Prostate Cancer

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- **What is the chance of a male developing prostate cancer? What is the chance of dying of prostate cancer?**

Most common serious cancer diagnosed and second most common cause of cancer death in males. The chance of developing prostate cancer is 1 in 9, but only 1 in 30 die from the disease.

- **What is the currently recommended screening regimen for prostate cancer?**

Currently, screening PSA **not** recommended for asymptomatic males with a normal digital rectal examination at the time of annual physical examination. Males age >50 **or** with a positive family history **or** who request the test may be offered PSA screening after appropriate counselling regarding the limitations of the test and the uncertainties regarding intervention versus observation in patients with early prostate cancer.

- **Describe your approach to patients in clinic (i.e. what does your staff person want you to tell him/her after your assessment)?**

1. **First, determine the TNM stage of the patient.**

Staging

T1 Not palpable/visible
- T1a <5% of TUR
- T1b >5% of TUR
- T1c needle biopsy

T2 Confined to prostate (must be palpable or seen on imaging)
- T2a One half of one lobe or less
- T2b More than one lobe, but not both lobes
- T2c Both lobes

T3 Extraprostatic extension
- T3a Extracapsular
- T3b Seminal vesicle

T4 Invades adjacent structures
(Bladder neck, external sphincter, rectum, levator muscles or pelvic wall)

Nx Not assessed
N0 Node negative
N1 Node positive

Mx Not assessed
M0 No evidence distant metastasis
M1 Distant metastasis

Stage

I T1a, G1 (well differentiated)
II T1a >G1 or T1b-T2
III T3
IV T4 or N1 or M1

2. Review the pathology

- The vast majority of neoplasms of the prostate are adenocarcinomas. Occasionally, other histologies (sarcoma, small cell tumors) may be seen.
- Prostate adenocarcinomas are graded by the Gleason score. This is the sum of two numbers, which represent the 2 most dominant patterns of differentiation scored from 1-5.
- Tumors may also be divided as well differentiated (Gleason 2-6), moderately differentiated (Gleason 7), and poorly differentiated (Gleason 8-10). Tumor grade is a strong prognostic factor in both treated (surgery or radiation) patients as well as patients where observation is elected.

Your staff person will also want to know certain factors from the pathology report that provide prognostic information:

- The presence or absence of perineural/lymphatic/vascular invasion
- Extension beyond the prostatic capsule into fat
- Number of cores involved/percentage of cores involved
- Which lobes were involved
- The presence of PIN (prostatic intra-epithelial neoplasia)

If the pathology is from a prostatectomy specimen:

- The status of the surgical margins (involved versus clear)
- Seminal vesicle invasion or extracapsular extension
- The presence or absence of nodal involvement (if sampled)

3. Review blood and radiological assessments

- Serum PSA
- Transrectal ultrasound done as part of biopsy confirmation will determine the size of the prostate and presence of nodules
- Bone scan (usually performed only if pre-treatment PSA > 20 or Gleason grade $\geq$8 or T3)

Not recommended:

- Abdominal ultrasound or CT or MRI of the abdomen or pelvis (low sensitivity and specificity, 50-70%, for both nodal disease and extraprostatic extension).

4. **With this information, most patients can be separated into 1. low risk, 2. intermediate risk, 3. high risk, 4. biochemical failure and 5.metastatic disease. See definitions below.**

Treatment Overview

Low risk patients have a high chance of disease control with single modality therapy or observation; intermediate risk patients generally require combined modality therapy for optimal disease control (various combinations of surgery, radiotherapy and hormonal therapy); high risk patients have a high chance of systemic failure with localized treatment modalities and should be considered for adjuvant hormone therapy.

1. Low Risk Prostate Cancer

T1, T2 (organ confined) **and** low PSA ($\leq$10) **and** low Gleason grade ($\leq$6)
Generally high chance of long term control/cure with single modality therapy

Overview of Options

- Active surveillance
- Radioactive seed implant (T1 or T2a) *****
- Radical prostatectomy
- Radical external beam radiotherapy
- Experimental therapies (cryosurgery, hyperthermia) as part of a clinical trial

Detailed Review of Options

Observation/Deferred Treatment/Deferred Treatment/Deferred Treatment
Active Surveillance:

An Active surveillance approach recognizes that many men with low risk prostate have indolent disease with a low rate of cancer related mortality. Monitoring with PSA (every 6-12 months) and periodic biopsy (every 1-3 years) can identify men with more aggressive disease who require treatment with surgery or radiotherapy. Currently this approach is being studied in randomized trials comparing active surveillance with deferred intervention versus early treatment.

