



Guidelines for the Management of  
**Prostate Cancer**



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**Comprehensive  
Version**



# Guidelines For The Management of Prostate Cancer

## Objective:

This guideline reviews the overall management (from initial presentation and diagnosis through referral, treatment and follow up) of prostate cancer in Nova Scotia. This guideline was written for an audience of *general practitioners and medical students*, not necessarily prostate cancer specialists. As such, it is a synthesis of knowledge and evidence, and reflects the practice policies of the Genitourinary Cancer Site Team in Nova Scotia (see Appendix I). A simplified discussion with flowcharts (practice pathways) will summarize the written contents.

Patients, family members and other non-health professionals are encouraged to review materials written specifically for them. The Canadian Cancer Society Information Service (1-888-939-3333 or [www.cancer.ca](http://www.cancer.ca)) is one source for this type of information.

## Preamble Note:

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. This guideline is intended to assist health care professionals to care for patients with prostate cancer.

Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and doctor (or other health professional) which are unique to each circumstance. Guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision.

This guideline will be reviewed in three years from publication date or earlier if important new evidence becomes available. Current versions of this guideline will be available on the *Cancer Care Nova Scotia* website ([www.cancercare.ns.ca](http://www.cancercare.ns.ca)).

These guidelines are designed for health care professionals, working in a variety of settings. For front-line health care givers, the short version of the guidelines will be a useful reminder of assessment and treatment. This version will be useful for those who prefer to read the full evidence-based discussions, which are located in the Appendices. Development of these guidelines is described in Appendix II.

## Comment on Clinical Research:

An important component of treatment decision-making for any patient is the potential for enrollment in relevant clinical research. The Genitourinary Cancer Site Team is committed to advancing patient care, through participation in clinical trials and other clinical research projects. At any point in time, there may be a clinical trial or other clinical research opportunity related to any component of this guideline. As specific trials or clinical research projects become available, eligible patients may be offered the opportunity to enroll in the relevant trial or research project. Every effort will be made to accommodate patients for clinical research participation, but there will be eligibility restrictions for each trial. Patients are encouraged to discuss clinical trials opportunities with their cancer specialist. Other researchers may also contact patients to offer participation in relevant trials. Current clinical trials are listed on the *Cancer Care Nova Scotia* website ([www.cancercare.ns.ca](http://www.cancercare.ns.ca)).

## Acknowledgements:

This guideline was written by a collaborative effort of the Genitourinary Cancer Site Team, and was sponsored by *Cancer Care Nova Scotia*. Portions of this practice guideline have been adapted from guidelines prepared by the British Columbia Cancer Agency and by the National Comprehensive Cancer Network. The guidelines also incorporate knowledge of current evidence by the cancer experts in Nova Scotia.

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For further information on this, or any other Practice Guideline, please contact the CST Co-Chairs, or members of the Guidelines Resource Team, *Cancer Care Nova Scotia* (Tel. 1-866-599-2267 or by e-mail [info@ccns.nshealth.ca](mailto:info@ccns.nshealth.ca))

### Guideline Approvals:

- Genitourinary Cancer Site Team-
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- Cancer Care Nova Scotia, Commissioner- *15 February 2006*

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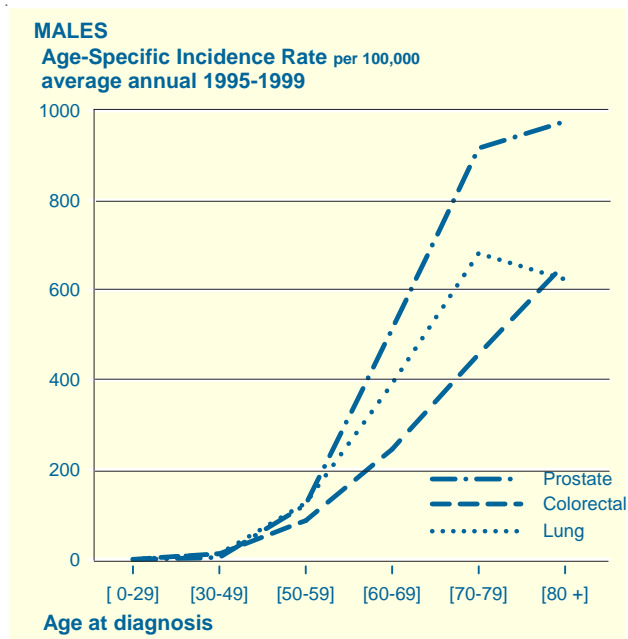
## Part 1. Introduction

### 1.1 Epidemiology

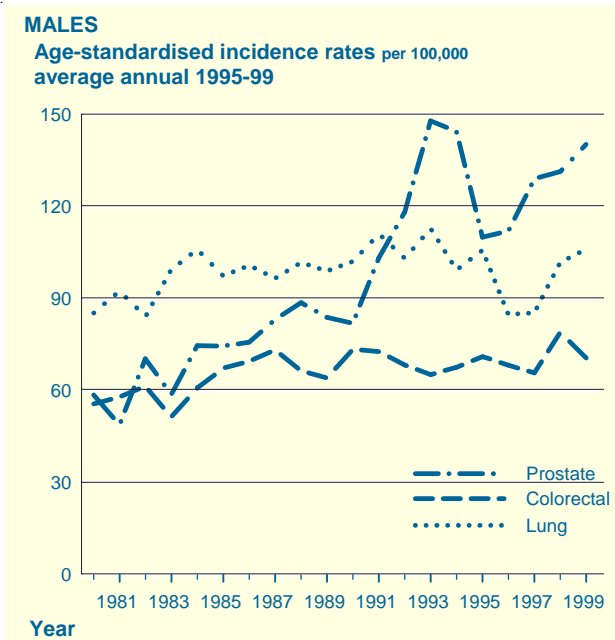
In males, prostate cancer is the most common non-cutaneous cancer diagnosed, and the second most common cause of cancer death. Age specific incidence<sup>1</sup> of prostate cancer increased steeply in men over the age of 60 (Figure 1). Age-standardized incidence<sup>1</sup> increased dramatically in the early 1990's, most likely due to improved detection through the use of the Prostate Specific Antigen (PSA) test (Figure 2). Age-standardized mortality<sup>1</sup>, however, has not changed significantly over the same time period of reporting (Figure 3).

Survival rates of men with prostate cancer<sup>1</sup> are substantially better than the other two leading cancers in men, lung cancer and colorectal cancer (Figure 4). The overall five year survival rate for prostate cancer patients in Nova Scotia was 93%. Survival for prostate cancer patients<sup>1</sup> was dependant on the stage of the cancer at diagnosis, ranging from 99% five-year survival for local malignancies to 27% for patients with distant metastases (Figure 5). Fortunately, over half of the patients (53%) were diagnosed with local disease.

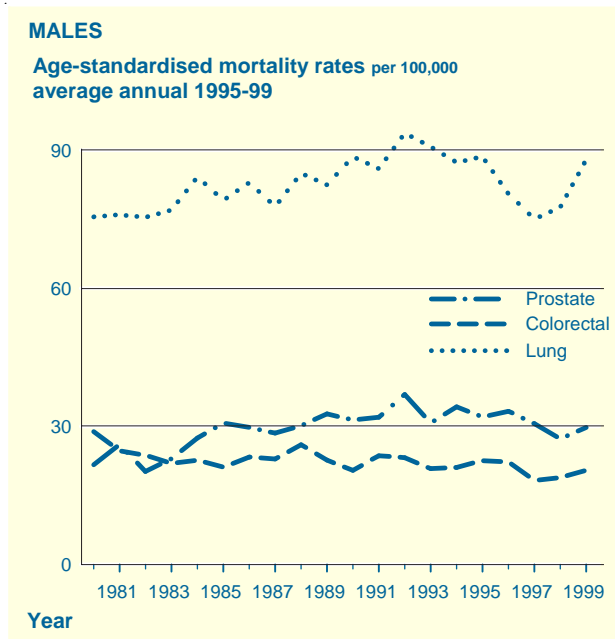
Figure 1. Age-specific incidence rate for common tumour sites, males, Nova Scotia 1995-1999



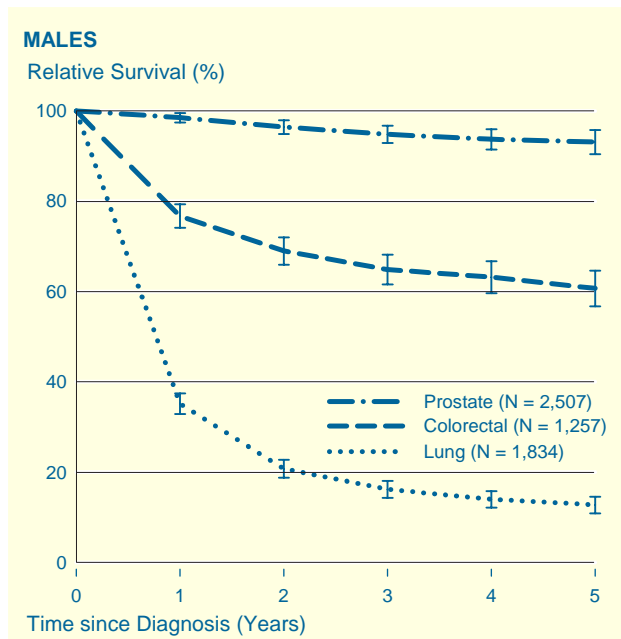
**Figure 2. Trends in age-standardized incidence rates for common tumour sites, males, Nova Scotia 1971-1999**



**Figure 3. Trends in age-standardized mortality rates for common tumour sites, males, Nova Scotia 1971-1999**

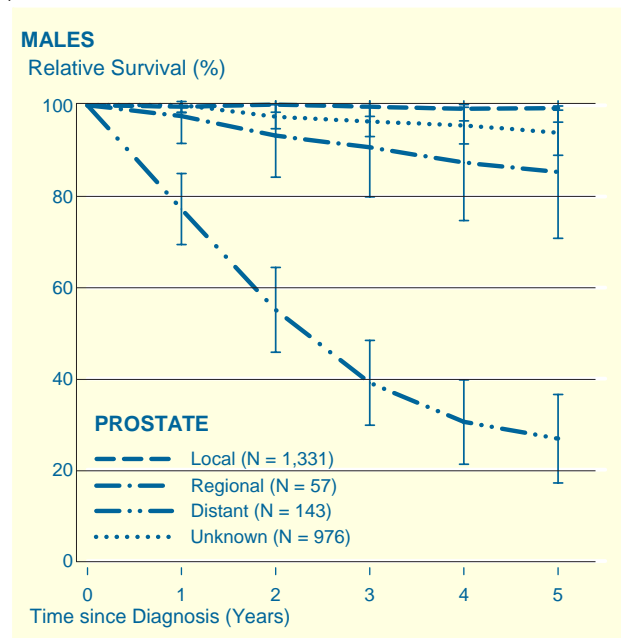


**Figure 4. Five-year relative survival for common tumour sites, males, Nova Scotia 1992-1996**  
The total number of cases (N) retained for analysis appears in parenthesis and a 95% confidence interval (—) is presented for each estimate.



**Figure 5. Prostate cancer survival by extent of disease, males, Nova Scotia 1992-1996**

The total number of cases (N) retained for analysis appears in parenthesis and a 95% confidence interval (—) is presented for each estimate.



## 1.2 Risk Factors

The lifetime risk of developing prostate cancer is approximately 10% and the risk of cancer related mortality is 3%. Risk of prostate cancer is higher in males with a first degree relative with prostate cancer.

## 1.3. Presentation

Patients may present with an elevated PSA without symptoms, with an asymptomatic prostate abnormality on digital rectal examination (DRE), or with lower urinary tract symptoms. Patients with metastatic disease or locally advanced disease may present with other symptoms referable to the sites of disease involvement (i.e. bone pain, visceral or lymphatic obstruction).

## 1.4 Screening<sup>2,3,4</sup>

See appendix II (CCNS – Prostate Screening Position Statement)

### 1.4.1 Prostate Specific Antigen (PSA)

#### Reference Ranges:

Normal values for PSA increase with age, as follows<sup>5</sup>:

40-49 yrs	less than 2.5 ng/mL
50-59 yrs	less than 3.5 ng/mL
60-69 yrs	less than 4.5 ng/mL
70-79 yrs	less than 6.5 ng/mL

### 1.4.2 Sensitivity And Specificity Of PSA Testing And Role Of Free PSA In Determining Risk Of Cancer:

PSA testing sensitivity is approximately 67.5% to 80% (using 4.0 ng/mL as the upper limit of normal). If only PSA testing is used for screening, 20% to 30% of tumours will be missed. To improve sensitivity, a number of methods have been suggested, including: i) digital rectal exam (DRE) for early detection screening; ii) age-adjustment of PSA, using lower limits for younger men (see Section 1.4.1.1); and iii) PSA velocity (rate of PSA change) as a prompt for biopsy.

A PSA velocity of 0.75 ng/mL per year may indicate the presence of prostate cancer. These three methods increase the sensitivity of early detection, but also increase the number of prostate biopsies performed.

Improving the specificity of early detection should reduce the number of unnecessary biopsies. To improve specificity, other methods have been suggested, including: i) using higher PSA cut-off levels for men over 60 years old; ii) using percent-free-PSA levels; and iii) using PSA density. Prostate cancer patients have lower fractions of free PSA relative to total PSA measured. Men with elevated PSA levels, but with a ratio of free/total PSA >20% to 25% have significantly lower risk of prostate cancer found on biopsy.

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## Part 2. Histology & Pathology

### 2.1 Histology

The vast majority of neoplasms of the prostate are adenocarcinomas. Occasionally, other histologies (sarcoma, transitional cell carcinoma, small cell carcinoma) may be seen. Prostate adenocarcinomas are typically graded by the Gleason score<sup>1,2</sup>: scores graded in the range 2-10. Tumours may also be divided as well differentiated (typically Gleason 2-6), moderately differentiated (Gleason 7), and poorly differentiated (Gleason 8-10). Tumour grade is a strong prognostic factor in both treated (surgery or radiation) patients as well as patients where observation is elected. To note, a Gleason score should not be assigned to biopsy specimen showing prostate cancer after the patient has been placed on androgen deprivation or finasteride (Propecia®, Proscar®).

### 2.2 Pathology

#### 2.2.1 Pathologic Assessment of Prostate Biopsy:

The pathology report for needle biopsy specimens<sup>3,4</sup> should include the following information:

- A comment concerning the adequacy of the specimen
- The presence or absence of malignancy
- The histologic type
- The histologic grade (Gleason Score)
- The presence or absence of perineural/lymphatic/vascular invasion
- Extension beyond the prostatic capsule into fat, if present
- Number of cores involved and percentage of surface area of cores submitted
- The presence of high grade Prostatic Intraepithelial Neoplasia (PIN), Atypical Small Acinar Proliferation (ASAP)

#### 2.2.2 Pathological Assessment of TURP Specimens:

Reports on transurethrally resected specimens should include the information required when reporting needle biopsy specimens, and in addition should include the percentage of chips showing tumour.

