



**Alberta Genito-Urinary Oncology Group  
Clinical Guidelines: Prostate Cancer  
April 2005**

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## **I. Early Diagnosis and Screening**

### **Standard method of detection for prostate cancer**

The standard methods of detection for prostate cancer are the digital rectal examination (DRE) and measurement of the serum prostate specific antigen (PSA), which should be done in fit men between 50 and 70 years of age where clinically indicated (ADD AMA guidelines re frequency of testing).

Although there is good evidence that it increases the detection rate of early stage clinically significant prostate cancers, there is no evidence to date that such early detection leads to reduced mortality; the “gold standard” for early detection tests.

Fit men age between the ages of 50 and 75 with at least ten years life expectancy should be made aware of the availability of PSA as a detection test for prostate cancer. They should be aware of the potential benefits and risks of early detection so they can make an informed decision as to whether to have the test performed.

Elevated PSA and/or abnormal DRE are not diagnostic of prostate cancer; they *do* serve to risk stratify patients. In early stage prostate cancer, a needle biopsy to confirm a diagnosis is standard and is most accurate when done using ultrasound guided sextant biopsies. Indications for biopsies include a clinical suspicion of prostate cancer based on the PSA and DRE findings.

### **Definitions**

Primary tumor (T)

- TX: Primary tumour cannot be assessed.
- T0: No evidence of primary tumour.
- T1: Clinically unapparent tumour neither palpable nor visible by imaging.
  - T1a: Tumor incidental histologic finding in five percent or less of tissue resected by TURP.
  - T1b: Tumor incidental histologic finding in more than five percent of tissue resected by TURP; Gleason score < 6.
  - T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA).
- T2: Tumour confined within prostate.\*
  - T2a: Tumour involves one half of one lobe or less.
  - T2b: Tumour involves more than one half of 1 lobe but not both lobes.
  - T2c: Tumour involves both lobes.
- T3: Tumour extends through the prostate capsule.\*\*
  - T3a: Extracapsular extension (unilateral or bilateral).
  - T3b: Tumour invades seminal vesicle(s).

- T4: Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

**\*Note:** Tumour found in one or both lobes by needle biopsy but not palpable or reliably visible by imaging is classified as T1c.

**\*\*Note:** Invasion into the prostatic apex or into but not beyond the prostatic capsule is not classified as T3 but as T2.

#### Regional lymph nodes (N)

Regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. They include the following groups (laterality does not affect the “N” classification): pelvic (not otherwise specified [NOS]), hypogastric, obturator, iliac (internal, external, NOS), and sacral (lateral, presacral, promontory (Gerota’s), or NOS).

Distant lymph nodes are outside the confines of the true pelvis. They can be imaged using ultrasound, computed tomography, magnetic resonance imaging, or lymphangiography, and include: aortic (para-aortic, periaortic, lumbar), common iliac, inguinal (deep), superficial inguinal (femoral), supraclavicular, cervical, scalene, and retroperitoneal (NOS) nodes. Because of stage migration associated with PSA screening, very few patients will be found to have nodal disease, so false-positive and false-negative results are common when imaging tests are employed. In lieu of imaging, risk tables are generally used to determine individual patient risk of nodal involvement.

- NX: Regional lymph nodes not assessed surgically.
- N0: No regional lymph node metastasis on pelvic node dissection.
- N1: Metastasis in regional lymph node(s) on pelvic node dissection.
- Involvement of distant lymph nodes is classified as M1a (see below).

#### Distant metastasis (M)\*

- MX: Distant metastasis cannot be assessed (not evaluated by any modality)
- M0: No distant metastasis
- M1: Distant metastasis
  - M1a: Nonregional lymph node(s)
  - M1b: Bone(s)
  - M1c: Other site(s) with or without bone disease

**\*Note:** when more than one site of metastasis is present, the most advanced category should be used.

#### Investigations for staging

Assessment for patients who are being considered for curative (radical) surgery or radiation should consist of:

- History and physical examination
- CBC, creatinine, urinalysis
- PSA (which should be done prior to biopsy)
- Radionuclide bone scan is indicated only in patients with high-risk disease
- CT scans are not routinely indicated except in high-risk patients

#### **Definition of risk categories: clinical staging**

- Low Risk: T1- T2b and Gleason score  $\leq 6$  and PSA  $\leq 10$ .
- Intermediate Risk: T2c or Gleason 7 or PSA  $> 10-20$ .
- High Risk: Any one of the following:
  - T3 or higher;

- Gleason score  $\geq 8$ ; or
- PSA > 20.

