Local Prostate Cancer

Effective Date: January, 2018
The recommendations contained in this guideline are a consensus of the Alberta Provincial GU 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.

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.

Participation of members of the Alberta Provincial GU Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial GU Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
BACKGROUND

Prostate cancer is the most common cancer among Canadian men, and is the 3rd leading cause of cancer related death in men in Canada. In 2016, it is estimated that 21,600 (age-standardized incidence rate of prostate cancer is 115 per 100,000) men will be diagnosed with prostate cancer in Canada, representing 21% of all new cancers in men. Approximately 1 in 8 Canadian men is expected to develop prostate cancer during their lifetime, and 1 in 27 will die from prostate cancer. In Alberta, 2600 new prostate cancer diagnoses are anticipated in 2016.

GUIDELINE QUESTIONS

- How should patients with localized prostate cancer be risk stratified?
- How should patients with localized prostate cancer be managed?
- How should patients with localized prostate cancer be followed after they have completed treatment?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial GU Tumour Team. Members of the Alberta Provincial GU Tumour Team include (medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists). Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial GU Tumour Team and a Knowledge Management Specialist 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 subsequently updated in January, 2018.

TARGET POPULATION

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

RECOMMENDATIONS

For a complete list of early diagnosis and screening recommendations please see the Early Diagnosis and Screening for Prostate Cancer guideline located (https://www.albertahealthservices.ca/info/cancerguidelines.aspx) and the Canadian Task Force on Preventive Health Care guidelines (http://canadiantaskforce.ca/guidelines/published-guidelines/prostate-cancer/)

1. Staging
   A. Assessment for patients who are being considered for active surveillance or treatment with curative intent should consist of:
      i. History and physical examination.
      ii. PSA (which should be done prior to biopsy).
      iii. Radionuclide bone scan and CT scan abdomen/pelvis is indicated only in patients with high-risk disease* or if clinical suspicion, and may be considered in select patients with high-tier intermediate risk disease*.
iv. MRI-prostate is not routinely recommended.

2. Definition of risk categories for clinical staging:
   A. Low-risk: Must have all of the following: T1-T2a/b, Gleason score ≤6 (Grade Group 1), PSA <10 ng/mL*.
   B. Intermediate-risk: This group can be further divided into low-tier intermediate (one intermediate risk feature) or high-tier intermediate (more than one intermediate risk feature). Intermediate-risk features include: T2c, Gleason score 7 (Grade Group 2-3), and PSA 10-20 ng/mL*.
   C. High-risk: Any one of the following: T3a or higher, Gleason score ≥8 (Grade Group 4-5), or PSA >20ng/mL*.
*In patients taking 5-alpha reductase inhibitors, measured PSA should be doubled for the purposes of risk stratification.

3. Any patient being considered for curative-intent treatment for prostate cancer should be strongly encouraged to explore treatment options with both urology and radiation oncology. Treatment options (e.g. 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.

5. Management of low-risk disease
   A. Active surveillance:
      i. 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).
      ii. The patient may choose to proceed with curative therapy due to personal preference at any time.
      iii. A reasonable surveillance protocol would include:
         a. PSA assessment every 3-6 months, DRE annually (at the physician's discretion).
         b. Consider repeat biopsies 1-2 years after initial diagnosis, then consider subsequent biopsies every 2-3 years or as clinically indicated.
         c. MRI-prostate can be considered if there is discordance between clinical and pathological information.
      iv. Disease progression:
         a. Pathological progression defined as presence of Gleason pattern ≥4 or an increase in the number of positive cores or percentage of core volume involved.
         b. 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.
         c. If there are signs of disease progression, intervention is recommended with curative therapy (i.e. radical prostatectomy, EBRT, or brachytherapy).
   v. For patients that will not benefit from curative therapy, watchful waiting or other therapies (e.g. androgen deprivation therapy (ADT) or palliative radiotherapy) can be considered, see the Advanced/ Metastatic Prostate Cancer guideline for a complete list of recommendations (http://www.albertahealthservices.ca/info/cancerguidelines.aspx).
B. Treatment options:
Radical treatment is not appropriate for patients with a life expectancy of <10 years.