#### 2.2.3 Pathological Assessment of Radical Prostatectomy Specimen:

Radical prostatectomy specimen resection margins should be marked with ink and these should be sampled generously. Obvious tumours should be sampled and random sections of apparently normal prostatic tissue should be taken. Pathology reports should include the following information:

- AP, lateral, and apex to base dimensions of the prostate gland in centimeters
- The presence or absence of tumour
- The extent and location of tumour
- The histologic type
- Gleason patterns and score
- The presence of high grade PIN (prostatic intra-epithelial neoplasia)
- The presence or absence of vascular/lymphatic/perineural invasion
- The presence or absence of extraprostatic extension
- The status of the surgical margins (involved versus clear)
- Seminal vesicle invasion
- The presence or absence of nodal involvement, number of nodes examined, presence of extranodal extensions (if sampled)

**Table 2.1 Gleason Grading System For Prostatic Adenocarcinoma: Histologic Patterns<sup>2</sup>**

<b>Pattern</b>	<b>Peripheral Borders</b>	<b>Stromal Invasion</b>	<b>Appearance of Glands</b>	<b>Size of Glands</b>	<b>Architecture of Glands</b>	<b>Cytoplasm</b>
1	Circumscribed pushing expansile	Minimal	Simple, round, monotonously replicated	Medium, regular	Closely packed rounded masses	Similar to benign epithelium
2	Less circumscribed; early infiltration	Mild, with definite separation of glands by stroma	Simple, round, some variability in shape	Medium, less regular	Loosely packed rounded masses	Similar to benign epithelium
3A	Infiltration	Marked	Angular with variation in shape	Medium to large	Variable packed irregular masses	More basophilic than patterns 1 & 2
3B	Infiltration	Marked	Angular with variation in shape	Small	Variable packed irregular masses	More basophilic than patterns 1 & 2
3C	Smooth, rounded	Marked	Papillary and cribriform	Irregular	Round to elongate masses	More basophilic than patterns 1 & 2
4A	Ragged infiltration	Marked	Microacinar, papillary and cribriform	Irregular	Fused with chains and cords	Dark
4B	Ragged infiltration	Marked	Microacinar, papillary and cribriform	Irregular	Fused with chains and cords	Clear (hypernephroid)
5A	Smooth, rounded	Marked	Comedocarcinoma	Irregular	Round to elongate masses	Variable
5B	Ragged infiltration	Marked	Difficult to identify gland lumens	Irregular	Fused sheets and masses	Variable

reprinted from: Table 7-3 from Bostwick DG: UROLOGIC SURGICAL PATHOLOGY, 1/e. p.360, © 1997 Mosby. with permission from Elsevier

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1. Gleason DF, Mellinger GT: Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol*, 1974; 111 (1): 58-64.
2. Gleason DF: Histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M: *Urologic Pathology: The Prostate*. Philadelphia: Lea and Febiger, 1977, pp 171-197.
3. Ljung BM, Cherrie R, Kaufman JJ: Fine needle aspiration biopsy of the prostate gland: a study of 103 cases with histological followup. *J Urol*, 1986; 135 (5): 955-8.
4. Algaba F, Epstein JI, Aldape HC, et al.: Assessment of prostate carcinoma in core needle biopsy—definition of minimal criteria for the diagnosis of cancer in biopsy material. *Cancer*, 1996; 78 (2): 376-81.

## Part 3. Diagnosis and Staging

### 3.1 Diagnosis- Prostate Biopsy:

An elevated PSA or abnormal DRE may indicate increased risk of prostate cancer, but they cannot determine a diagnosis of prostate cancer. The only method to confirm the presence of prostate cancer is a prostate biopsy. Usually, a prostate biopsy is performed transrectally with ultrasound guidance. Transrectal ultrasound (TRUS) has poor ability to diagnose prostate cancer<sup>1</sup>, so a normal TRUS with abnormal DRE or elevated PSA should not be used as a criterion to avoid prostate biopsy. Prostate cancer is rarely diagnosed at the time of TURP.

#### 3.1.1 Minimum Workup At The Time Of Prostatic Biopsy:

- Full history and physical examination, PSA blood test
- Bilateral biopsy of prostate with at least eight cores sampled. Additional samples may be taken from suspicious nodules or ultrasound abnormality, where appropriate

### 3.1.2 Indications For Re-Biopsy When No Invasive Cancer Present:

- Focus of ASAP or PIN (see 2.2.1) in a man eligible for curative therapy
- Progressively rising PSA
- Suspicious nodule

### 3.2 Staging Investigations

- Serum PSA will guide selection of staging studies for newly diagnosed prostate cancer
- Laboratory investigations: hemoglobin, liver function tests, creatinine, testosterone, alkaline phosphatase
- Consider bone scan, if PSA >10 ng/mL, or if Gleason Grade  $\geq 7$ , if disease is locally advanced, or if there are symptoms suggestive of metastases<sup>2,3,6,7</sup> (such as weight loss, bone pain)
- CT or MRI<sup>4,5</sup> pelvis scans may be considered if a patient has an increased likelihood of lymph node metastases (>20%), a Gleason score  $\geq 8$ , PSA > 20 ng/mL, T3 or T4 lesion<sup>4-7</sup>.
- A pelvic lymph node dissection<sup>8,9</sup> may be performed in very selected cases

**Table 3.2.1 T (Tumour) Definitions<sup>10</sup>**

<i>Clinical:</i>	
T X	Primary tumour cannot be assessed
T 0	No evidence of a primary tumour
T1	Clinically inapparent tumour, neither palpable nor visible by imaging T1a Tumour incidental finding in 5% or less of tissue resected T1b Tumour incidental finding in more than 5% of tissue resected T1c Tumour identified by needle biopsy (e.g. because of elevated PSA)
T 2	Tumour confined within prostate (Note: tumour found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging is classified as T1c) T2a Tumour involves one-half of one lobe or less T2b Tumour involves more than one-half of one lobe, but not both lobes T2c Tumour involves both lobes
T 3	Tumour extends through prostate capsule (Note: invasion into the prostatic apex or into, but not beyond, the prostatic capsule is classified as T2) T3a Extracapsular extension (unilateral or bilateral) T3b Tumour invades seminal vesicle(s)
T 4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall
<i>Pathologic (pT):</i>	
pT1	<i>There is no pathologic T1 classification</i>
pT2	Organ confined pT2a Unilateral, involving one-half of one lobe or less pT2b Unilateral, involving more than one-half of one lobe, but not both lobes pT2c Bilateral disease
pT3	Extraprostatic extension pT3a Extraprostatic extension (positive surgical margin indicated by an R1 descriptor- residual microscopic disease) pT3b Seminal vesicle invasion
pT4	Invasion of bladder, rectum

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**Table 3.2.2 N (Node) Definitions<sup>10</sup>**

<i>Clinical:</i>	
NX	Regional lymph nodes were not assessed
N0	No metastasis to regional lymph nodes
N1	Metastasis in regional lymph node(s)
<i>Pathologic (pT):</i>	
pNX	Regional lymph nodes not sampled
pN0	No positive regional lymph nodes
pN1	Metastasis in regional lymph node(s)

**Table 3.2.3 M (Metastasis) Definitions<sup>10</sup>**

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

**Stage Groupings: TNM Subsets<sup>\*10</sup>**

Stage I	T1a	N0	M0	G1	Stage IV	T4	N0	M0	Any G
Stage II	T1a	N0	M0	G2, 3-4		Any T	N1	M0	Any G
	T1b	N0	M0	Any G		Any T	Any NM1	Any G	
	T1c	N0	M0	Any G	* Grading not generally used for staging at Capital District Health Authority				
	T1	N0	M0	Any G					
	T2	N0	M0	Any G					
Stage III	T3	N0	M0	Any G					

**References:**

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## Part 4. Referral Information for the New Patient Visit

A letter of referral and a pathology report documenting the cancer diagnosis are the usual minimal requirements for a referral of adult patients to a tertiary cancer center. A referral need not be delayed due to incomplete results from tests (either due to test scheduling delays or waiting time for test results).

### Local Urologist

- Refer as per usual practice within local community or health care district

### Referral to the QEII Health Sciences Centre

Referrals to the Capital Health/QEII Cancer Care Program (CCP) may be faxed to the Referrals Office at 902-473-6079 (tel. 902-473-5140 or 902-473-6098). It is preferred that referrals be accompanied by the CCP Referral Form available upon request at the above phone numbers or available for downloading at [www.cdha.nshealth.ca/physicianupdate](http://www.cdha.nshealth.ca/physicianupdate). For urgent or emergent referrals, please page the appropriate specialist on call through the QEII HSC Locating service (902-473-2220) to discuss the referral.

### Referral to the Cape Breton Cancer Centre

Referrals to the Cape Breton Cancer Centre may be directed to the referrals/booking office at 902-567-7774 (fax 902-567-7911). For urgent or emergent referrals, please page the appropriate specialist on call through the Cape Breton Regional Hospital Locating service (902-567-8000) to discuss the referral.

### Referral Information

#### Letter of Referral\*

A legible referral or consultation letter highlighting presenting signs, symptoms and pertinent findings

#### Laboratory Results\*

- a. Serum PSA (prostate specific antigen) levels- including old results\*
- b. CBC (complete blood counts)

#### Biopsy Reports\*

- a. Prostate biopsy reports
- b. TURP biopsy reports

#### Operative Reports (relevant to the cancer)\*

- a. Prostatectomy
- b. Orchiectomy
- c. Other procedures

#### Diagnostic Imaging Reports\*

- a. Transrectal Ultrasound of prostate-reports\*
- b. Bone scans (with films) \*
- c. Any relevant chest radiographs (with films)
- d. Any relevant CT scans
- e. Any other relevant diagnostic imaging

#### Other Information

- a. Any relevant consultation reports
- b. Renal function test results (if done)
- c. Relevant bloodwork: BUN, creatinine, calcium (if done)
- d. Detailed information on any previous chemotherapy or radiotherapy of current malignancy
- e. Any information on previous malignancies
- f. Information on co-existing medical conditions and allergies

\* Specific information which is necessary for proper triage of referrals

Please note: If the referring physician would like to discuss a case with a specialist, feel free to call the appropriate specialist (Radiation Oncology, Medical Oncology, or Urology, by calling 902-473-2222- ask for the specialist on call or a specific physician at this number). If any tests or reports are pending, the date of the procedure, and the location of the procedure should be noted, so that the reports may be obtained when available. Send in the referral while awaiting these results, to facilitate a timely appointment for your patient.

## Part 5. Treatment

*Note: For optimal patient care, psychosocial management is integrated with medical/surgical management of the disease and symptoms.*

### 5.1 Curative Treatment Options By Risk Category:

Pretreatment PSA<sup>1-8</sup>, grade<sup>9-13</sup> and clinical stage are prognostic factors for outcome following surgery<sup>14-16</sup>, radiotherapy<sup>17-21</sup>, expectant management<sup>22-25</sup> (See Appendix III for principles of expectant management) or observation<sup>26,27</sup> (See Appendix IV for principles of observation) for non-metastatic disease. Various prognostic schemes combining different categories of these factors have been proposed<sup>28-31</sup> and, in general, these schemes stratify patients into low, intermediate and high risk categories. Low risk patients have a high chance of disease control with single modality therapy (or expectant management in selected patients); high risk patients have a high chance of systemic failure with localized treatment modalities and should be considered for adjuvant therapy. Treatment of intermediate risk patients is controversial.

### 5.2 Definition Of Risk Categories With Treatment Options<sup>32</sup>:

#### 5.2.1 Low Risk

T1-T2a  
**and**  
Low PSA (< 10ng/mL)  
**and**  
Low Gleason Grade ( $\leq 6$ ):

#### Treatment Options:

Patients may choose one of these options in discussion with their doctor<sup>13,33</sup>

- Radical prostatectomy<sup>14,16,34-38</sup> (see Appendix V)
- External beam radiotherapy alone<sup>38-44</sup> (see Appendix VI)
- Brachytherapy<sup>45-47</sup> (seed implant- see Appendix VI)
  - not available in Nova Scotia

- Expectant Management<sup>22,48-51</sup>
- Observation<sup>13,52-54</sup>

#### 5.2.2 Intermediate Risk:

T2b-T2c  
**or**  
PSA = 10-19 ng/mL  
**or**  
Gleason Grade = 7:

#### Treatment Options:

Patients may choose one of these options in discussion with their doctor<sup>13,33</sup>

- Radical prostatectomy<sup>14,16,25,35-37</sup> with or without pelvic lymph node dissection (PLND)
- Neoadjuvant Androgen deprivation therapy (ADT- also known as hormonal therapy) (see Appendix VII) and radical external beam radiotherapy<sup>55</sup>
  - ADT given for 2-8 months prior to radiotherapy<sup>56</sup>
  - ADT concurrent with radiotherapy may be given<sup>55</sup>
- Dose-escalated conformal external beam radiotherapy (3D)<sup>25,57</sup>
- ADT may be used as primary treatment if contraindication to radiotherapy and radical prostatectomy.
- Expectant Management<sup>53</sup>
- Observation<sup>13,34,53,58</sup>

#### 5.2.3 High Risk:

T3-T4  
**or**  
Gleason Grade  $\geq 8$   
**or**  
PSA > 20ng/mL

#### Treatment Options:

Patients may choose one of these options in discussion with their doctor<sup>59</sup>

- Neoadjuvant ADT<sup>25,55,56,60-62</sup> and external beam radiotherapy (including elective treatment of pelvic lymph nodes<sup>63,64</sup>) (see Section 5.2.2)

with or without 2-3 years of adjuvant ADT<sup>55,56,65-69</sup>

- Radical prostatectomy<sup>70-73</sup> – for highly selected patients with low volume disease; Not recommended for T3b-T4 patients
  - Post operative radiotherapy and/or ADT may be required
- ADT may be used as primary treatment in very high risk patients with low chance of cure<sup>74-76</sup>
- Observation<sup>77</sup>

### 5.3 Post-Prostatectomy Management

#### Post-operative PSA Undetectable or PSA < 0.2mg/mL

##### pT2, pT0 NX,N0 M0 negative margin

- Observation, standard follow-up management<sup>25</sup>

##### pT2 (positive margin), pT3a NX,N0 M0

Options:

- Radiation Therapy<sup>4,10,78-82</sup> (+/- ADT)
- Observation, standard follow-up management

##### pT3b NX,N0 M0

Options:

- Radiation Therapy<sup>4,10,78-82</sup> (+/- ADT)
- ADT alone
- Observation, standard follow-up management<sup>25</sup>

##### pT4 NX,N0 M0

Options:

- Radiation Therapy (+/-ADT)
- ADT alone

##### pTX N+ M0

Options:

- ADT<sup>25,83</sup>
- Observation, standard follow-up management

#### Post-operative PSA Detectable

PSA ≥ 0.2 ng/mL – See Salvage Therapy Section 5.4

## 5.4 Salvage therapy

### 5.4.1 Salvage Radiotherapy Post-Radical Prostatectomy<sup>25,79,81,84,85</sup>

Should be considered in the setting of rising PSA (on at least two subsequent measurements) after radical prostatectomy (minimum PSA > 0.2 ng/dL) or first post-operative PSA > 0.2 ng/dL in patients who are more likely to have disease isolated to the prostatic bed.

