Local Prostate Cancer

Effective Date: November, 2020
Background

Prostate cancer is the most commonly diagnosed cancer among Canadian men, and is the third leading cause of cancer-related death. The age-standardized incidence rate of prostate cancer in Canada is 118 per 100,000 men, and there will be an estimated 22,900 new cases of prostate cancer diagnosed in Canada in 2019, representing 20% of all new cancers in men.\(^1\) Approximately 1 in 9 Canadian men are expected to develop prostate cancer during their lifetime, and 1 in 29 will die from their disease. In Alberta, 2900 new prostate cancer diagnoses are anticipated by the end of 2019.\(^1\)

Guideline Questions

1. How should patients with localized prostate cancer be risk stratified?
2. How should patients with localized prostate cancer be managed?
3. How should patients with localized prostate cancer be followed after they have completed treatment?

Search Strategy

For the most recent version of the guideline, the PubMed database was searched using the following criteria: (local[All Fields] AND ("prostate"[MeSH Terms] OR "prostate"[All Fields])) AND (Clinical Trial, Phase III[ptyp] AND ("2018/01/01"[PDAT] : "2020/12/31"[PDAT])).

Target Population

Adult men (18 years of age or older) with a suspicion or recent diagnosis of localized prostate cancer.

Recommendations


Staging

1. Assessment for patients who are being considered for active surveillance or treatment with curative intent should consist of:
   a. History and physical examination
   b. PSA – should be done prior to biopsy
   c. Radionuclide bone scan and CT scan abdomen/pelvis – indicated only in patients with high-risk disease* or if there is clinical suspicion of high-risk disease, and may be considered in select patients with high-tier intermediate risk disease*
   d. MRI-prostate may be useful before treatment to assess the extent of local disease or for treatment planning on a case-by-case basis
e. PSMA PET is a novel imaging modality (currently under investigation and not yet Health Canada approved), that may provide utility in treatment decision making in certain cases. Currently any patient requiring PSMA PET would need an out-of-province referral.

*In patients taking 5-alpha reductase inhibitors, measured PSA should be doubled for the purposes of risk stratification.

2. Risk categories for clinical staging:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>low risk</td>
<td>All of the following: T1-T2a/b, Gleason score ≤6 (Grade Group 1), [Moch] PSA &lt;10 ng/mL*</td>
</tr>
<tr>
<td>low-tier intermediate risk</td>
<td>One of the following intermediate risk features: T2c, Gleason score 7 (Grade Group 2-3), and PSA 10-20 ng/mL* 8</td>
</tr>
<tr>
<td>high-tier intermediate risk</td>
<td>More than one of the following intermediate risk features: T2c, Gleason score 7 (Grade Group 2-3), and PSA 10-20 ng/mL* 8</td>
</tr>
<tr>
<td>high risk</td>
<td>Any one of the following: T3a or higher, Gleason score ≥8 (Grade Group 4-5), or PSA &gt;20 ng/mL*</td>
</tr>
</tbody>
</table>

Percentage of positive cores may be taken into consideration.

*In patients taking 5-alpha reductase inhibitors, measured PSA should be doubled for the purposes of risk stratification.

Treatment: General Principles

3. All patients being considered for curative-intent treatment for prostate cancer should explore treatment options with specialists from both urology and radiation oncology. Treatment options such as prostatectomy, brachytherapy, and/or external beam radiotherapy (EBRT) have equivalent cancer-specific outcomes, with different toxicity profiles.

4. Patients should be offered clinical trials wherever available.

Management of Low-Risk Disease

5. Active Surveillance2,3
   - This is the preferred management option in low-risk patients with the understanding that curative treatment will be offered if follow-up demonstrates either worrisome PSA elevation or worsening biopsy characteristics (e.g. Gleason grade and/or volume changes).
   - The patient may choose to proceed with curative therapy due to personal preference at any time.
   - A reasonable surveillance protocol includes:
     - PSA assessment every 3-6 months, DRE annually, at the physician's discretion.
Confirmatory biopsies should be done within 2 years after initial diagnosis, then consider subsequent biopsies every 2-3 years or as clinically indicated. Risks of biopsy may dictate frequency of biopsies. MRI-prostate can be considered if there is discordance between clinical and pathological information, but routine use of MRI is not a replacement for biopsy at this time.4

Disease progression:
- Pathological progression is defined as the presence of Gleason pattern ≥4.
- Additional factors to consider repeat biopsy include:
  - Clinical progression: increase in clinical stage (on DRE) from baseline status.
  - Biochemical progression: PSA doubling time <3 years.
- If there are signs of disease progression, intervention is recommended with curative therapy (i.e., radical prostatectomy, EBRT, or brachytherapy).