i. **Radical prostatectomy**
   a. Open retropubic prostatectomy.
   b. Robotic assisted laparoscopic surgery.
   c. Both treatments have similar oncological outcomes; furthermore, a wait time of up to 3 months for treatment in low-risk prostate cancer is not associated with worse outcomes.
   d. Pelvic lymph node dissection in this group is optional, but yield is very low in low-risk patients.

ii. **Low dose rate (LDR) Brachytherapy**
   a. Patients with pubic arch interference may not be eligible for brachytherapy.
   b. Patients with borderline pubic arch interference may be considered for a short course of ADT to reduce gland size.
   c. Patients with a prior transurethral resection (TURP) should be assessed on an individual basis.
   d. Patients with significant baseline obstructive symptoms may not be eligible for brachytherapy (i.e. American Urological Association symptom score >20).

iii. **External beam radiotherapy**
   a. 3D-conformal radiotherapy or intensity modulated radiation therapy (IMRT) should be utilized to deliver an International Commission on Radiation Units (ICRU) dose to the prostate of 74-78 Gy in 1.8-2.0 Gy fractions.
   b. Hypofractionated radiation (e.g. 60 Gy in 20 fractions) may be considered.
   c. Daily image guidance is standard of care.
   d. The clinical target volume (CTV) is defined as the prostate alone.

iv. **Cryosurgery**
   a. There is less long-term data for efficacy and toxicity compared to the other treatment modalities.

C. Alternative therapeutic options for patients who are not eligible or declining standard therapies:
   i. High intensity focused ultrasound (HIFU)

D. Follow-up
   i. PSA every 6 to 12 months for 5 years, then yearly.
   ii. Evaluation of treatment morbidity and/or complications.

6. Management of intermediate-risk disease
   **A. Treatment options**:
   i. **Radical prostatectomy plus bilateral pelvic lymph node dissection**
   ii. **External beam radiotherapy**

   a. 3D-conformal radiotherapy or intensity modulated radiation therapy (IMRT) should be utilized to deliver an International Commission on Radiation Units (ICRU) dose to the prostate of 74-78 Gy in 1.8-2.0 Gy fractions.
   b. Hypofractionated radiation (e.g. 60 Gy in 20 fractions) may be considered.
   c. Short term (neoadjuvant + concurrent, 4-6 months total) ADT may be considered for select patients undergoing radiotherapy (REF 33, 34).
   d. The clinical target volume (CTV) is defined as the prostate +/- seminal vesicles.
iii. Brachytherapy
   a. Brachytherapy alone is a treatment option for low-tier intermediate risk patients (REF 31-33).
   b. EBRT with a brachytherapy boost (+/- ADT) is an option for patients with high-tier intermediate risk disease20-22.
   c. Brachytherapy may be delivered as either low dose rate (LDR) or high dose rate (HDR)20-22.
   d. Short term (neoadjuvant + concurrent, 4-6 months total) ADT may be considered for select patients undergoing brachytherapy (REF 33, 34).

iv. Cryosurgery23.
   a. There is less long-term data for efficacy and toxicity compared to the other treatment modalities.

C. Follow-up
   i. PSA every 6 to 12 months for the first 5 years, then yearly.
   ii. Evaluation of treatment morbidity and/or complications.