Consideration for staging and % of cores involved based on a 6 core prostate biopsy.

- Low Risk: < 33 % of cores.
- Intermediate Risk: 34% – 50% of cores.
- High Risk: > 50 % of cores involved.

## II. Low-Risk Disease

### Management options

1. Active surveillance: May later require potentially curative intervention, and patients may be candidates for RCTs.
2. If active intervention is being considered, treatment (surgery/radiation) should begin no more than six weeks from the time of diagnosis.
3. Low risk patient should not have a lymph node sampling dissection.
4. External beam radiotherapy (EBRT). Current criteria are: 3D conformal planning or IMRT; GTV = prostate alone; ICRU dose range of 70-74 Gy at 180-210 cGy per fraction.
5. LDR Brachytherapy: Prostate volume: if > 65 cc, not eligible. If 50-65 cc, consider short course hormones to reduce gland size to an implantable volume. Patients with a prior TURP should be assessed on an individual basis.
6. Cryosurgery – needs to be presented to patients as a treatment option for low risk disease.

## III. Intermediate risk

### Management options

Patients should have the opportunity of being seen in consultation by a urologist or radiation oncologist depending on who is the primary consultant.

1. Radical prostatectomy
  - The urologist should discuss the risk of a positive margin and its implications.
  - Patient selection should include consideration for the risk of margin involvement.
    - While adjuvant/salvage radiation may improve progression free outcome following prostatectomy, there is no evidence to suggest intentional combination of surgery followed by radiation is superior to either treatment alone in appropriately selected patients
    - Avoid radical prostatectomy on patients with evidence of extraprostatic disease on the biopsies.
  - Situations in which surgery is the preferred treatment:
    - Patients with normal life expectancy > 20 yrs
    - Patients with significant LUTS.
    - Contraindications to radiotherapy (e.g. previous pelvic radiotherapy, inflammatory bowel disease, collagen vascular disease)

**Note:** Neoadjuvant hormonal therapy prior to radical prostatectomy is not recommended outside of a clinical trial

## 2. EBRT

- The optimal radiation dose-fractionation regimen ± short-course androgen suppression for intermediate risk patients is being explored in on-going clinical trials. Patients should be encouraged to participate in clinical trials.
- If radiation alone is used for intermediate risk patients, the ICRU prostatic dose should be between 73 and 78 Gy, at the oncologist's discretion.
- Short term (neoadjuvant + concurrent) hormones may be used for patients undergoing radiotherapy

## 3. Brachytherapy

Brachytherapy is not routinely recommended outside of clinical trial. However, individual consideration can be given to intermediate risk patients with PSA < 10 and limited involvement on biopsy specimens.

## 4. Cryosurgery

Cryosurgery is available for selected T1-T3 patients with gland volume < 60cc, PSA < 20, and any Gleason score

## 5. Watchful waiting

Expectant management may be considered for patients with life expectancy < 10 years. The frequency/intensity of follow up may be considered separately for “watchful waiting” vs. “active observation” patients.

- For patients on “watchful waiting”, who are not likely to benefit from curative therapy, hormonal therapy will be initiated at the time of clinical/symptomatic progression of disease.
- For patients on “active observation”, may still benefit from curative therapy if the disease demonstrates aggressiveness which may result in a shortening of the otherwise expected lifespan. Radical local therapy may be initiated if PSA doubling time is short, or if there is an increase in Gleason score on repeat biopsy.

## Follow-Up

- PSA every six months x two years, then yearly.
- DRE yearly.
- Evaluation of treatment morbidity/complications.

## IV. High-Risk Disease

### Management options

#### 1 Patients with >10 years life expectancy:

- Combination of hormones and radiation.
- Radical prostatectomy may be considered in selected cases if the LN is negative, if < T3a and a single high –risk parameter are present.
- Any open clinical trial.
- Patients with high-risk disease should have an RT consult.
- Cryoablation may be considered an option in selected cases.
- Counsel patients and primary care physician regarding the effects of prolonged testosterone suppression.
  - Baseline and yearly bone mineral density studies.
  - Appropriate daily doses of calcium and vitamin D.