Biochemical relapse-free survival (but not overall survival) is superior if radiotherapy initiated when PSA < 1 ng/dL, and PSA doubling time > 10 months, and PSA recurrence post-prostatectomy > 18 months

### 5.4.2 Salvage Therapy Post-Radiotherapy<sup>25</sup>

In a highly selected subset of patients (e.g. low risk disease at diagnosis and long PSA doubling time and long disease-free interval) with three consecutive rises in PSA 3-4 months apart<sup>86</sup> **and** PSA ≥ 1.5 ng/mL, options may include:

- Prostatectomy
- Brachytherapy/seed implant
  - not available in Nova Scotia
- Cryotherapy
  - not available in Nova Scotia

## 5.5 Metastatic Cancer of the Prostate

Patients with metastatic or clinically detectable lymph node disease are considered to be incurable and are generally offered immediate ADT<sup>76,87</sup>. This could include:

- LHRH agonist<sup>74,88-93</sup>
- LHRH agonist plus antiandrogen<sup>92-94</sup>
- Orchiectomy<sup>74,95,96</sup>

Other patients who have extremely high-risk disease (without proven distant disease) who are unlikely to be cured and/or those who have significant co-morbid disease may be considered for immediate or delayed ADT alone<sup>55</sup>.

## 5.6 Hormone Refractory Prostate Cancer

Hormone refractory prostate cancer is defined by rising PSA, worsening radiographic disease, or worsening symptoms while on ADT. Castrate testosterone levels should be confirmed (< 1.75 nmol/L) and effective ADT implemented if not the case.

Secondary hormonal manipulations may be indicated. These may include:

- Addition of antiandrogen agent to orchiectomy or LHRH agonist<sup>92-94</sup> (See Appendix VII)
- Discontinuation of antiandrogen if patient has been receiving one<sup>97-100</sup>
- Other less commonly-used manipulations<sup>101</sup> (See Appendix VII)

Symptom control should be optimized, especially analgesic therapy and supportive measures. The palliative care team should be consulted. Other interventions aimed at improving symptom control may include:

- Urological intervention (e.g. TURP)
- Radiotherapy (localized or hemibody)<sup>102</sup>
- Low dose steroids<sup>103</sup> (i.e., prednisone 5-10 mg/day or dexamethasone 1-2 mg/day)
- Systemic radionuclides<sup>104-106</sup> (See Appendix X)
- Palliative chemotherapy (See Appendix VIII)
  - Docetaxel plus prednisone<sup>106-107</sup> (See Appendix IX)
  - Mitoxantrone plus prednisone<sup>108</sup>
- Bisphosphonate therapy
  - Data is emerging to indicate zoledronic acid decreases skeletal events (e.g. pathologic fractures, need for radiotherapy, need for surgery, spinal cord compression) and decreases pain in hormone refractory prostate cancer<sup>109</sup>.

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## Part 6. Follow-up

### 6.1 Follow-up after Curative Therapy

The goal of follow up after curative therapy is to detect recurrence and to monitor for side effects from the treatment. In addition, followup visits should include reassessment and management of any supportive care issues, including psychosocial, sexual and/or incontinence problems. The follow up schedule after curative radiotherapy or radical prostatectomy will depend on a number of factors<sup>1</sup>, including the initial clinical or pathological stage of the disease, acute or chronic toxicities, the post therapy PSA levels, or rising PSA levels. The following schedules are recommended after each of these curative treatments. The physician should review the followup schedule with each patient before completion of initial treatment, so that the patient has an understanding of what to expect.

#### 6.1.1 Follow-up after Curative Radiotherapy

Year	Frequency	Provider	Tests
1-5	every 6-24 months	RO	Clinical assessment, DRE
1-5	every 3-4 months	RO	PSA *
>5	every 1-3 years	RO	Clinical assessment, DRE
>5	every 3-6 months	RO	PSA

\* Serum testosterone may be monitored in patients receiving ADT

RO: radiation oncologist, for follow-up of treatment effectiveness and long-term toxicity

DRE: digital rectal examination

PSA: prostate specific antigen

#### 6.1.2 Followup after Curative Radical Prostatectomy

Year	Frequency	Provider	Tests
1-3	every 3-12 months	U	PSA, Clinical assessment
3- Ongoing	every 6-12 months	U	PSA, Clinical assessment

U: urologist

PSA: prostate specific antigen

### 6.2 Follow-up for patients with Metastatic Disease

The interval, investigations, and providers will be determined by the patient's clinical condition and symptoms.

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## Part 7. Supportive Care Issues

### 7.1 Psychosocial Needs

Prostate cancer patients, like all cancer patients, may have a number of supportive care needs, often including the need for psychosocial support<sup>1,2</sup>. The psychosocial needs will differ from newly diagnosed men, to those living with the cancer, and to those who fail treatment.

Psychosocial support may be needed for help to cope with the cancer experience. For some patients, mental health support may be needed. There is about 25% chance of clinically significant depression, anxiety and adjustment difficulties<sup>3-6</sup>. In addition, one must also pay attention to the impact of the cancer on the patient's partner. Prostate cancer and its treatment may cause or exacerbate erectile dysfunction<sup>7,8</sup>, urinary incontinence, a change in mood and sleep patterns. It is the responsibility of the attending health caregivers to provide basic support through the continuum of disease. This should include basic screening for signs of depression<sup>12,13</sup> in the patient. Where available, cancer patient navigators are a valuable resource for patients. There may be peer support groups in local communities to help patients.

Screening for distress (see Section 8.12) should be included in patient visits at diagnosis and other key transition points (e.g. six months after treatment completion, disease recurrence, progression to advanced disease). For high risk patients, distress screening should be included at each visit. Risk factors to consider in selecting the frequency of distress screening include<sup>14</sup>:

- age < 60
- mental health history
- social isolation
- receiving ADT (hormone therapy)
- greater burden of illness

- advanced stage of cancer
- unresolved urinary incontinence
- high sexual dissatisfaction
- multiple life stressors

If possible, partners should be involved in the process of screening for distress.

If there are specific needs beyond the abilities of the front-line caregivers, a referral to the Psychosocial Oncology Team at either of the Cancer Centres, or an appropriate local resource (eg. mental health specialists), may be considered. Specialized psychosocial support may be offered by psychosocial counsellors, psychologists, psychiatrists, social workers, clinical nurse specialists, or other trained professionals.

### 7.2 Symptom Management

The treatment of prostate cancer is complex and may include surgery, external beam radiotherapy, brachytherapy, ADT, or chemotherapy. These treatments have specific and overlapping side effects, which may affect quality of life. Common side effects include erectile dysfunction, urinary incontinence, loss of libido, hot flashes, and mood swings.

#### 7.2.1 Erectile Dysfunction and Sexual Health

Following prostate cancer treatment, there is a high incidence of erectile dysfunction (ED)<sup>15-19</sup>, up to 85% depending on the treatment. Prior to treatment, 30-40% of men report pre-existing ED as a result of other factors<sup>7,8,20</sup>. Therefore, it is important to assess sexual issues prior to treatment, to determine baseline and to identify the degree of concern for the patient and his partner<sup>8-11,21,22</sup>. This assessment can identify many issues beyond baseline ED. It is recommended that the man's partner should be allowed to participate in the pre-treatment assessment<sup>23</sup>. (Query their

current level of sexual activity, how satisfied they are with this and how concerned they are about possible changes.) If necessary, consider initiation of sexual counselling to address aspects of the couple's relationship<sup>24,25</sup>.

Following radical prostatectomy or radical radiotherapy, at 6-12 weeks post-treatment, a visit should be planned to discuss possible resumption of sexual activity (including issues such as the return of erections, morning fullness)<sup>26-30</sup>. At this time, consideration may be given to initiate oral therapy with a phosphodiesterase enzyme inhibitor<sup>31-38</sup> (e.g. sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®)) to stimulate erectile tissue. It is important to note with the patients that the purpose of these oral agents is to preserve tissue and enhance penile health, not necessarily for sexual relations.

A follow-up visit should be planned for 3-12 months after treatment to discuss the couple's sexual function and satisfaction. If the oral agent is not working, consider prostaglandin injections<sup>39-41</sup> (e.g. alprostadil (Caverject®)) and a referral to erectile dysfunction (ED) clinic (Note: only available in Halifax). Another option could be referral for couples counselling or sex therapy, where available. This should be re-assessed at 12 months, or as necessary.

### **7.2.2 Urinary Incontinence**

Urinary incontinence is another common consequence of prostate cancer treatment<sup>24,25</sup>. This can be very distressing to patients, especially if not addressed early in the treatment. This potential adverse effect should also be discussed before treatment, along with an assessment of pre-treatment bladder function. Patients should be instructed on Kegel exercises and advised on the use of incontinence products.

About 2-3 weeks after surgery, the catheter is usually removed. Upon removal of the catheter, patients should be able to demonstrate Kegel exercises. There should also be a discussion with the patient about incontinence. Patients often need reassurance that this is expected, and they may need information on different incontinence products.

At three months after treatment, a follow-up visit should be planned to discuss how the patient is doing with incontinence. If possible, a referral for urodynamic assessment (where available) may be considered to assess options for bio-feedback training to help the patient regain control.

If the patient is still having trouble with incontinence problems at 12 months post-treatment, consider referral for an incontinence device (a pump that is inserted during day surgery).

### **7.2.3 Loss of Libido, Hot Flashes, Mood Swings**

These symptoms are caused by testosterone reduction and occur during hormonal treatment, and possibly for months to years afterwards. Supportive care and or medications (see Appendix VII) may be considered.

### **7.2.4 Proctitis**

Chronic irritation of the lower rectum occurs in about 10% percentage of prostate cancer patients treated with external radiation. The symptom of mild rectal bleeding usually develops within 6-12 months after radiation, due to vessel telangiectasia. It may last for years, usually improving with time. Proctitis may also cause discomfort during defecation or rectal urgency.

Any patient with persistent rectal bleeding needs full assessment including

colonoscopy by a gastroenterologist or surgeon. Once confirmed, radiation-induced proctitis can be treated symptomatically by modifying diet (to ensure avoidance of constipation) and with medications or procedures, listed below.

For patients with clinically significant symptoms of proctitis (rectal urgency, tenesmus, pain with bowel movements) treatment with either Anusol®- HC (*Hydrocortisone Acetate – Zinc Sulfate*) suppositories 1 PR q8h prn or Proctosone® or Proctosedyl® (*Hydrocortisone Acetate – Framycetin Sulfate – Cinchocaine HCL – Esculin*) suppositories 1 PR q8h prn, is recommended. If these do not provide adequate relief, Proctofoam™- HC (*Hydrocortisone Acetate – Pramoxine HCL*), Anugesic® - HC (*Pramoxine HCL – Hydrocortisone Acetate – Zinc Sulfate*), Xylocaine® (*Lidocaine HCL*) jelly 2%, all given PR q8h prn, or oral analgesics can be prescribed, in severe cases.

For bleeding occurring more than one year after radiation treatment, mesalamine (Salofalk®, Rowasa®) suppositories 1000mg PR for two weeks, repeated on a monthly basis, can be helpful. Occasionally, local therapy such as laser treatment is required for refractory bleeding requiring transfusion. Hyperbaric oxygen can also be helpful for recurrent bleeding. If life-threatening bleeding occurs, instillation of Formalin has also been shown to be effective to stop bleeding. In cases of complete, persistent incontinence, severe refractory rectal pain or fistula, defunctioning colostomy should be considered.

### 7.3 Other Resources

Some prostate cancer patients may benefit from involvement of the local palliative care service, for advanced symptom management expertise and end of life care when appropriate.

Referral to palliative care is available across the province, as illustrated in Figure 8.13.

Guidelines for the management of symptoms are under development by the CCNS Supportive Care Cancer Site Team. As these guidelines are completed, they are posted on the *Cancer Care Nova Scotia* website ([www.cancercare.ns.ca](http://www.cancercare.ns.ca)). Current CCNS symptom management guidelines are:

- Management of Nausea & Vomiting (2004)
- Management of Cancer-Related Pain (2006)
- Management of Oral Complications from Cancer Therapy (2006)

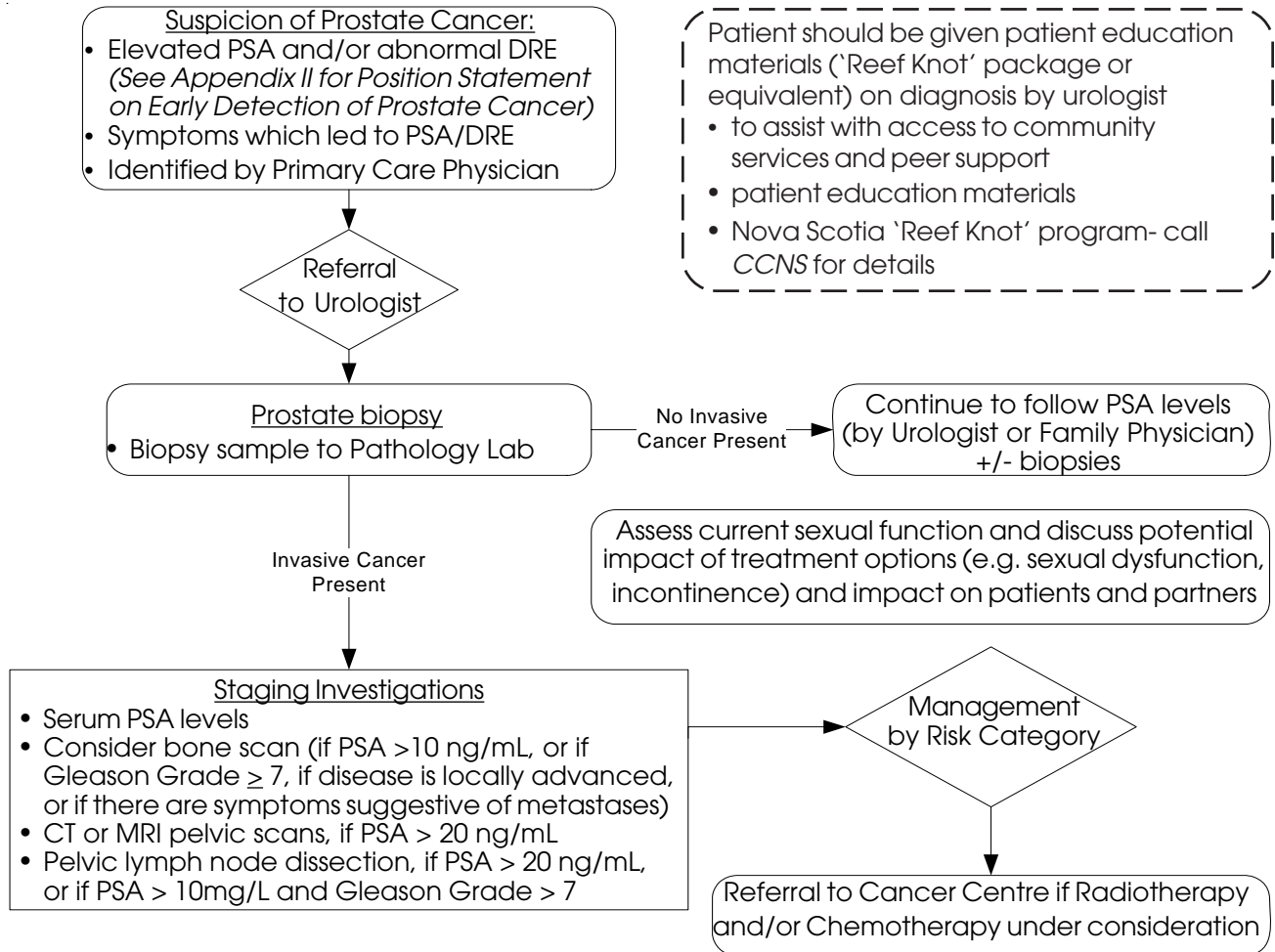
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## Part 8. Practice Pathways