7. Management of high-risk disease
   A. Treatment options5:
      i. EBRT + ADT 24-26
         a. 3D-conformal radiotherapy, intensity modulated radiation therapy (IMRT) should be utilized to deliver an International Commission on Radiation Units (ICRU) dose to the prostate of 74-78 Gy in 1.8-2.0 Gy fractions
         b. There is growing evidence for hypofractionation (ie: 68Gy in 25 fractions) in this patient group
         c. The clinical target volume (CTV) is defined as the prostate + seminal vesicles +/- regional lymph nodes..
         d. EBRT with a brachytherapy boost (+/- ADT) is an option for patients with high risk disease20-22.
         e. ADT should be administered for an 18 – 36 month duration and may be initiated prior to radiotherapy or concurrently with EBRT 27.
         f. 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).
         g. Refer to the Bone Health for Prostate cancer guideline for recommendations regarding bone health for patients on ADT (http://www.albertahealthservices.ca/info/cancerguidelines.aspx)
      ii. Radical prostatectomy and pelvic lymphadenectomy28
         a. Should be considered only for patients where the intent is to achieve negative margins.
         b. Patients should be counselled that there is a significant likelihood of requiring post-operative radiotherapy +/- ADT.
      iii. Cryosurgery
         a. Cryosurgery can be considered in patients with Gleason score ≥8, as long as PSA <20 AND clinical stage T1-T2. Patients must understand that there is a higher risk of biochemical failure compared to those with low or intermediate risk disease.
There is less long-term data for efficacy and toxicity compared to the other treatment modalities.

8. Post-prostatectomy Treatment
   A. Radical RT\textsuperscript{29}
      i. Patients with any of the following pathological risk factors for local recurrence should be offered referral to a radiation oncologist for a discussion regarding adjuvant therapy within 6 months of surgery:
         a. Positive surgical margins
         b. Seminal vesicle involvement (pT3b)
         c. Extraprostatic extension (pT3a)
      ii. Early salvage radiotherapy should be considered at the time of biochemical failure (PSA $\geq 0.2$ ng/mL on at least 2 readings)
      iii. ADT can be considered in post-operative radiation therapy; the optimal type and duration of ADT has not been established.
      iv. The standard clinical target volume (CTV) is the prostate bed; addition of pelvic lymph node regions may be considered
      v. The total dose to the prostate bed should be at least 60-66Gy in standard fractionation

   B. Alternative therapeutic options of those patients not eligible for, or declining curative local treatment:
      i. ADT alone\textsuperscript{24-26}
         a. Refer to the Bone Health for Prostate cancer guideline for recommendations regarding bone health for patients on ADT (http://www.albertahealthservices.ca/info/cancerguidelines.aspx)

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

9. Biochemical recurrence following local radical therapy\textsuperscript{30}
   A. Definition of biochemical recurrence:
      i. Following prostatectomy
         PSA $\geq 0.2$
      ii. Following radiotherapy
         PSA nadir $+2$ ng/mL
   B. Investigations (to rule out metastatic disease)
      Post-op: if PSA $>2$
      Post-RT: for all patients being considered for definitive salvage therapy
         i. Bone scan
         ii. CT scan
      iii. Post-RT: Repeat prostate biopsy to confirm local recurrence
   C. Local Salvage Therapy
      i. Post-radical prostatectomy:
         a. Salvage radiotherapy, with or without concurrent or adjuvant ADT
         b. ADT can be considered in post-operative radiation therapy; the optimal type and duration of ADT has not been established
c. The standard clinical target volume (CTV) is the prostate bed; addition of pelvic lymph node regions may be considered

d. The total dose to the prostate bed should be at least 60-66Gy in standard fractionation

ii. Post-radiotherapy:
Recommended options include:

a. Salvage Cryosurgery
b. Salvage Brachytherapy
c. ADT alone if salvage therapy is not offered
SEARCH STRATEGY

For the 2018 update, guidelines were updated according to a consensus meeting without a formal literature search.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADT</td>
<td>Androgen deprivation therapy</td>
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<td>CTV</td>
<td>Clinical target volume</td>
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<td>EBRT</td>
<td>External beam radiotherapy</td>
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<td>HDR</td>
<td>High dose rate</td>
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<td>HIFU</td>
<td>High intensity focused ultrasound</td>
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<td>ICRU</td>
<td>International commission on radiation units</td>
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<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
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<tr>
<td>LDR</td>
<td>Low dose rate</td>
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<tr>
<td>PSA</td>
<td>Prostate specific antigen</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<td>TURP</td>
<td>Transurethral resection</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2018. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
REFERENCES


