staging and the surgical margin status.

If adverse pathology features are reported present in the prostate specimen (extracapsular extension, extension of cancer to the surgical margin or the seminal vesicles) there is an increased risk of cancer recurrence and cancer mortality after 10 years from surgery. Thus, a detailed discussion with the patient must proceed to address the risks and benefits of proceeding with radiation therapy within six months from surgery. This treatment approach is called adjuvant radiation therapy. Three randomized prospective studies have demonstrated a decrease in cancer recurrence and mortality with the use of adjuvant radiation therapy.

Following prostatectomy patients are monitored for cancer recurrence by monitoring PSA values. The PSA level should be undetectable after surgery. A rising PSA following surgery is typically the first sign that the cancer has returned, and is considered a biochemical recurrence. Biochemical recurrence, or a rising PSA, within 10 years of surgery is noted in 18%, 35%, and 45% of low, intermediate, and high risk patients respectively. Death from prostate cancer within 10 years of surgery is noted in 0.3%, 3%, and 5% of low, intermediate, and high risk patients respectively.

Radiation Therapy

Various radiotherapy options exist with unique treatment and technical issues related to each modality. Options for treatment include intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), low-dose rate brachytherapy, and high-dose rate brachytherapy. -

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 on pretreatment and intraoperative image-guidance according to a computer optimized planning algorithm.

High-dose rate brachytherapy uses temporary catheters implanted in the prostate to allow for the delivery of a high-activity radiation source, again based on image-guidance and optimization algorithms.

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.

Options for **intermediate-risk prostate cancer** include IMRT, SBRT, low-dose rate brachytherapy, and high-dose rate brachytherapy. Additionally, combination therapy of external beam combined with brachytherapy can be also considered.

For **high-risk prostate cancer** 24-36 months of androgen deprivation therapy (ADT) as an adjunct to either external beam radiotherapy alone or external beam radiotherapy combined with brachytherapy is recommended.

ADT can cause sexual side effects, hot flashes, decreased bone mineral density, gynecomastia, depression, fatigue, and weight gain. Patients who receive long-term ADT versus short-term ADT experience these symptoms for a longer period of time.

Hypofractionation

Traditionally, EBRT is delivered with standard daily fractionation schedules with about 1.8-2.0 Gy per day. The rationale for this approach is that most tumors are thought to have rapid proliferation and are best treated with standard fractionation. There is mounting evidence that certain tumors, including prostate cancer, may be effectively treated with accelerated regimens of external beam radiotherapy employing daily dose fractions of 3.0 Gy or higher. Clinical trials support the use of moderate dose hypofractionation radiotherapy protocols demonstrating comparable effectiveness and minimal risk of increased acute side effects or late complication. 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.

Proton beam Radiation Therapy

The predominant forms of EBRT are delivered by photon therapy, generated by a machine such as a linear accelerator or by a radioactive source such as a cobalt-60 unit. Proton therapy utilizes positive charged particles with superior physic advantages over photons as they deposit radiation dose at precise targets, with sparing of normal tissues beyond defined tumor targets. A 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."

Alternative Modalities

There are other treatment options that use either cold or heat temperatures to destroy prostate tissue. **Cryotherapy** (freezing) is the oldest modality and has been available for decades. **High Intensity Focused Ultrasound** (HIFU) is available and was FDA approved to destroy prostate tissue and some surgeons use it as an option. **RADIOFREQUENCY ABLATION** and **LASER** are currently investigational.

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)

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)

Surgery

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 retropubic 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)

Radiation Therapy

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 high 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)