### 8.1 Diagnosis and Referral of Prostate Cancer- Overview



#### **Referral Information:**

A letter of referral is the minimal requirement for a referral. A referral need not be delayed due to delays in scheduling tests or delayed reporting of tests

#### **Local Urologist**

- Refer as per usual practice within local community or health care district

#### **QEII Health Sciences Centre:**

- Faxed referrals to the QEII Cancer Care Program (CCP) Referrals Office at 902-473-6079 (tel. 902-473-5140 or 902-473-6098). It is preferred that referrals be accompanied by the CCP Referral form available upon request at the above phone numbers or available for downloading at [www.cdha.nshhealth.ca/physicianupdate](http://www.cdha.nshhealth.ca/physicianupdate)

#### **Cape Breton Cancer Centre:**

- Direct referrals to the Referrals/Booking office at 902-567-7774 (fax 902-567-7911)

#### **Urgent Referrals:**

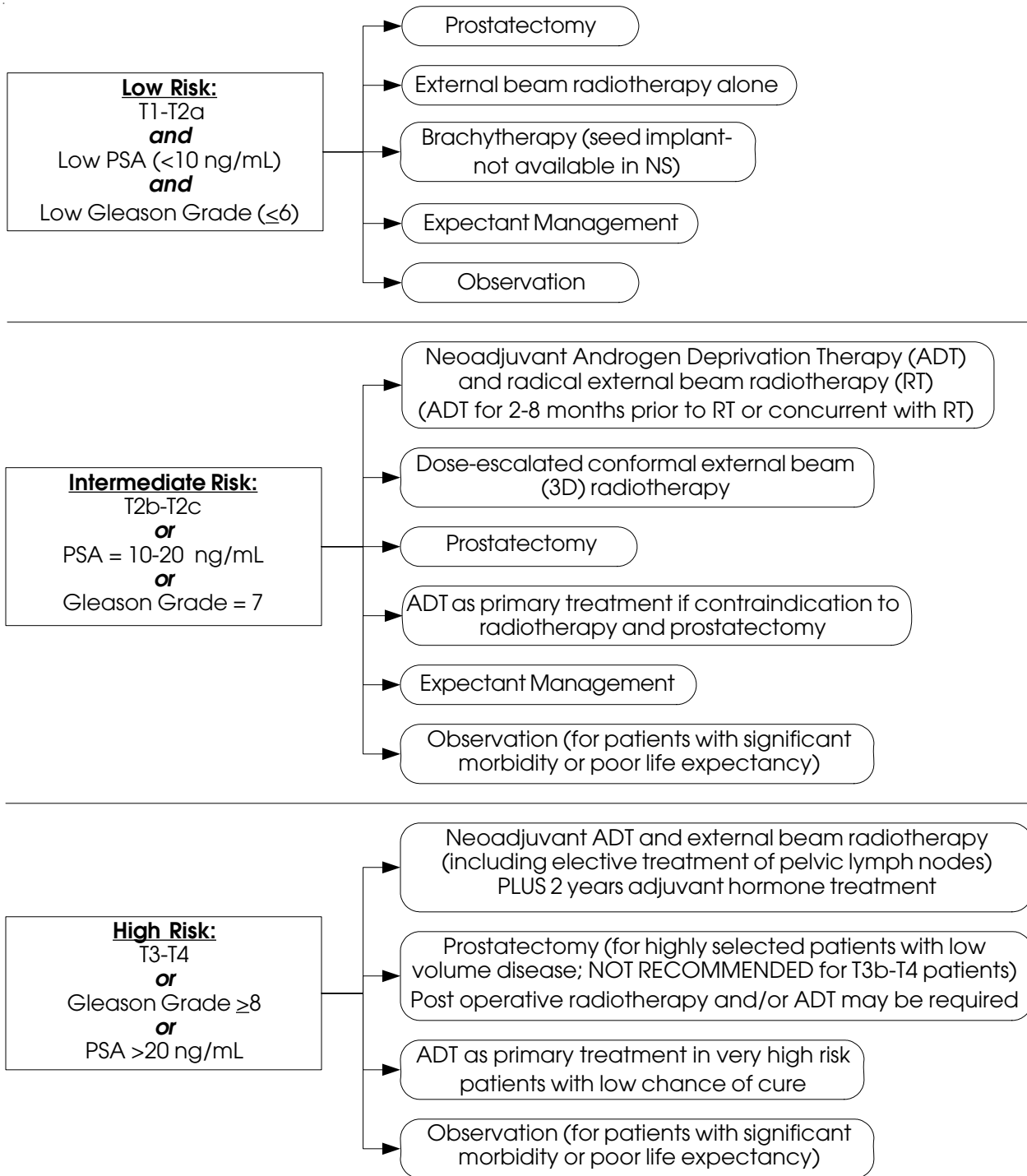
- For urgent or emergent referrals, in Halifax- page the appropriate specialist on call through the Locating service (902-473-2220); in Cape Breton- page the appropriate specialist on call through the Locating service (902-567-8000)

#### **Referral Information:**

- Letter of Referral\*
- Laboratory Results\*- CBC, PSA (including old results)
- Biopsy Pathology Reports
- Operative Reports (prostatectomy, orchiectomy, other)
- Diagnostic Imaging Reports (TURP, bone scans, chest X-ray, CT scans, other)

\* Specific information which is necessary for proper triage of referrals

## 8.2 Initial Treatment Options for Prostate Cancer



## 8.3 Observation

- Observation consists of medical follow up where it is unlikely that the patient will be treated with radiation therapy or surgery for cure due to a limited life expectancy or severe medical co-morbidities. Treatment at symptomatic progression will likely consist of ADT with additional interventions given with the intent of improving impairments in prostate cancer-specific health-related quality of life.

## 8.4 Expectant Management

- Expectant management involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses or if symptoms become imminent
- Patients with clinically localized cancers that are candidates for definitive treatment and choose expectant management should have regular follow up
  - DRE and PSA every six months
  - Needle biopsy of the prostate may be repeated within 6 mo of diagnosis if initial biopsy was < 10 cores or assessment discordant (eg, palpable tumour contralateral to side of positive biopsy)
  - Needle biopsy should be performed within 18 months if > 10 cores obtained initially, then periodically
- A repeat biopsy may be indicated for any sign of disease progression by exam or markers

## 8.5 ADT (Androgen Deprivation Therapy - Hormonal Regimens)

The choice of initial orchiectomy or androgen deprivation (hormonal) agent(s) for any individual patient will depend on many factors

- Combined Androgen Blockade (CAB- LHRH agonist plus non-steroidal antiandrogen agent) is not routinely indicated
- Monotherapy with nonsteroidal antiandrogens is not routinely indicated
- After initial failure of ADT, secondary hormonal manipulation should be tried (eg. addition of a non-steroidal antiandrogen or discontinuation of non-steroidal antiandrogen if already on)
- Other hormonal manipulations, such as ketoconazole or estrogens may be tried. Some phase II trials show a decline in PSA. There are no randomized data to support any survival advantage

### OPTIONS:

#### 1. Orchiectomy

The testicles are surgically removed. The procedure is done as an outpatient, usually done under local anesthetic. Surgical castration (orchiectomy) is permanent.

#### 2. LHRH Agonists

Goserilin (Zoladex®) 3.6 mg SC Depot q28d OR 10.8 mg SC Depot q84d  
Leuprolide (Lupron®-IM, Eligard®-SC) 7.5 mg q28d OR 22.5 mg q84d (3mo) IM/SC Depot  
OR 30 mg q112d (4 mo)/ 45 mg q168d (6mo) SC Depot  
Buserilin (Suprefact®) 6.3 mg SC Depot q56d OR 9.45 mg IM Depot q120d

Note: Due to an initial rise in testosterone levels, patients should be given a non-steroidal antiandrogen (see below) for 2-4 weeks at the same time as their first LHRH agonist dose

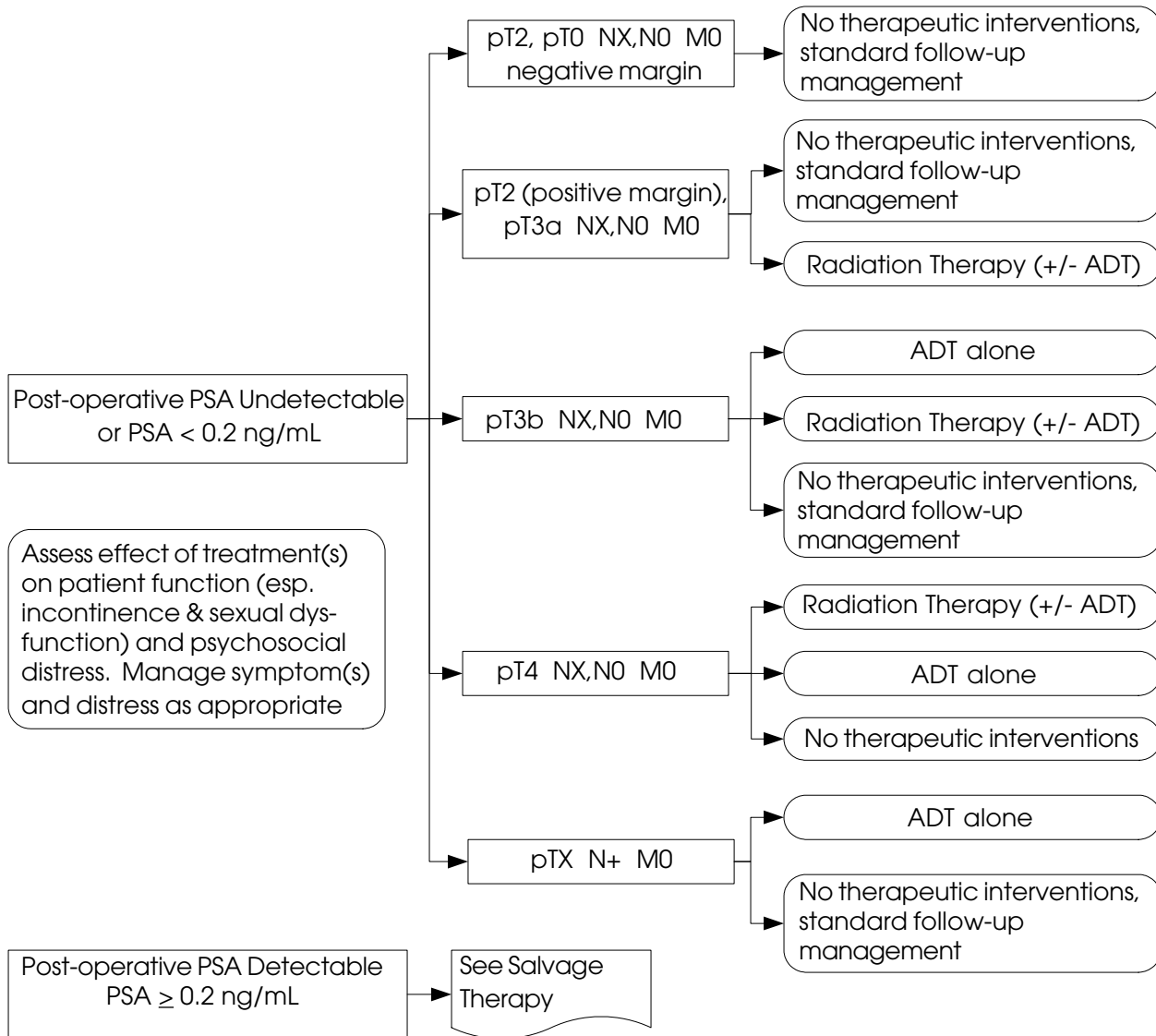
#### 3. Non-steroidal Antiandrogen Agents

Flutamide (Euflex®) 250 mg PO TID  
Bicalutamide (Casodex®) 50 mg PO daily, up to 150 mg PO daily to TID  
Nilutamide (Anandron®) 50 mg PO BID or TID

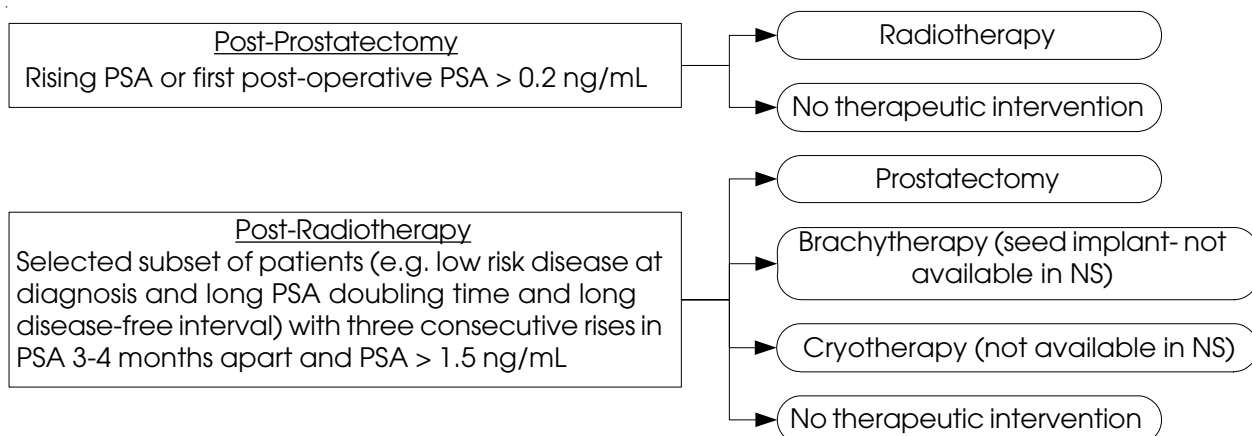
#### 4. Other Hormonal Treatments

Cyproterone (Androcur®) 50-100 mg PO BID or TID  
Megestrol (Megace®) 80-160 mg PO daily  
Ketoconazole (Nizoral®) 400 mg PO TID (+/- Hydrocortisone 20 mg qAM & 10 mg qPM)  
Estrogens- e.g. Diethylstilbestrol 1 mg PO Daily