- Start bisphosphonate, or endocrine referral, if evidence of osteoporosis.
  - Hot flushes, night sweats.
  - Situations in which radiation is the preferred treatment.
    - “High” risk of margin being positive with prostatectomy.
    - Borderline surgical candidate with respect to risk of operative complications move to high-risk section.
2. Patients with < 10 year life expectancy:
- Hormonal therapy.
  - Hormonal therapy and local RT.
  - Hormonal therapy and TURP if persistent obstructive symptoms.

### V. Post Prostatectomy Radical RT

Following radical prostatectomy, the PSA would be expected to fall to undetectable levels. Where this does not happen, patients may be considered for additional treatment. In some patients, the PSA falls to undetectable levels and then rises. In either situation, patients should be referred for an opinion about additional treatment from a radiation oncologist as soon as the PSA is > 0.4 ng/ml. Patients who are most likely to benefit from radiotherapy to the prostatic bed are those with a positive surgical resection margin, PSA < 2 ng/ml, PSA doubling time > 10 months and a Gleason Score of  $\leq 7$ .

### VI. Advanced Disease

#### Stage T<sub>1-4</sub> N<sub>1-3</sub> M<sup>0</sup>

Staging	Pathologic node positive vs. radiologic node positive. Node positive (N1-3, or N+) – can be either pathologic ( <i>e.g.</i> after attempted radical prostatectomy), or clinical ( <i>e.g.</i> obviously enlarged lymph nodes on CT scanning, in an appropriate clinical context).
Management	<p>The role of radiotherapy (pelvis + prostate) is evolving. Treatment approach is a balance between improved progression free survival against unnecessary treatment/toxicity.</p> <p>RT probably recommended for patients with pathologic node (+) at time of attempted radical prostatectomy (Level 3 evidence Zagars 2001).</p> <p>RT for clinical (radiologic) nodal involvement (enlargement) should be offered to those with normal life expectancy of <math>\geq 10</math> years.</p> <p>Long-term hormonal therapy is recommended for all patients. Duration is indefinite for those not undergoing RT. For those undergoing RT, hormone duration may be limited to two to three years (RTOG 8531, EORTC/Bolla).</p> <p>Semi-annual clinical evaluation and PSA, if it will affect management.</p>
Duration of F/U	Age dependent.

**Stage T<sub>1-4</sub> N<sub>1-3</sub> M<sup>+</sup>**

Indications	Symptomatic disease or asymptomatic disease.
Staging	PE, PSA, bone scan, CT scan, if clinically indicated
Management	<p>Hormonal therapy: Castration remains the treatment of choice. One has the option of offering the patient either surgical castration or treatment with a LHRH analogue. These treatments are equally effective and the risks, benefits and economic implications should be discussed with the patient. When an LHRH analogue is first introduced, a non-steroidal antiandrogen<sup>2</sup> should be used for the first month in order to block the potential initial testosterone flare.</p> <p>Hormonal therapy at this time includes:</p> <ul style="list-style-type: none"><li>• Surgical castration</li><li>• Medical castration (LHRH analogue).</li><li>• Eligard (leuprolide gel) SQ Q12-16 weekly as is funded by ACB drug budget.</li><li>• Buserelin is available as an alternative if patients are unable to tolerate Eligard.</li><li>• Goserelin and leuprolide depot if patients are unable to tolerate either leuprolide gel or buserelin.</li><li>• Single agent antiandrogens.</li></ul> <p>Nonsteroidal antiandrogens can be administered to those patients wishing to maintain potency. The trade off is that there may be a slight reduction in disease-free survival. To date there is insufficient data to recommend bicalutamide at the 150 mg/day dose and it is not approved by Health Canada.</p> <ul style="list-style-type: none"><li>• Flutamide 250 mg TID</li><li>• Bicalutamide 50 mg QD</li><li>• Nilutamide 150 mg QD</li></ul> <p>Total Androgen Blockade (TAB) with castration plus a nonsteroidal antiandrogen is not recommended. Based on the last meta-analysis, the survival advantage at five years is only 3%. The first meta-analysis showed a similar advantage favouring the single modality arm. There is insufficient evidence to support the routine use of TAB. Its use primarily will be in patients on clinical trials where TAB is mandated.</p>
F/U	PSA 3 – Six months following the initiation of therapy to evaluate and then as clinically indicated. PSA should not be done as a routine but only when it will affect management.
Duration of F/U	Age dependent.