For patients that will not benefit from curative therapy, watchful waiting or other therapies such as androgen deprivation therapy (ADT) or palliative radiotherapy can be considered. Refer to clinical practice guideline for Advanced/ Metastatic Prostate Cancer for recommendations.

6. Treatment Options for Low-Risk Disease:5
- Radical treatment is not appropriate for patients with a life expectancy of <10 years.
- **Radical prostatectomy** options include open retropubic prostatectomy or robotic-assisted laparoscopic surgery. [Bill-Axelson, Iverson, Wilt]
  - Both treatments have similar oncological outcomes, and a wait time of up to 3 months for treatment in low-risk prostate cancer is not associated with worse outcomes.
  - Pelvic lymph node dissection in this group is optional, but yield is very low in low-risk patients.
- **Low dose rate (LDR) brachytherapy:**6
  - Patients with pubic arch interference may not be eligible for brachytherapy.
  - Patients with borderline pubic arch interference may be considered for a short course of ADT to reduce gland size.
  - Patients with a prior transurethral resection (TURP) should be assessed on an individual basis.
  - Patients with significant baseline obstructive symptoms may not be eligible for brachytherapy (i.e. American Urological Association symptom score >20).
- **External beam radiotherapy:**7
  - Intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) should be used for delivery
  - Hypofractionated radiation may be considered.9
  - Daily image guidance is the standard of care.
The clinical target volume (CTV) is defined as the prostate alone.

- **Whole gland cryosurgery** is an alternative therapeutic option for patients who may not be good candidates for surgery or radiation. There is less long-term data regarding efficacy and toxicity compared to the other treatment modalities.\(^\text{10}\)
- **Whole gland high intensity focused ultrasound (HIFU)** is not a recommended treatment option for low-risk disease.\(^\text{11}\)

7. Follow-up for Low-Risk Disease:
- PSA every 6 to 12 months for 5 years, then yearly.
- Evaluation of treatment morbidity and/or complications.

### Management of Intermediate-Risk Disease

8. Treatment Options for Intermediate Risk Disease:\(^\text{5}\)
- **Radical prostatectomy plus bilateral pelvic lymph node dissection.**\(^\text{12}\)
- **External beam radiotherapy**\(^\text{8,13,14}\)
  - Intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) should be used for delivery
  - Hypofractionated radiation may be considered.\(^\text{9,15-17}\)
  - Short term (neoadjuvant + concurrent, 4-6 months total) ADT may be considered for select patients undergoing radiotherapy.\(^\text{18,19}\)
  - The CTV is defined as the prostate +/- seminal vesicles.
- **Low-dose rate (LDR) Brachytherapy**
- **EBRT with a brachytherapy boost ( +/- ADT)** is an option for patients with high-tier intermediate risk disease.\(^\text{7,20,21}\)
  - Brachytherapy may be delivered as either LDR or high dose rate (HDR).\(^\text{7,20,21}\)
  - Short term (neoadjuvant + concurrent, 4-6 months total) ADT may be considered for select patients undergoing brachytherapy.\(^\text{18,19}\)
- **Active surveillance** may be considered for select patients with low-tier intermediate risk prostate cancer.
- **Whole gland cryosurgery** is an alternative therapeutic option for patients who may not be good candidates for surgery or radiation. There is less long-term data regarding efficacy and toxicity compared to the other treatment modalities.\(^\text{22}\)
- **Whole gland high intensity focused ultrasound (HIFU)** is not a recommended treatment option for intermediate-risk disease.\(^\text{11}\)

9. Follow-up for Intermediate-Risk Disease:
- PSA every 6 to 12 months for the first 5 years, then yearly.
- Evaluation of treatment morbidity and/or complications.
Management of High-Risk Disease

All high-risk disease patients should be encouraged to discuss treatment options with both a Urologist and Radiation Oncologist before starting treatment.