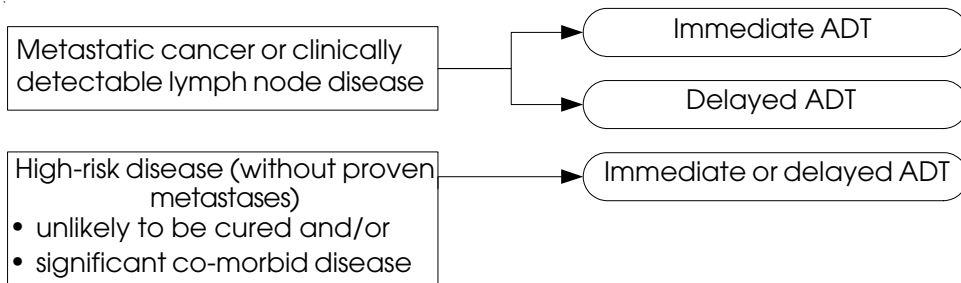
## 8.6 Post-Prostatectomy Management



## 8.7 Salvage Therapy

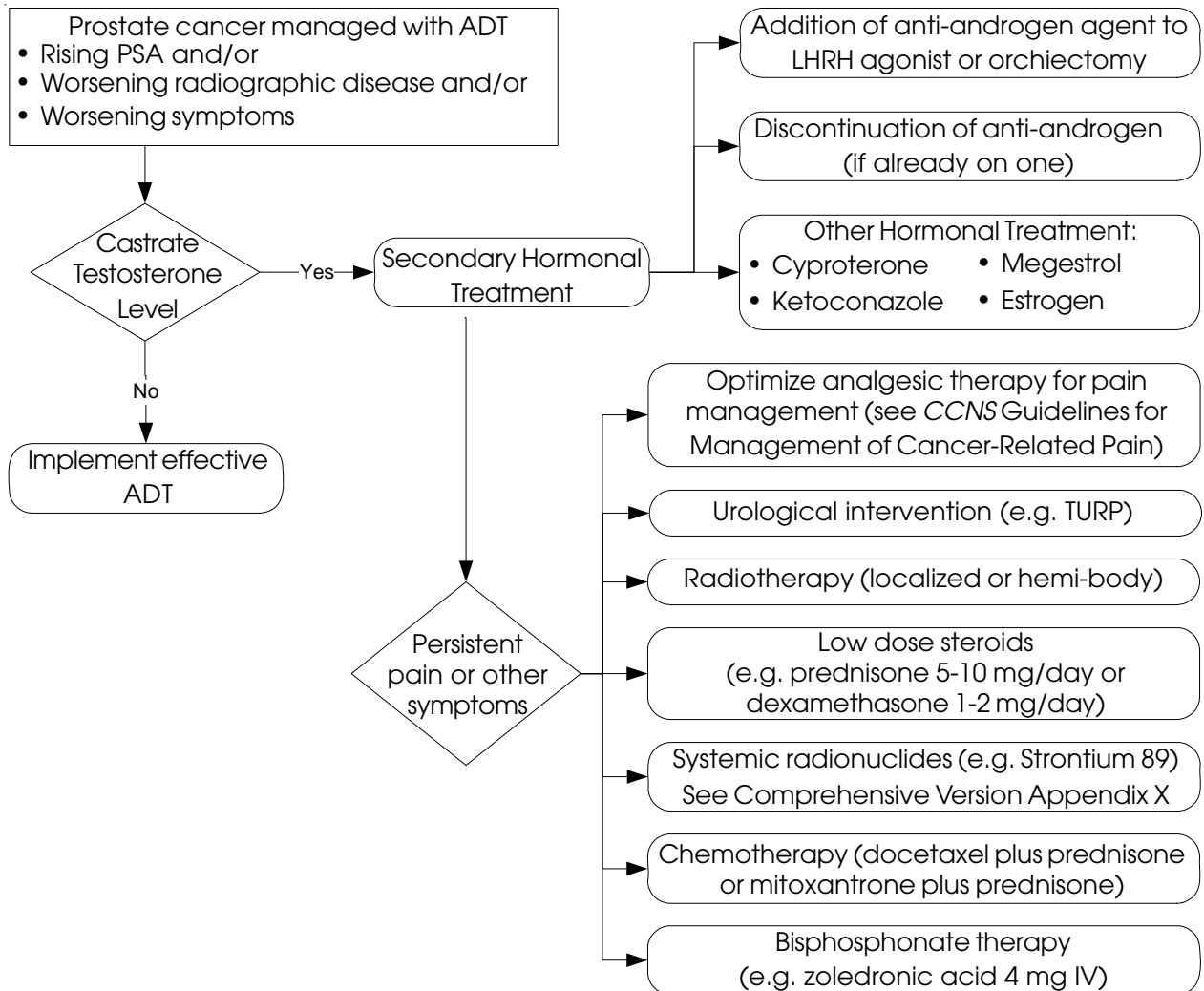


## 8.8 Metastatic and Incurable Prostate Cancer

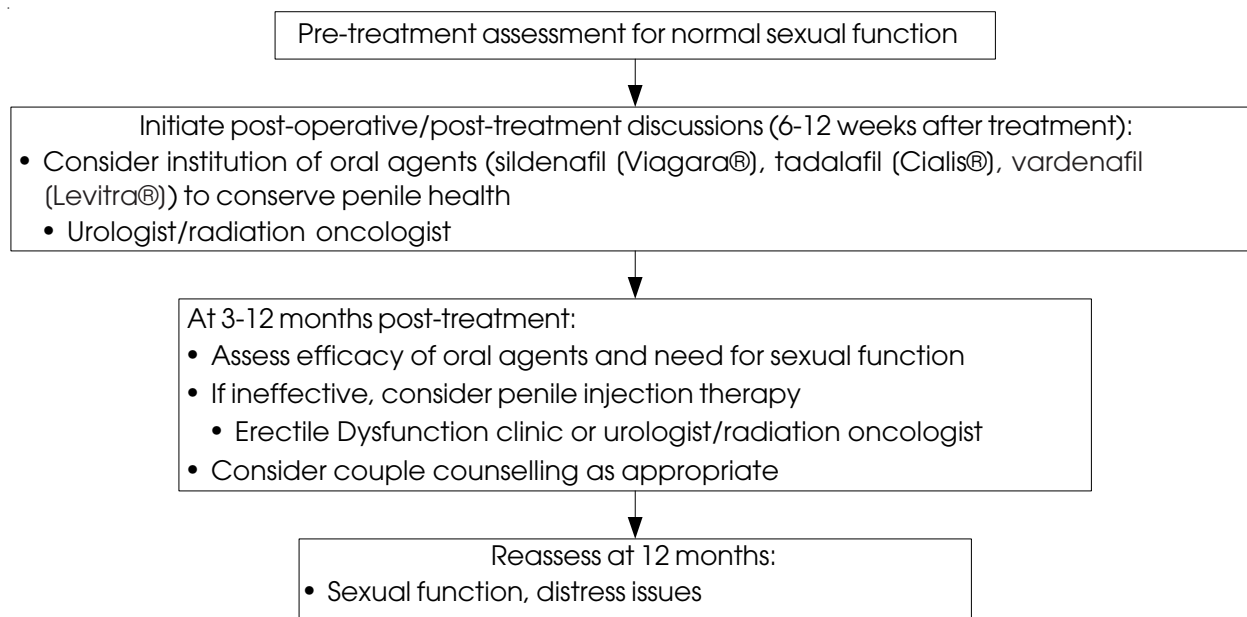


Consider referral to Palliative Care service (see page 29) and/or provincial home care service

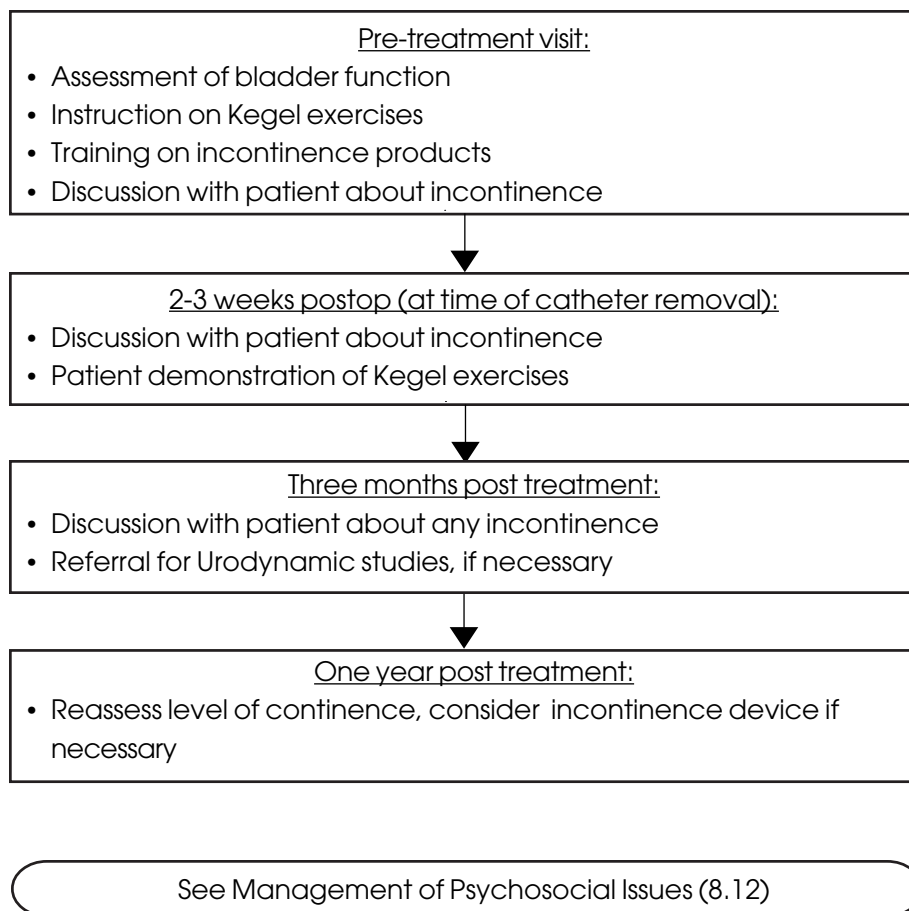
## 8.9 Hormone Refractory Prostate Cancer



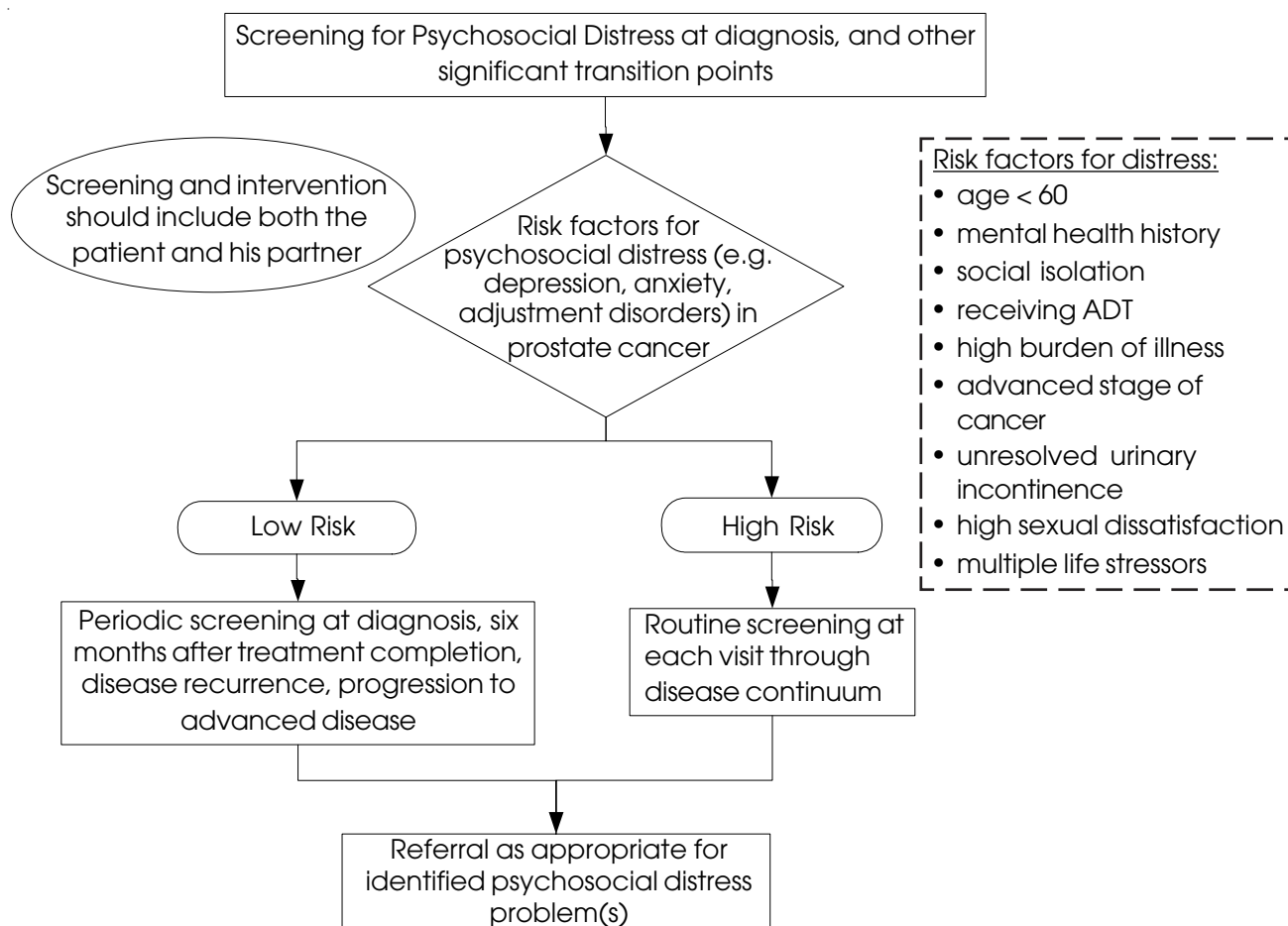
## 8.10 Management of Sexual Dysfunction



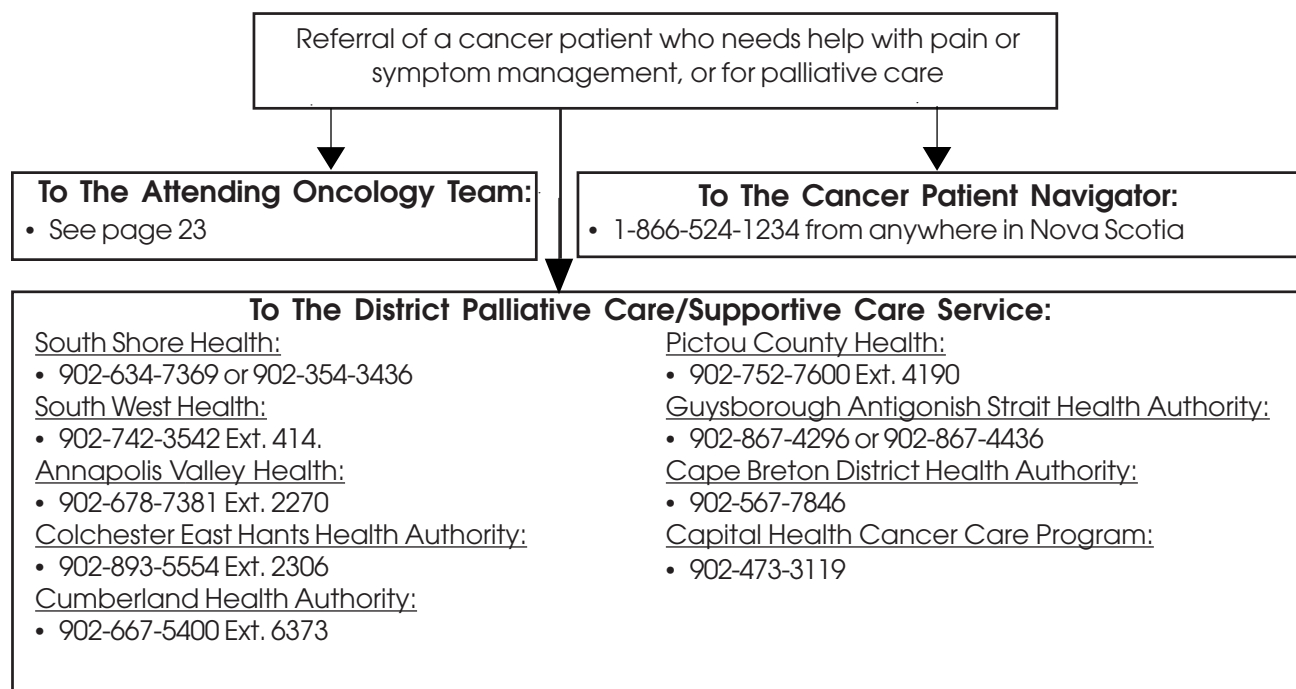
## 8.11 Management of Incontinence



## 8.12 Management of Psychosocial Issues



## 8.13 Management of Pain and Other Symptoms



## APPENDIX I- Genitourinary Cancer Site Team Members

Lori Wood, Medical Oncology Lead, Capital Health (Co-Chair)  
Derek Wilke, Radiation Oncology Lead, Capital Health (Co-Chair)  
Ricardo Rendon, Urologic Oncology, Capital Health (Surgical Oncology Lead)

Tete Ago, Radiation Oncology, Cape Breton Cancer Centre  
David Bell, Urologic Oncology, Capital Health  
Larry Broadfield, CCNS Systemic Therapy Program  
Rekha Gupta, Pathology, Capital Health  
Helmut Hollenhorst, Radiation Oncology, Capital Health  
Cheryl Lamkey, Oncology Nurse, Capital Health  
Heather MacKenzie (Site Team Secretary)  
Sue Marsh, Urology Nurse, Capital Health  
Sheryl Pace, Clinical Trials Nurse, Capital Health  
Jill Petrella, CCNS Quality Co-ordinator  
Rob Rutledge, Radiation Oncology, Capital Health  
Marlene Sellon, Oncology Pharmacy, Capital Health  
Marketa Skala, Radiation Oncology, Capital Health

**No conflicts of interest have been identified by members of the Genitourinary Cancer Site Team, or others involved in writing the Prostate Cancer Guideline that could have compromised the recommendations of this guideline.**

## APPENDIX II- Position Statement on Early Detection of Prostate Cancer

### Background

Prostate cancer is the most commonly diagnosed cancer<sup>1</sup> and the second leading cause of cancer deaths in Canadian men<sup>2</sup>. Nova Scotia has the third highest rate of deaths from prostate cancer in Canada<sup>3</sup>.