## Stage M<sup>+</sup>

### Hormone insensitive disease

Indications	Symptomatic disease or asymptomatic metastatic disease.
Staging	As clinically indicated: bone scan; CT scans; MRI. A serum testosterone should be measured to ensure that the testosterone is in the castrate range.
Management	Treatment benefits primarily palliative, although chemotherapy may now confer a small survival advantage.

#### **Palliative Radiotherapy:**

EBRT to symptomatic sites. Strontium 89 (Metastron®) not recommended for routine use, but available for appropriate indications, including:

- Multiple painful sites of bone metastases on both sides of diaphragm
- Patient and/or tumor factors contraindicating the use of multiple fields of EBRT for palliation
- Adequate bone marrow reserve (NB: Platelet count > 100)
- No evidence of impending spinal cord compression

#### **Chemotherapy:**

Taxotere 75mg/m<sup>2</sup>, Q3weekly in combination with prednisone at dose of 5 mg bid. Mitoxantrone 12mg/m<sup>2</sup> in combination with prednisone available as alternate systemic therapy and as second line chemotherapy.

Bisphosphonate Therapy: Treatment with bisphosphonates will be discussed below for patients with metastatic HRPC.

F/U	As clinically indicated to evaluate response to therapy. Patients on docetaxel should be evaluated for response after two to three courses for PSA and symptomatic response. Treatment should be continued for as long as a response is occurring and the morbidity of treatment is manageable.
Duration of F/U	As clinically indicated.

## VII. Bone Health

### **Non-metastatic patients**

Patients with prostate cancer who do not have bone metastases but who do require androgen deprivation therapy (ADT) are at risk for accelerated bone loss. Part of the integrated management plan for patients starting on ADT is to consider long-term bone health. The concern is that osteoporosis is associated with a significantly higher risk of fracture and that fractures are themselves associated with higher mortality.

All patients should ensure adequate calcium and vitamin D intake, using supplements if necessary. For patients starting long-term ADT, an assessment of risk for osteoporosis should be performed.

**Low risk for osteoporosis:** no high-risk characteristics.

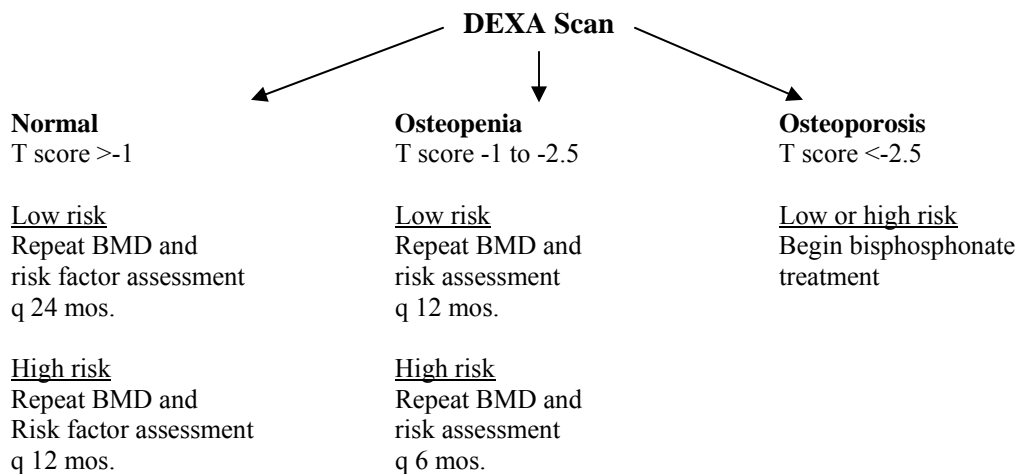
**High risk for osteoporosis** includes any of the following:

- ADT > 6 months
- Previous fracture
- Family history of osteoporosis
- Low body weight
- Smoker
- Excessive alcohol intake
- Steroid use
- Low vitamin D levels