10. Treatment Options for High-Risk Disease:\(^5\)

- **EBRT + ADT**\(^{23-26}\)
  - There is growing evidence for hypofractionation in this patient group.\(^{27}\)
  - The CTV is defined as the prostate + seminal vesicles +/- regional lymph nodes.
  - EBRT with a brachytherapy boost (+/- ADT for 12 months) is an option for patients with high risk disease.\(^7,20,21\)
  - ADT should be administered for an 18 – 36 month duration and may be initiated prior to radiotherapy or concurrently with EBRT.\(^{26}\)
  - An anti-androgen could be co-administered with a LHRH agonist and be continued for at least 7 days (for possible flare in testosterone with initial LHRH agonist alone).
  - Refer to the clinical practice guideline on Bone Health for Prostate Cancer for recommendations regarding bone health for patients on ADT [link].

- **Radical Prostatectomy and Pelvic Lymphadenectomy** should be considered only for patients where the intent is to achieve negative margins. Patients should be counselled that there is a significant likelihood of requiring post-operative radiotherapy +/- ADT.

- **Whole gland cryosurgery** is an alternative therapeutic option for patients who may not be good candidates for surgery or radiation. There is less long-term data regarding efficacy and toxicity compared to the other treatment modalities.\(^{22,28}\)

11. Follow-up for High-Risk Disease:

- First post-operative PSA should be done 4-12 weeks after surgery.
- Routine PSA should be done every 6 months, unless otherwise specified.

12. Post-prostatectomy Treatment Options

- **Early salvage radiation therapy** is the preferred strategy over adjuvant radiation therapy, and should be considered at the time of biochemical failure (PSA \(\geq 0.2\) ng/mL on at least 2 readings).\(^{29,30,39,40}\)

- **Adjuvant radiation therapy** may be considered in patients with the following pathologic characteristics\(^31\):
  - Significant positive surgical margins
  - Seminal vesicle involvement (pT3b) and/or extraprostatic extension (pT3a)
  - Positive lymph nodes

- ADT can be considered with post-operative radiation therapy in select high-risk patients; the optimal type and duration of ADT has not been established.\(^{32,33}\)
- The CTV is the prostate bed; addition of pelvic lymph node regions may be considered in select high-risk patients.\(^{34-36,41}\)
• The total dose to the prostate bed should be at least 66Gy in standard fractionation.

13. ADT alone is an alternative therapeutic option for patients who decline or are not eligible for curative local treatment. Refer to the clinical practice guideline on Bone Health for Prostate Cancer for recommendations regarding bone health for patients on ADT [link].

Biochemical Recurrence Following Local Radical Radiation Therapy

14. The definition of a biochemical recurrence is PSA nadir +2 ng/mL.

15. Investigations to rule out metastatic disease include a bone scan and a CT scan. For post-radiotherapy patients, a repeat prostate biopsy is recommended to confirm local recurrence if local salvage therapy is being considered.

16. Recommended options for salvage local therapy include salvage cryosurgery or salvage brachytherapy. If salvage local therapy is not offered, or if the patient fails salvage local therapy, initiation of ADT is indicated.

• Intermittent therapy is not inferior to continuous therapy.  
• There is no absolute PSA threshold for initiating ADT, but a range of 5-10 is reasonable; and consideration should also be given to PSA doubling time.


Development and Revision History
This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members include urologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in January 2017, and was updated in January 2018, March 2020, and November 2020.

Maintenance
A formal review of the guideline will be conducted in 2020. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations
ADT, androgen deprivation therapy; CT, computed tomography scan; CTV, clinical target volume; DRE, digital rectal exam; EBRT, external beam radiotherapy; HDR, high dose rate; HIFU, high intensity focused ultrasound; ICRU, international commission on radiation units; IMRT, intensity modulated radiotherapy; LDR, low dose rate; LHRH, luteinizing hormone-releasing hormone; MRI, magnetic resonance imaging; PSA, prostate specific antigen; TURP, transurethral resection

Disclaimer
The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Funding Source
Financial support for the development of CancerCare Alberta’s evidence-based clinical practice guidelines and supporting materials comes from the CancerCare Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Conflict of Interest Statements
Dr. Brita Danielson reports receiving honoraria from Janssen, Amgen, BMS, Bayer, and Ferring.

Dr. Harvey Quon reports other funding from Astellas, Pfizer, Merck, Sanofi, Bayer, Janssen, and is an independent contractor with Alberta Health Services.

Derek Tilley has nothing to disclose.