### CCNS Position on Early Identification of Prostate Cancer

*Cancer Care Nova Scotia* does not at this time support the implementation of a comprehensive population-based prostate cancer screening program for Nova Scotia. While we know that the PSA test may be used to detect early stage prostate cancer, there is insufficient evidence to suggest at this time that a decline in mortality rates from prostate cancer can be directly attributed to screening.<sup>4,5,6</sup> As new evidence emerges, this statement will be re-evaluated.

*Cancer Care Nova Scotia* believes that early identification of prostate cancer requires a partnership between Nova Scotian men and their physicians.

- Men need to be aware of prostate cancer, and what it may mean for them.
- Men who have concerns about prostate cancer should discuss them with their physician.
- Physicians should discuss the potential benefits of early detection of prostate cancer with men over 50 who do not exhibit urological symptoms and those who are considered to be at greater risk for prostate cancer.

The risk of prostate cancer increases with age, especially after the age of 50.<sup>7</sup> Men who have a family history of prostate cancer are more likely to develop prostate cancer.<sup>8</sup> American evidence suggests that men of African heritage are at higher risk of prostate cancer.<sup>9</sup> Physicians are encouraged to discuss the risks and benefits of prostate screening with men in a higher risk category beginning at the age of 40.

Early detection of prostate cancer involves the use of both the Digital Rectal Exam (DRE) and serum PSA determination. The PSA blood test may be used to detect prostate cancers at an early stage. This test is available to Nova Scotian men through their family physicians and following a discussion of the risks and benefits of prostate cancer screening. Men who have difficulty accessing this test through their physician should request a referral to another physician. It is important to recognize that PSA is accepted to be useful in the evaluation of symptomatic prostate disorders.

## Guidelines for Health Professionals

The Genito-Urinary (GU) Cancer Site Team recommends that:

- Health professionals be aware of prostate cancer as the most common cancer in men.
- Health professionals recognize the increasing incidence of clinically significant prostate cancer reflecting the increased life expectancy of the current male population.
- Health professionals be aware of the natural history of prostate cancer. It is not advised to screen patients with significant co-morbidities or a limited life expectancy.
- Early detection of prostate cancer involves both the DRE and serum PSA determination.
- Age adjusted PSA reference values be the standard when PSAs are ordered.
- Appropriate counselling (including the risks and benefits of prostate cancer screening) be provided to men prior to initiating screening and that informed consent should be documented.
- Men who choose to be screened should be screened on an annual basis. The need for screening be re-evaluated as necessary based on the man's health status.
- Student physicians continue to be trained in the technique of proper male genitourinary examination including DRE, and learning opportunities for practicing physicians be provided.
- Men who present with urological symptoms or have suspicious findings on physical examination require appropriate diagnostic investigations, including age-adjusted PSA and DRE regardless of age.

*This statement was developed by the Genito-Urinary Cancer Site Team of Cancer Care Nova Scotia, with input from provincial stakeholders including health professionals and prostate cancer consumers.*

Release date: January, 2002.

<sup>1</sup> National Cancer Institute of Canada. (2001). *Canadian Cancer Statistics 2001*, p 25 .

<sup>2</sup> Ibid. p.27.

<sup>3</sup> Capital District Health Authority *Why Do We Need to Change the Way We Think About Health?*

<sup>4</sup> Meyer F & Fredet Y (1998). Prostate cancer: 4. Screening in *CMAJ* 159: 968-72.

<sup>5</sup> Greenlee RT, Hill-Harmon MB, Murray T, et al. (2001). 'Cancer statistics, 2001' *CA: A Cancer Journal for Clinicians* 51(1): 15-36.

<sup>6</sup> Prostate Cancer Alliance of Canada. (1998). *Early detection of Prostate Cancer*.

<sup>7</sup> *Canadian Cancer Statistics 2000* p. 49.

<sup>8</sup> Alberta Medical Association. (1997). *Guideline for Use of PSA and Screening for Prostate Cancer*, p. 2.

<sup>9</sup> MacIntosh, H.J Natl Cancer Inst 1997 Feb 5;89(3):188-189 *Why do African-American men suffer more prostate cancer?*

## APPENDIX III- Expectant Management

- **Expectant management** involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses or if symptoms become imminent
- Patients with clinically localized cancers that are candidates for definitive treatment and choose expectant management should have regular follow up
  - DRE and PSA every six months
  - Needle biopsy of the prostate may be repeated within 6 mo of diagnosis if initial biopsy was < 10 cores or assessment discordant (eg, palpable tumour contralateral to side of positive biopsy)
  - Needle biopsy should be performed within 18 months if > 10 cores obtained initially, then periodically
- A repeat biopsy may be indicated for any sign of disease progression by exam or markers
- Advantages of expectant management:
  - Avoid side effects of definitive therapy
  - Quality of life/ normal activities retained
  - Risk of unnecessary treatment of small, indolent cancers is reduced
- Disadvantages of expectant management:
  - Risk of progression and/or metastases
  - Subsequent treatment may be more intense with increased side effects
  - Increased anxiety
  - Requires frequent medical exams and periodic biopsies
  - Uncertain long term natural history of prostate cancer
  - Timing and value of periodic imaging studies is not yet determined

## APPENDIX IV- Observation

**Observation** consists of medical surveillance where it is unlikely that the patient will be treated with radiation therapy or surgery for cure due to a limited life expectancy or severe medical co-morbidities. Treatment at symptomatic progression will likely consist of Androgen Deprivation Therapy (ADT) with additional interventions given with the intent of improving impairments in prostate cancer-specific health-related quality of life.

## APPENDIX V- Surgical Guidelines for Radical Prostatectomy

### **Radical Retropubic Prostatectomy**

Patients are admitted the same day of their surgery and, on average, stay in the hospital for two nights. The radical retropubic prostatectomy is performed under general anesthesia. An infraumbilical midline incision is used. The dorsal vein complex is controlled and divided. The urethra is divided just distal to the prostatic apex. At this point a nerve-sparing technique is used if indicated. The lateral pedicles of the prostate are controlled and divided. The Denonvillier's fascia is divided and the superior portion of the prostatic pedicles is controlled and divided. The seminal vesicles are dissected and the vas deferentia are divided. The prostate is completely excised using a bladder neck sparing or non-bladder neck sparing technique. The specimen is sent for permanent sections in the pathology laboratory. Hemostasis is performed. The bladder neck is tapered. The bladder neck is everted. The anastomosis is performed with absorbable sutures. If necessary, a urethral catheter is inserted and left on average for 10 days. A drain is left in place. The incision is closed in two layers.

The procedure can also be performed laparoscopically or transperineally.

#### Acute side effects/complications

- bleeding (common but severe bleeding requiring a transfusion is rare)
- urinary extravasation (common but rarely significant)
- lymphocele/edema (rare)
- infection/DVT/infarct (rare)

#### Late side effects/consequences

- impotence (depends on whether a nerve-sparing procedure is performed)
  - 100% if nerve-sparing prostatectomy is not performed
  - 70% if unilateral nerve-sparing prostatectomy is performed
  - 40% if bilateral nerve-sparing prostatectomy is performed
- long term (more than 12 months) urinary incontinence
  - mild stress incontinence 10-30%
  - distress from severe incontinence 2-3%

### **Nerve Sparing Prostatectomy**

A method to decrease the risk of postradical prostatectomy erectile dysfunction is to perform a Nerve Sparing procedure. As the neurovascular bundles lie outside the capsule and fascia of the prostate, cancer control is not compromised by a Nerve Sparing procedure when the tumour is organ confined. Many clinical scenarios have been proposed outlining indications and contraindications for a Nerve Sparing prostatectomy, but currently there is no single approach that has been widely adopted. The main eligibility criteria for a Nerve Sparing procedure among the majority of authors are:

#### Indications for Nerve-Sparing Radical Prostatectomy may include:

1. normal preoperative erectile function; and
2. clinical T1 or T2 prostate cancer; and
3. PSA < 10 ng/mL; and
4. Gleason score  $\leq 7$

## APPENDIX VI- Technical Guidelines for Radiotherapy for the Treatment of Non-Metastatic Prostate Cancer

### A) Technical Guidelines for External Beam Radiotherapy for the treatment of Non-Metastatic Prostate Cancer

#### 1. Contouring

Every patient will have the prostate gland and visible extent of the primary tumour outlined as the Gross Tumor Volume (GTV). The rectum will be outlined, at least 1 cm beyond the outermost Planning target volume (PTV: a construct that represents a 3 – dimensional expansion of the GTV, to account for potential microscopic spread of cancer cells, and day – to – day organ motion and systematic and random errors in patient positioning). If the seminal vesicles are to be included as either part of the GTV or Clinical target volume (CTV: a construct that represents a 3 – dimensional expansion of the GTV, to account for potential microscopic spread of cancer cells), then they will be contoured as well. At least one PTV will be defined to facilitate planning and generation of dose – volume histograms. Other organ contouring is optional.

#### 2. Risk stratification

All patients with non-metastatic, regional node negative prostate cancer will be categorized according to a risk-adapted approach, as outlined in the Canadian Consensus Guideline<sup>1</sup>, dividing patients into 3 risk strata (Low, Intermediate, and High Risk) as follows. **Low risk** patients are those patients who have prostate cancer **with all** of the following features: PSA < 10 ng/mL, Gleason score of 6 or less, and T stage T2a or less (as defined in the 2002 AJCC staging system<sup>2</sup>). **High risk** patients have **any one** of the following features: T3<sub>a/b</sub> T stage, Gleason score of 8 or greater, or PSA ≥ 20 ng/mL. **Intermediate risk** patients are all others.

#### 3. Guidelines for Low Risk Patients

**Use of Androgen Deprivation:** Androgen deprivation is not required, but may be considered for patients who have marked Urinary Obstructive or Irritative symptoms, or when reduction of the size of the prostate is required to meet dose-volume constraints on normal tissues (either Bladder or rectal volume). Duration prior to radiotherapy = 2 – 8 months.

##### i) Dose

**Minimum dose to innermost PTV = 70 Gy in 35 fractions, range 70–74 Gy\***(see treatment technique footnote).

##### ii) Margin beyond GTV to innermost PTV

Margins will be chosen to cover the innermost PTV with a minimum of 95% of the prescribed dose, while minimizing dose to normal tissue

**Minimum margin: Superior/Inferior Direction = 1.0 cm**  
**Anterior/Posterior Direction = 1.0 cm (7mm posterior if multiphase)**  
**Lateral Direction = 0.5 cm**

##### iii) Treatment technique

Treatment can be in either 1 or 2 phases, using a conformal 4-Field Box technique. Margin reductions after 46–60 Gy can be employed if multiple phases are to be used.

Shielding will be created using MLC. At the Nova Scotia Cancer Centre, a 4mm margin from the PTV to shield edge will usually provide an adequate margin to account for the physical penumbra of the beam, and provide at least 95% coverage of the PTV. Utilization of the auto-block function in AcQSim is encouraged to facilitate the creation of shielding.

\* If doses greater than 70 Gy are to be used, a non-four-field, shrinking-field technique is encouraged to spare normal tissue.

#### **iv) Dosimetry**

Optimal beam weighting will provide as uniform a dose distribution as possible. The PTV(s) will be encompassed by at least the 95% isodose volume, and the dose prescribed to the ICRU Reference point (isocentre, 100% isodose volume). The maximum target dose should be positioned, if achievable, in the anterior aspect of the treated volume. The accepted deviation of the 95% isodose volume inside the PTV is 2mm. Any greater deviation will require adjustment of the field border or shielding, and new DRR's generated, and approved by the treating oncologist.

Recent data suggests that the probability of RTOG Grade II or greater rectal toxicity is a function of the relative volume of rectum that receives 70 Gy<sup>3</sup>. Summed plan (phase I and phase II) Cumulative Rectal Dose - Volume histograms will be created for all patients, and the following information recorded:

- 1) The relative volume of rectum that receives 70 Gy
- 2) The relative volume of rectum that receives 55 Gy

Absolute volumes can also be requested, but are not mandatory.

To meet acceptable normal tissue toxicity, the volume of rectum that receives 70 Gy should be less than 25%, and the volume that receives 55 Gy should be equal to, or less than 50%. In absolute volume, the volume of rectum that receives 70 Gy should be less than 15 cc.

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### **4. Guidelines for Intermediate Risk Patients**

**Treatment approach:** Patients will be treated with either Neo - adjuvant Hormonal therapy and Conventional Radiotherapy or Dose-escalated radiotherapy, with or without Neoadjuvant Hormonal therapy (see document "Dose-escalated 3-Dimensional Conformal Radiotherapy for the treatment of Prostate Cancer).

**Duration of Neo - adjuvant Androgen Deprivation** = 4-12 months total (2-8 months prior to radiotherapy).

**Time of Simulation** = at most 1 month prior to start of radiotherapy.

#### **A) Neo - adjuvant Hormonal therapy and Conventional Radiotherapy**

##### **i) Dose**

**Minimum dose to innermost PTV = 70 Gy in 35 fractions, range 70-76 Gy\*.**

##### **ii) Margin beyond GTV to innermost PTV**

Margins will be chosen to cover the innermost PTV with a minimum of 95% of the prescribed dose, while minimizing dose to normal tissue

**Minimum margin for Phase I** (see section on treatment of seminal vesicles and/or pelvis below):

**Superior/Inferior Direction = 1.4-1.5 cm**

**Anterior/Posterior Direction = 7 mm-1.5 cm**

**Lateral Direction = 0.9-0.5 cm**

### Minimum margin for Phase II:

Superior/Inferior Direction = 1.0 cm

Anterior/Posterior Direction = 7mm-1.0 cm

Lateral Direction = 0.5 cm

### iii) Treatment technique

Treatment can be in either 1 or 2 phases, using a conformal 4 – Field Box technique. Margin reductions after 46–60 Gy can be employed if multiple phases are to be used.