**Recommendations**

1. Calcium 1500mg and Vitamin D 800IU daily for all men on ADT.
2. Baseline DEXA scan for all patients going on long-term (>6mos) ADT
3. If DEXA reveals osteoporosis (T-score <-2.5) then bisphosphonate therapy should be initiated as per standard treatment protocols. Treatment of osteoporosis with bisphosphonates should be undertaken with oral agents that have been approved by Health Canada for the treatment of osteoporosis (i.e. alendronate, etidronate). IV bisphosphonates such as zoledronic acid are not approved for this indication.
4. If DEXA reveals osteopenia (T-score -1 to -2.5) or normal findings then close f/u as suggested below and initiate treatment with bisphosphonates only if osteoporosis is diagnosed.
5. Concurrent bisphosphonate treatment at the initiation of ADT to prevent bone loss and the development of osteoporosis cannot be recommended at this time. Studies of immediate bisphosphonate use concurrent with ADT have been undertaken and in small sample sizes have been shown to increase bone mineral density (BMD). However, this has not translated into a change in fracture risk, hence, the lack of recommendation to routinely use bisphosphonates prophylactically.
6. The diagnosis and treatment of osteoporosis may be undertaken by the person most familiar with the treatment of this condition. This may be the family physician but the individual who prescribes ADT (urologist, MO, RO) should raise the issue and notify the family physician, through the consult note, of the recommendations regarding the management of bone health.

**Suggested strategy for ADT induced bone-loss management in prostate cancer patients**



### **Metastatic patients – hormone sensitive**

Patients either presenting with *de novo* metastatic bone disease or those who become metastatic after primary therapy will undergo ADT as part of standard management. This ADT will be life long so as per the above recommendations; an assessment of bone health and risk should be undertaken, including a DEXA scan to assess BMD.

Several bisphosphonates have been studied in the setting of overt metastatic disease when patients are still hormone sensitive. Pamidronate and clodronate have both been shown to be statistically no better to placebo in delaying or reducing skeletal related events (SREs), altering overall survival or reducing bony pain. Zoledronic acid has not been studied in the clinical setting of hormone sensitive metastatic bone disease, thus no conclusions can be made about its efficacy in this population.

Patients who have no pain but who are metastatic and being placed on ADT follow the above guidelines for management of bone health. It should be stressed that there are no studies currently available that demonstrate that the use of any bisphosphonate in the setting of hormone sensitive metastatic prostate cancer will alter SREs or survival.

### **Recommendations**

1. All men being placed on ADT for metastatic prostate cancer should have a baseline assessment of osteoporosis risk and have a DEXA scan. Treat.
2. The routine use of any prophylactic bisphosphonate (in the absence of DEXA scan proven osteoporosis) for the prevention/delays of osteoporotic skeletal complications cannot be recommended at this time.
3. The use of a bisphosphonate in this clinical setting cannot be claimed to alter SREs or survival. Should men become hormone refractory, consider changing bisphosphonate use to zoledronic acid (see metastatic patients- hormone refractory).

### **Metastatic patients – hormone refractory (HRPC)**

Far more work has been done examining the role of bisphosphonate use in the HRPC patient population. Bisphosphonates have been compared to placebo either as monotherapy or in conjunction with chemotherapy usage. Endpoints have included overall survival, SREs, pain control and QOL improvement.

Studies using less potent bisphosphonates such as clodronate have been negative for all endpoints and the same is true of pamidronate. Only zoledronic acid has been shown to improve outcome by delaying median time to SRE and numbers of SREs without any effect on patient-rated QOL. It should be noted that the treatment effect was relatively small. It should be noted however that in the zoledronic acid study, only patients with no pain or mild to moderate pain were eligible. Thus, comments regarding the utility of zoledronic acid to reduce bone morbidity and improve QOL in patients with severe pain are unable to be made.

### **Recommendation**

1. For patients with HRPC and evidence of bony metastatic disease, monthly zoledronic acid can be considered for reduction in SREs.
2. Dosing of zoledronic acid should be tailored to the patient's kidney function (new labeling information coming from FDA).
3. Patients should be continuously monitored to ensure adequate renal function.
4. If patient clinic condition deteriorates and severe pain develops (narcotic analgesics are required) the routine administration of zoledronic acid should be reviewed and potentially stopped.

At the present time zoledronic acid is not included on ACB formulary and therefore will be the responsibility of the patient to cover the costs of the drug and its administration. This will be either through their health insurance or to personally to cover the cost of the drug. AB Blue Cross does not presently cover it, although a submission has been made to them. Arrangements will need to be made for a site for the administration of the agent as it cannot be given at the ACB facilities due to resource limitations.

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