Local Prostate Cancer

Effective Date: January, 2017

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.
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 20161.

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).

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 (http://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*.
2. Definition of risk categories for clinical staging:
   A. Low-risk: Must have all of the following: T1-T2a/b, Gleason score ≤6, 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) for those patients who do not clearly segregate into low or high risk groups. Intermediate-risk features include: T2c, Gleason score 7, and PSA 10-20 ng/mL.*
   C. High-risk: Any one of the following: T3a or higher, Gleason score ≥8, or PSA >20 ng/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 a urologist and a radiation oncologist. 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. Curative intervention may be required later and patients may be candidates for clinical trials.
   iv. Patients with localized, low-risk prostate cancer can consider an active surveillance protocol to monitor their disease for signs of disease progression. 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 further biopsies every 2-3 years or as clinically indicated.
   v. Disease progression:
      a. Pathological progression defined as presence of Gleason pattern ≥4 or an increase in the number of positive cores.
      b. Additional factors to consider repeat biopsy include:
         - Clinical progression: increase in clinical stage from baseline status.
         - Biochemical progression: PSA doubling time <3 years.
      c. If there are signs of disease progression, intervention is recommended with curative therapy (radical prostatectomy, EBRT, or brachytherapy).
   vi. For patients that will not benefit from curative therapy, watchful waiting or other therapies (e.g. hormonal therapy 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**\(^6\)\(^-\)\(^8\) options include:
   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**\(^9\)\(^-\)\(^11\)
   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 hormones 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**\(^12\)
   a. 3d-conformal radiotherapy or intensity modulated radiation therapy (IMRT) should be utilized to deliver an International Commission on Radiation Units (ICRU) dose of 74-78 Gy in 1.8-2.0 Gy fractions\(^13\).
   b. Hypofractionated radiation (e.g. 60 Gy in 3 Gy fractions) may be considered\(^14\).
   c. Daily image guidance is standard of care
   d. The clinical target volume (CTV) is defined as the prostate alone.

C. **Alternative therapeutic options for patients who are not eligible or declining standard therapies:**
   i. Cryosurgery\(^15\).
   ii. High intensity focused ultrasound (HIFU)\(^16\).

D. **Follow-up**
   i. PSA every 6 to 12 months for 5 years, then yearly.
   ii. Digital rectal examination yearly, but may be omitted if PSA undetectable.
   iii. Evaluation of treatment morbidity and/or complications.

6. **Management of intermediate-risk disease**
   A. **Treatment options**\(^5\):
      i. **Radical prostatectomy plus bilateral pelvic lymph node dissection**\(^17\).
      ii. **External beam radiotherapy**\(^13\)\(^,\)\(^18\)\(^,\)\(^19\)
         a. Based on current evidence, the recommended prescribed dose to the target is 74-78 Gy in standard fractionation.
         b. Hypofractionated radiation (e.g. 60 Gy in 3 Gy fractions) may be considered\(^14\).
         c. Short term (neoadjuvant + concurrent) androgen deprivation therapy (ADT) may be considered for select patients undergoing radiotherapy (REF 33, 34).
      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 disease\(^20\)\(^-\)\(^22\).
c. Brachytherapy may be delivered as either low dose rate (LDR) or high dose rate (HDR)\textsuperscript{20-22}.

d. Short term (neoadjuvant + concurrent) androgen deprivation therapy (ADT) may be considered for select patients undergoing radiotherapy (REF 33, 34).

B. Alternative therapeutic options for patients who are not eligible or declining standard therapies:
   i. Cryosurgery\textsuperscript{23}.

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

7. Management of high-risk disease

A. Treatment options\textsuperscript{5}:
   i. EBRT + ADT\textsuperscript{24-26}
      a. Radiotherapy should treat the prostate planning target volume with 74-78 Gy in standard fractions +/- regional lymph nodes
      b. EBRT with a brachytherapy boost (+/- ADT) is an option for patients with high risk disease\textsuperscript{20-22}. c. Hypofractionated radiation (e.g. 60 Gy in 3 Gy fractions) may be considered\textsuperscript{14}.
      d. ADT should be administered for at 18 – 36 months duration and may be initiated prior to radiotherapy or concurrently with EBRT\textsuperscript{27}.
      e. 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.
      f. 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 lymphadenectomy\textsuperscript{28}
      a. Patients should be counselled that they there is a significant likelihood of requiring post-operative radiotherapy +/- ADT.

iii. Post-prostatectomy radical RT\textsuperscript{29}
   a. 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:
      - Positive surgical margins
      - Seminal vesicle involvement (pT3b)
      - Capsular perforation (pT3a)
   b. Early salvage radiotherapy should be considered at the time of biochemical failure (PSA $\geq 0.2$ ng/mL on at least 2 readings)
   c. ADT can be considered in post-operative radiation therapy; the optimal type and duration of ADT has not been established.

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.
   iii. Low-risk patients (pT2, Gleason ≤ 3+4, margins negative) may have PSA done yearly.
SEARCH STRATEGY

For the 2017 update, guidelines were updated according to a consensus meeting without a formal literature search.

For the 2015 update, no formal literature review was conducted.

For the 2014 update of this guideline, the Pubmed database was searched using the search terms Locally Advanced Prostate Cancer and Metastatic Prostate Cancer from 2010 to 2014. Only phase III trials were evaluated for inclusion.

For the 2012 update of this guideline, Ovid Medline was searched using the term Prostatic neoplasms (MeSH term, subheadings drug therapy, surgery, therapy and radiotherapy), limited to clinical trials involving humans published in English, between August 2011 and August 2012. Articles were excluded if they were not phase II-IV trials, did not include survival or recurrence outcomes, was retrospective. Cochrane Database of Systematic Reviews was searched using the term “prostate cancer”, published 2011-2012.

Medline & Embase were further searched using the term prostate cancer (keyword), limited to clinical trials related to “therapy (best balance of sensitivity and specificity) involving male humans published in English between August 2011-2012.
GLOSSARY OF ABBREVIATIONS

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

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 2017. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

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.

COPYRIGHT DISCLOSURE

Copyright © (2017) Alberta Health Services.

This material is protected by Canadian and other international copyright laws. All rights reserved. This material may not be copied, published, distributed or reproduced in any way in whole or in part without the express written permission of Alberta Health Services (please contact the Guideline Resource Unit Manager at CancerControl Alberta at guru@ahs.ca).
REFERENCES