\* If doses greater than 70 Gy are to be used, a non – four – field, shrinking – field technique is encouraged to spare normal tissue.

For Doses greater than 74 Gy, intra–prostatic Fiducial Markers for prostate position verification are required.

Shielding will be created using MLC. A 4 mm margin from the PTV to shield edge will usually provide an adequate margin to account for the physical penumbra of the beam, and provide at least 95% coverage of the PTV. Utilization of the auto–block function in AcQSim is encouraged.

- **If the risk of seminal vesicle involvement or pelvic lymph node involvement is greater or equal to 15% (see below), then it is recommended to treat these structures as part of the phase I CTV. Treatment of these structures is not mandatory, and at the discretion of the treating radiation oncologist.**
- **Risk of seminal vesicle involvement can be estimated by the following equations, or by referring to the published “Partin” tables<sup>4</sup>.**

$$\% \text{ Chance SV involvement} = \text{PSA} + [(GS - 6) \times 10]$$

$$\% \text{ Chance Pelvic Lymph node involvement} = \frac{2}{3} \text{PSA} + [(GS - 6) \times 10]$$

### Phase I – technique depends on definition of PTV1

#### 1) Phase I PTV when SV included in CTV1

PTV1 = GTV + SV + 1.0 – 1.5 cm margin beyond SV

#### 2) Phase I PTV when Pelvic lymph nodes included in CTV1

PTV1 = GTV + SV + External, Internal, and pre – sacral lymph nodes + 1.0 – 1.5 cm margin beyond vessels adjacent to nodal groups at risk.

### iv) Dosimetry as per Low risk protocol

#### B) Dose – Escalated Radiotherapy, with or without Neo – adjuvant Hormonal therapy

See document “Dose–escalated 3–Dimensional Conformal Radiotherapy for the treatment of Prostate Cancer” for full details. A brief summary follows:

#### i) Dose

**Minimum dose to innermost PTV = 72 Gy in 36 fractions, range 72–76 Gy\*.**

#### ii) Margin beyond GTV to innermost PTV

Margins will be chosen to cover the innermost PTV with a minimum of 95% of the prescribed dose, while minimizing dose to normal tissue

**Minimum margin for Phase I (see section on treatment of seminal vesicles and/or pelvis below):**

**Superior/Inferior Direction = 1.4–1.5 cm**  
**Anterior/Posterior Direction = 7mm–1.5 cm**  
**Lateral Direction = 0.9–1.5 cm**

**Minimum margin for Phase II:**

**Superior/Inferior Direction = 1.0 cm**  
**Anterior/Posterior Direction = 7mm–1.0 cm**  
**Lateral Direction = 0.5 cm**

### **iii) Treatment technique**

Treatment can be in either 1 or 2 phases, using a conformal 4-Field Box technique. Margin reductions after 46–60 Gy can be employed if multiple phases are to be used.

- \* If doses greater than 70 Gy are to be used, a non-four-field, shrinking-field technique is encouraged to spare normal tissue.  
For Doses greater than 74 Gy, intra-prostatic Fiducial Markers for prostate position verification are required.

Shielding will be created using MLC. A 4mm margin from the PTV to shield edge will usually provide an adequate margin to account for the physical penumbra of the beam, and provide at least 95% coverage of the PTV. Utilization of the auto-block function in AcQSim is encouraged.

- **If the risk of seminal vesicle involvement or pelvic lymph node involvement is greater or equal to 15% (see below), then it is recommended to treat these structures as part of the phase I CTV. Treatment of these structures is not mandatory, and at the discretion of the treating radiation oncologist.**
- **Risk of seminal vesicle involvement can be estimated by the following equations, or by referring to the published “Partin” tables<sup>4</sup>.**

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## **5. Guidelines for High Risk Patients**

**Treatment approach:** Patients will be treated with Neo – adjuvant Hormonal therapy and Conventional Radiotherapy. Two years of treatment with an LHRH agonist following radiotherapy is also recommended, especially for High Grade (Gleason score 8–10) tumours.

**Duration of Neo – adjuvant Androgen Deprivation** = 6 months total (4 months prior to radiotherapy, 2 months concurrently).

**Time of Simulation** = 3 months after initiation of androgen deprivation.

**Total Dose = 70 - 71 Gy in 35 fractions**

### **Treatment technique**

Treatment will be in 2 phases:

**Phase I – Seminal vesicle and Pelvic lymph nodes are recommended to be included in CTV1**

PTV1 = GTV + SV + External, Internal, and pre – sacral lymph nodes + 1.5 cm margin

**Phase II = as per Low risk protocol definition**

## **6. Recommendations for Bladder and Rectal filling**

**For consistency, patients can be treated:** 1) **Bladder Full** – see below  
2) **Rectum empty** – see below

### **Bladder filling Protocol** (for simulation and treatment)

- 1) Patient to empty bladder 30 min. prior to treatment
- 2) Patient will drink 10 oz. of water prior to treatment

### **Rectal emptying Protocol** (for simulation and treatment)

- 1) Patient to have a bowel movement on each day prior to their treatment, using a laxative of their choice, to be reviewed by the radiation therapist, nurse or physician to ensure appropriateness of use.
- 2) If the patient is unable to achieve reliable rectal emptying, he should use the rectal emptying protocol as per the “Dose – escalated, conformal patients”, utilizing:
  - a. Two tablespoons of Milk of Magnesia each night before simulation and before each radiation treatment, until
  - b. The patient consistently achieves an empty rectum, or has excessive diarrhea or abdominal cramping.
- 3) If the patient does not have a bowel movement on the day of simulation or treatment, they are to use one Bisacodyl (Dulcolax®) suppository (10mg) to facilitate rectal emptying.
- 4) If excessive abdominal or rectal gas, as per the following criteria:
  - a. As experienced by the patient by self-reporting.
  - b. As visualized on Portal Imaging, on a consistent basis

Then Simethicone (Ovol®) 80–160 mg PO BID will be recommended

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## ***B) Technical Guidelines for Brachytherapy alone or with External Beam Radiotherapy for the treatment of Non-Metastatic Prostate Cancer***

### **1. Organ contouring and risk stratification**

**See** Technical Guidelines for External Beam Radiotherapy for the treatment of Non-Metastatic Prostate Cancer **sections 1 and 2.**

### **2. Indications for Permanent Seed Monotherapy**

- a) Patients must meet all of the following criteria:
- i) Staging criteria:
    - T1c- T2b (not bilateral, i.e. not T2c)
    - Gleason score 6 (3+3) or less, or:
      - i. Gleason 7(3+4), if <1/3 of cores positive for invasive prostate cancer, minimum sextant biopsies, octant preferred
    - PSA < 10 or:
      - i. PSA < 15, if <1/3 of cores positive for invasive prostate cancer, minimum sextant biopsies, octant preferred
      - ii. Anatomical and clinical criteria:
  - No previous TURP

- Prostate volume less than 50 cc (if larger, consider 3 months, unless it is > 75 cc in which case androgen deprivation is unlikely to reduce volume sufficiently to provide a good implant)
- No pubic arch interference; this is evaluated at the time of the planning ultrasound
- Significant Irritative or obstructive urinary symptoms

## b) Dose = 160 Gy

### **3. Indications for Combination Permanent Seed Monotherapy or HDR temporary implant and External Beam therapy**

- Intermediate risk prostate cancer, with the same anatomical and clinical criteria as listed in section B, 2. Seminal vesicles and regional lymph nodes to be treated as in section A, 4) iii.
- **Dose** = 45 Gray in 25 fractions to prostate ± seminal vesicles or regional lymph nodes by external beam and either:
  - i. 105 Gy Permanent seed; or
  - ii. 2 temporary HDR implants 8 to 9 Gy per implant

### **4. Indications for Combination Androgen Deprivation, External Beam therapy and HDR brachytherapy boost**

- High risk prostate cancer, with the same anatomical and clinical criteria as listed in section B, 2. Seminal vesicles and regional lymph nodes to be treated as in section A, 4) iii.
- Androgen deprivation for 2 to 3 years
- **Dose** = 45 Gray in 25 fractions to prostate + seminal vesicles and regional lymph nodes and 2 temporary HDR implants 8 to 9 Gy per implant.

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## **References**

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2. Greene FL, et al. American Joint Committee on Cancer Staging Manual – 6<sup>th</sup> Edition. 2002. Lippincott Raven Publishers, Philadelphia, PA.
3. Pollack A, Zagars GK, Smith LG, Lee JJ, von Eschenbach AC, Antolak JA, Starkschall G, Rosen I. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. (Clinical Trial. Clinical Trial, Phase III. Journal Article. Randomized Controlled Trial) *Journal of Clinical Oncology*. 18(23): 3904-11, 2000 Dec 1.
4. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. (Journal Article) *Urology*. 58(6): 843-8, 2001 Dec.

## APPENDIX VII- Systemic Androgen Deprivation Therapy (Hormonal) Regimens

The choice of initial orchiectomy or androgen deprivation (hormonal) agent(s) for any individual patient will depend on many factors.

The advantages of orchiectomy are:

- One procedure with no need for future injections every 1-4 months
- Cost (no need to pay for expensive prescription drugs, etc.)

The advantages of LHRH agonists are:

- Potentially reversible actions
- No surgical procedure

Combined Androgen Blockade (CAB- LHRH agonist plus non-steroidal antiandrogen agent) is not routinely indicated.

After initial failure of ADT, secondary hormonal manipulation should be tried (eg. addition of a non-steroidal antiandrogen or discontinuation of non-steroidal antiandrogen if already on) Monotherapy with nonsteroidal antiandrogens is not routinely indicated.

Other hormonal manipulations, such as ketoconazole or estrogens may be tried. Some phase II trials show a decline in PSA. There are no randomized data to support any survival advantage.

### **OPTIONS:**

#### **1. Orchiectomy**

- The testicles are surgically removed. The procedure is done as an outpatient, usually under local anesthetic. Surgical castration (orchiectomy) is permanent.

#### **2. LHRH Agonists**

Goserilin (Zoladex®) 3.6 mg SC Depot q28d  
or 10.8 mg SC Depot q84d  
Leuprolide (Lupron®-IM, Eligard®-SC) 7.5 mg IM/SC Depot q28d  
or 22.5 mg IM/SC Depot q84d  
or 30 mg IM/SC Depot q120d  
Buserilin (Suprefact®) 6.3 mg SC Depot q56d  
or 9.45 mg IM Depot q120d

Note: Due to an initial rise in testosterone levels, patients should be given a non-steroidal antiandrogen (see below) for 2-4 weeks at the same time as their first LHRH agonist dose

#### **3. Non-steroidal Antiandrogen Agents**

Flutamide (Euflex®) 250 mg PO TID  
Bicalutamide (Casodex®) 50 mg PO daily, up to 150 mg PO daily to TID  
Nilutamide (Anandron®) 50 mg PO BID or TID

#### 4. Other Hormonal Treatments

Cyproterone (Androcur®) 50-100 mg PO BID or TID

Megestrol (Megace®) 80-160 mg PO daily

Ketoconazole (Nizoral®) 400 mg PO TID

(+/- Hydrocortisone 20 mg qAM & 10 mg qPM)

Estrogens- e.g. Diethylstilbestrol 1 mg PO Daily

#### ***Common Hormonal Therapy Adverse Effects***

##### Acute/Early Side Effects:

- Fatigue (common)
- Sweats, hot flashes (common)
- Loss of libido; erectile dysfunction while on hormones

##### Side Effects with Long Term Use (>6 months):

- Loss of muscle mass
- Osteoporosis
- Anemia
- Gynecomastia/nipple tenderness
- Cognitive changes
- Lipid profile changes

##### Extra Toxicities of Non-Steroidal Antiandrogen Agents:

- Diarrhea
- Liver dysfunction (with Flutamide)
- Night blindness (with Nilutamide)
- Alcohol intolerance (with Nilutamide)
- Interstitial pneumonitis (rarely with Nilutamide)

##### Management of ADT Side Effects:

1. Hot Flashes
  - Consider Venlafaxine (Effexor®) 37.5-75 mg PO daily
  - or Cyproterone (Androcur®) 50 mg PO daily
2. Gynecomastia/Nipple Tenderness
  - Consider external beam radiotherapy
3. Osteoporosis
  - Patients should be encouraged to take Vitamin D and calcium supplements
  - Patients should be screened with DEXA scans
  - If osteoporosis present, consider bisphosphonate agent

## APPENDIX VIII- Systemic Chemotherapy Regimens

### Chemotherapy Regimens

#### Docetaxel-Prednisone Chemotherapy

Docetaxel 75 mg/m<sup>2</sup> IV Day 1 q21 days  
Prednisone 5 mg PO BID  
Dexamethasone premedication required

#### Mitoxantrone-Prednisone Chemotherapy

Mitoxantrone 12 mg/m<sup>2</sup> IV Day 1 q21 days  
Prednisone 5 mg PO BID

### **Common Chemotherapy Adverse Effects**

#### Side Effects:

- Myelosuppression, neutropenia
- Stomatitis
- Nausea, vomiting, diarrhea
- Anorexia
- Fatigue
- Hypersensitivity, neurosensory effects, alopecia, fluid retention, joint aches/ discomfort (with Docetaxel)
- Congestive heart failure (rarely with Mitoxantrone)

#### Side Effects with Prednisone

- Hyperglycemia
- Gastric irritation
- Fluid retention
- Mood changes
- Decreased ability to sleep
- Skin fragility/easy bruising
- Osteoporosis (with long term use)
- Loss of muscle mass (with long term use)

## APPENDIX IX- Guidelines for the Use of Docetaxel in Hormone Refractory Prostate Cancer (HRPC)

### Capital District Health Authority/*Cancer Care Nova Scotia*

#### Guideline Questions

- Does docetaxel induce objective responses, improve time to disease progression (TTP), demonstrate improvement in pain and prolong survival in patients with metastatic HRPC?
- Does the magnitude of benefit including toxicity and quality of life (QOL) warrant the routine use of this agent in symptomatic HRPC patients?
- Should docetaxel be given to symptomatic (HRPC) patients that are currently on mitoxantrone and prednisone?
- Is there sufficient evidence to recommend the use of docetaxel in asymptomatic HRPC patients?
- Is there currently a role for the use of docetaxel in HRPC patients with rising prostate-specific antigen (PSA) but no evidence of metastatic disease?

#### Objectives

- To make recommendations regarding the use of docetaxel in patients with HRPC.

#### Outcome Measures

- To review response rates (RR), TTP, pain responses, PSA responses, progression-free survival (PFS) or overall survival (OS).
- Toxicity and QOL are considered.

#### Evidence

- Two phase III randomized, controlled, multicentre studies have been reported.
- One trial (Tannock et al 2004 - TAX 327 Study) randomized (n=1006) metastatic HRPC patients to docetaxel q3 weeks plus prednisone, weekly docetaxel plus prednisone or mitoxantrone plus prednisone. The primary endpoint was OS. Secondary endpoints included PSA response, pain response, measurable response, QOL and toxicity (Level II evidence) (Published).
- The second trial (Petrylak et al 2004 - SWOG 99-16 Study) randomized (n=770) patients with progressive metastatic HRPC to a combination of docetaxel and estramustine versus mitoxantrone and prednisone. The primary endpoint was OS. Secondary endpoints included PFS, objective RR, PSA response and toxicity (Level II evidence) (Published).

#### Benefit

- With a median follow-up of 20.7 months, the phase III TAX 327 Study demonstrated an improved median OS of 18.9 months (Hazard Ratio (HR) = 0.76) (95% CI 0.62-0.94) in the docetaxel/prednisone (every 3 week) arm compared to 16.5 months in the mitoxantrone/prednisone arm (p=0.009). There were significant improvements in the docetaxel/prednisone (every 3 week) arm compared to the mitoxantrone/prednisone arm in terms of pain response (35% versus 22%, p=0.01), PSA response (45% versus 32%, p=0.0005) and QOL measured by the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire (22% versus 13%, p=0.009).
- With a median follow-up of 32 months, the phase III SWOG 99-16 Study demonstrated an improved median OS of 17.5 months in the docetaxel/estramustine arm compared to 15.6 months in the mitoxantrone/prednisone arm (p=0.02). The HR was 0.80 (95% CI 0.67-0.97).

There were significant improvements in the docetaxel/estramustine arm compared to the mitoxantrone/prednisone arm in terms of median TTP (6.3 months versus 3.2 months,  $p < 0.001$ ), and PSA response (50% versus 27%,  $p < 0.001$ ). Pain relief was similar in both groups although no data on how this was measured was reported.

### **Adverse Effects**

Docetaxel (every 3 week regimen) in the TAX 327 Study demonstrated similar grade 3 or 4 hematologic toxicities as the mitoxantrone arm with the exception of neutropenia (32% versus 22%  $p \leq 0.05$ ). Adverse events led to the withdrawal of 11% of patients in the docetaxel (every 3 week) arm compared to 10% in the mitoxantrone/prednisone arm.

The docetaxel/estramustine arm of the SWOG 99-16 trial reported higher rates of toxicity (grade 3 or 4) than the mitoxantrone/prednisone combination. The group given docetaxel/estramustine had significantly higher rates of grade 3 or 4 neutropenic fevers (5% versus 2%,  $p = 0.01$ ), cardiovascular events (15% versus 7%,  $p = 0.001$ ), nausea and vomiting (20% versus 5%,  $p < 0.001$ ), metabolic disturbances (6% versus 1%,  $p < 0.001$ ) and neurologic events (7% versus 2%,  $p = 0.001$ ). There were eight treatment related deaths in the docetaxel/estramustine group and four treatment related deaths in the mitoxantrone/prednisone group. Adverse events led to the withdrawal of 16% of patients in the docetaxel/estramustine arm compared to 10% in the mitoxantrone/prednisone arm.

### **Evidence Based Recommendation**

Systemic chemotherapy has played a limited role in the treatment of HRPC for a number of years. The goal of treatment has been palliation of symptoms and an overall improvement in QOL. The trial reported by Tannock et al (1996) evaluated a “palliative response” with a combination of mitoxantrone/prednisone clearly showing a statistically significant benefit of using mitoxantrone/prednisone over prednisone alone (29% vs 12%,  $p = 0.01$ ). Unfortunately there was no benefit in OS. The duration of palliation was longer in patients who received chemotherapy (median 43 weeks vs 18 weeks,  $p < 0.0001$ ). The data were confirmed by the trial reported by Kantoff et al (1999) comparing mitoxantrone/hydrocortisone versus hydrocortisone alone. There was a delay in time to treatment failure (TTF) and disease progression in favour of the combination arm but no difference in OS. There was an improvement in QOL in terms of pain control.

The two trials by Tannock et al 2004 and Petrylak et al 2004 are the first trials to report a survival benefit using a new chemotherapy agent, docetaxel, in HRPC. With the significant toxicity profile of estramustine, **the combination of docetaxel/prednisone (every 3 week regimen) represents a new standard first-line chemotherapy for patients with metastatic HRPC.**

There are no data available with respect to patients who have only a rise in their PSA with no evidence of metastatic disease. Patients enrolled in these trials were excluded if they had previous exposure to anthracyclines. Patients who are currently on mitoxantrone/prednisone and achieving a clinical benefit should not be switched to docetaxel.

## APPENDIX X- Systemic Radionucleotide Guidelines

(Adapted from Cancer Care Ontario Practice Guideline #3-6; 10/01)

### Guideline Question I

What is the role of strontium<sup>89</sup> in effective palliation of patients with stage D endocrine-refractory prostate cancer and multiple sites of painful bone metastases?

### Practice Guideline

- Strontium<sup>89</sup> is recommended for use in patients with endocrine-refractory carcinoma of the prostate who have multiple uncontrolled painful sites of metastases on both sides of the diaphragm, not adequately controlled with conventional analgesic therapy and in whom the use of multiple single fields of external beam radiation is not possible.
- Strontium<sup>89</sup> has proven efficacy in the palliation of hormone-refractory painful bony metastases from prostate cancer.
- Strontium<sup>89</sup> has not been shown to lengthen the average duration of patient survival. There is limited evidence to determine its relative efficacy compared to wide-field irradiation. Specific indications, recommendations for administration, and the need for further data about the treatment are summarized in the report.

### Indications for strontium<sup>89</sup> therapy in this clinical setting

All of the following are required:

1. Hormone refractory metastatic prostate cancer with osteoblastic metastases
2. Multiple sites of pain poorly controlled with conventional narcotics
3. Ambulatory for more than ½ of the day (ECOG Performance Status ≤ 2)
4. Adequate bone marrow reserve and renal function

### Guideline Question II

What is the role of strontium<sup>89</sup> in effectively palliating patients with stage D hormone-refractory prostate cancer receiving local radiotherapy for isolated painful bony metastases?

### Practice Guideline

- Strontium<sup>89</sup> is not recommended for routine use as an adjunct to local radiotherapy in this clinical setting.
- Strontium<sup>89</sup> is known to temporarily reduce analgesic intake and to modestly delay the need for treatment of sites of new pain, when used as an adjunct to local field radiotherapy and when compared to placebo adjunct therapy. The clinical significance of these benefits is not certain.
- Strontium<sup>89</sup> has not been shown to lengthen the average duration of patient survival in this setting and there is no evidence to determine its relative efficacy compared with wide-field irradiation. The need for further data about the treatment is summarized in the report.

### Contraindications for Strontium<sup>89</sup>

1. Life expectancy < 6 months

2. Impending pathological fracture or epidural compression of neural structure within spinal canal
3. Patient taking calcium supplements
4. Patient with an indwelling catheter or neostomy tubes
5. Solitary area of bone pain

## APPENDIX XI- Guideline Development Process

This guideline was written by Members of the Genitourinary Cancer Site Team, with additional input by Dr. D. MacLeod, Susan Marsh and Dr. Lorna Butler for the Supportive Care section, and supported by Larry Broadfield. Specific recommendations were based upon evidence routinely reviewed by the expert members of the CST and by consensus development among the CST members. Upon completion of an initial draft, the guideline was reviewed by the entire Genitourinary CST for critical appraisal. Format issues were resolved in collaboration with the Guidelines Resource Team of *Cancer Care Nova Scotia*.

This guideline was written for an audience of general practitioners and other health professionals, not necessarily prostate cancer specialists. As such, it is a synthesis of knowledge and evidence, and reflects the practice policies of the Genitourinary Cancer Site Team in Nova Scotia. The written text on management is supported by the graphic flowcharts in the 'Practice Pathways' section. These flowcharts are reproduced in a stand-alone short version of the guideline, called the "Quick Reference Version".

Once the draft document was approved by the CST, it was distributed to a group of community reviewers. Community reviewers included identified urologists, pathologists, family doctors, medical and radiation oncologists, nurses (including community, med-surg, oncology, administrative and general hospital nurses, clinical nurse specialists and nurse practitioners), pharmacists, and other health professionals from health care districts in Nova Scotia, New Brunswick, Newfoundland, and Prince Edward Island. All responses were anonymous. Most reviewers were given the Quick Reference Version for review. Responses to the draft review were collected on a standard guideline review questionnaire.

### Community Reviewer Results

There were 43 responses to the draft guideline. By discipline and province, there were:

17 Physicians	31 Nova Scotia
19 Nurses	8 New Brunswick
3 Pharmacists	1 PEI
4 Other	3 Newfoundland

The Guideline Review Questionnaire was structured to solicit feedback on: Usefulness, Format, Content and Dissemination. There were category questions and open-ended questions in all areas, collected on a standard guideline review questionnaire. Results are presented below.

### Usefulness of the Guideline

There were 4 questions on the usefulness of this guideline.

*A guideline on this topic will be useful to clinicians.*

Strongly Agree =	23	Agrees	41
Agree =	18	Disagrees	0
Neither Agree/Disagree =	0	No Answer	2
Disagree =	0		
Strongly Disagree =	0		

*Would you use this guideline in your own practice?*

Yes = 35      No = 2      Unsure = 4

*How do you think this Guideline would be useful to you and other Health Professionals?*

Decision aid when caring for a patient = 33  
 Better understanding about how prostate cancer is detected and managed = 35  
 Aid for teaching health care professional students about prostate cancer = 22  
 Aid patient education on prostate cancer = 22

*In what ways do you think this Guideline might not be useful?*

Some recommended treatment practices are not practical or available in your setting = 14  
 Some recommended treatment practices are unlikely to be accepted by your patients = 3  
 Do not believe in guideline as decision aid = 1  
 Unanswered = 19  
 Comments = 3

It is clear from the feedback responses that the guidelines were felt to be useful by clinicians, and would be used in clinical practice. The guideline would be useful as a decision aid, aid for teaching health care professionals and patients, and would help practitioners to better understand prostate cancer. Three respondents noted, however, that some treatments discussed in the guideline might not be available locally, or may not be acceptable to some patients. One respondent felt that guidelines are not useful as a decision aid.

### Guideline Format:

There were three questions on the usefulness of this guideline.

*The format of the guideline is easy to use.*

Strongly Agree =	5	Agrees	39
Agree =	34	Disagrees	0
Neither Agree/Disagree =	3	No Answer	1
Disagree =	3		
Strongly Disagree =	0		

*The Practice Pathways (flowcharts/ algorithms) are easy to understand.*

Strongly Agree =	6	Agrees	38
Agree =	32	Disagrees	0
Neither Agree/Disagree =	4	No Answer	1
Disagree =	0		
Strongly Disagree =	0		

*In which other format(s) should this CCNS guideline be developed once it is approved?*

- Pocketbook copy mailed to all appropriate clinicians (approx. 4"x7") = 21
- Pocketbook copy available on request = 9
- Comprehensive version on request = 10
- Multiple versions on CCNS website = 14
- Downloadable for Palm Pilot or other PDA = 16
- Presentations in conjunction with Continuing Education activities = 20

*Additional Comments = 6*

Of 43 respondents, most agreed that the format was easy to use. The results were similar when asked if the flowcharts were easy to understand. On the question of other formats, there was some support for a pocketbook version (approx 4" by 7") and also a downloadable PDA version. It is the practice of CCNS to post all versions of

each guideline on the website and to send any guideline version on request, so these options are already in place.

### Guideline Content:

There were two questions on the content of this guideline.

*Overall, you agree with the content and recommendations of this guideline.*

Strongly Agree =	7	Agrees	28
Agree =	21	Disagrees	0
Neither Agree/Disagree =	2	No Answer	12
Disagree =	0		
Strongly Disagree =	0		

*Comments:*

Additions to the guideline = 14

Deletions from the guideline = 1

Changes to the guideline = 7

*Does the Quick Reference Version contain the appropriate information?*

Yes = 11                      Unsure = 1

No = 0                         Comments = 5

None of the 43 respondents disagreed with the content or recommendations, although 12 did not answer the question. Twelve respondents answered the question about the content in the Quick Reference Version; of these, 11 agreed with the amount of content and 1 was unsure. From these results, it would appear that the content is correct and that right amount is included in the QRV.

### Guideline Dissemination:

This guideline should be disseminated to all appropriate practitioners in:

- Nova Scotia = 18                      Do Not Disseminate = 2
- Atlantic Canada = 22                No Answer = 2

*In your opinion, should this guideline be disseminated to appropriate health care practitioners:*

- Once it is approved, and periodically afterwards as new versions are approved = 29
- Only in response to a patient referral for specialist care (e.g. to a cancer centre) = 2
- Practitioners should be notified when it is available on the website, and they can get it themselves as they choose = 14
- No Answer = 2
- Comments = 2

*If you do not think this guideline should be disseminated, please check ALL the reasons below:*

Other provinces have their own guideline development processes = 4

Not the mandate of *Cancer Care Nova Scotia* to distribute guidelines outside Nova Scotia = 5

No Answer = 14

*Other Dissemination Suggestions = 22*

Twenty nine respondents felt that CCNS should send the guideline to health care practitioners once approved and when new versions are approved. Others thought that practitioners should get the guidelines themselves from the website. About half the respondents thought the guidelines should be disseminated in Nova Scotia and the other half said across Atlantic Canada. Two felt the guidelines should not be disseminated. Even though four respondents felt that other provinces have their own guideline processes and five felt that it is beyond the mandate of CCNS to distribute outside Nova Scotia, the results from this and previous community review processes (for other guidelines) are consistent that most health care professionals favour dissemination across the entire region. The plan is to distribute the Quick Reference Version to a large group of health care professionals and to suggest the website for access to the Full Version and to the Comprehensive Version.

### **Reconciliation of Guideline with Feedback Results**

All feedback was reviewed and appropriate changes were made to the draft guideline. The QRV was shortened to 8 pages. Many editorial changes were made to the Full Version. The edited document was returned to the Genitourinary Cancer Site Team (CST) for final review and approval.

### **Quality Control Review**

Upon review of the feedback from the community reviewers, and incorporation of appropriate comments, the guidelines were reviewed by the Guidelines Resource Team against the AGREE tool for guideline

evaluation. The quality components from the AGREE criteria were identified within the guideline.

The guideline will be reviewed three years after approval or revised as new evidence becomes available.

The development of this guideline was funded indirectly by CCNS via a stipend for the Genitourinary Cancer Site Team's operations. CCNS staff also support the guideline development process. CCNS directly funded the design, printing and dissemination of the guideline survey as well as the approved guideline. The views and interests of CCNS have not influenced the Genitourinary CST's recommendations in this guideline.

### **Publication and Dissemination**

The approved guideline is published in a Full Version, and a Quick Reference Version (just the Practice Pathways). The Full Version will be circulated in hard copy to prostate cancer specialists (from multiple disciplines) as well as to the cancer chemotherapy clinics and regional hospital pharmacies in Nova Scotia. The Quick Reference Version will be circulated to all health care professional subscribers to the *CCNS In Practice* newsletter (physicians, pharmacies, oncology nurses and others in Nova Scotia and Atlantic Canada). Copies of either version will also be made available to healthcare professionals in Prince Edward Island, Newfoundland, and New Brunswick. Others who are interested may request hard copies by contacting *Cancer Care Nova Scotia (CCNS)* at 1-866-599-2267 or download from the CCNS website ([www.cancercare.ns.ca](http://www.cancercare.ns.ca)). In addition, the Comprehensive Version (Full Version plus all current Appendices) will be published on the CCNS website only.



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