Radioactive Seed Implant, also known as brachytherapy *

- **What are the inclusion criteria for brachytherapy?**
  Gleason $\leq$6
  PSA $\leq$10
  No prior TUR
  Technically feasible (smaller prostate size and favorable pelvic anatomy)
- **What are the possible side-effects of brachytherapy?**

Acute side effects:
- Infection or bleeding (rarely)
- Lower urinary tract symptoms
- Urinary Retention (uncommon)

Late side effects
- Incontinence (rare)
- Impotence (approximately 50%)
- Erectile dysfunction

External Beam Radiotherapy

- **Describe the logistics of this treatment**

A simulation lasting less than an hour is required where a CT is used to obtain three-dimensional anatomical data. Tattoo marks on the skin will be made that are permanent. These help in positioning the patient for daily treatment. Treatments are daily, Monday to Friday, excluding holidays and weekends. Each treatment takes 10 to 15 minutes each day and a course of treatments lasts approximately 7 weeks.

- **What are the possible side-effects of external beam radiotherapy?**

Acute side effects:
- Fatigue
- Lower urinary tract symptoms

Late side effects:
- Chronic cystitis and/or proctitis (usually mild, self limited)
- Hematuria, hematochezia (rarely severe, rule out other concurrent pathology)
- Bowel obstruction; urethral stricture; severe proctitis or cystitis (rare)
- Erectile dysfunction

Radical Prostatectomy

- **What happens if the patient undergoes prostatectomy?**

Inpatient, 3-5 days, general anaesthetic generally indicated for younger patients; no/few medical comorbidities. Open and minimally invasive (laparoscopic or robot assisted laparascopic approaches.

- **What are the possible side-effects of surgery?**

Acute side effects/complications
- infection/bleeding/DVT/infarct (rarely)
- indwelling catheter (1-2 weeks)
- urinary leak (rare)
- lymphocele/edema (rare)

Late side effects/consequences
- erectile dysfunction (common)
- stress incontinence 10-30%
- total incontinence 2-3%

- **When would you consider radiation after surgery?**

Post prostatectomy radiotherapy considered for:

- pathologic evidence of extraprostatic extension (pT3) or positive margins
- persistent or rising PSA after prostatectomy with no evidence of metastatic disease

2. Intermediate Risk Prostate Cancer:

T1/2 **and** PSA 10-20 and/or Gleason 7. Usually requires more intensified or combination of treatment.

Overview of Treatment Options

- Dose escalated external beam radiotherapy +/- hormonal therapy
- Prostatectomy+ node dissection +/-postop radiotherapy
- Investigational: brachytherapy and external beam radiotherapy

Detailed Review of Options

External Beam Radiotherapy

See above **Radical Prostatectomy**
See above

Hormonal Therapy

Can be given for 3-8 months prior to radiotherapy to reduce tumor burden and prostate bulk prior to definitive therapy, but the effect on long term survival is subject of ongoing clinical trials. May also be given after radiation for up to 3 years for men with higher risk disease.

LHRH agonist (leuprolide/buserelin/goserelin)
Antiandrogen (bicalutamide) often given for 1st six weeks of LHRH agonist to prevent tumor flare.

- **What are the possible side-effects of hormonal therapy?**

Acute/early side effects:

- Fatigue (common)
- Sweats, hot flashes (common)
- Hepatitis or liver dysfunction, DVT/pulmonary embolus (rare)
- Loss of libido; erectile dysfunction while on hormones

Side effects with long term use (>6 months):

- Loss of muscle mass
- Osteoporosis
- Anemia
- Gynecomastia

3. High Risk Prostate Cancer

T3, T4 (extraprostatic spread or seminal vesicle involvement) or T1, T2 (organ

confined) with higher PSA (>20) or higher Gleason grade (8-10) **or** prostate cancer metastatic to pelvic lymph nodes (biopsy confirmed). High risk of both systemic and/or local failure with surgery or radiation alone Protracted hormonal therapy (>2-3 years) may be associated with a survival benefit when compared to radiotherapy alone in randomized controlled trials.

Overview of Treatment Options

- Radical external beam radiotherapy + adjuvant hormonal therapy x 2-3 years
- Prostatectomy **generally not** recommended
- Experimental therapy as part of a clinical trial

Detailed Review of Options

External Beam Radiotherapy

See above

Hormonal Therapy

Long term (2-3 years) LHRH agonist (leuprolide/buserelin/goserelin). Orchiectomy is an alternative to medical androgen suppression for permanent hormone suppression. Several trials have shown a survival benefit to combine hormones and radiation compared to radiation or hormone treatment alone.

Side effects:

- **What Follow-up Regimen after Radical Therapy would you offer?**

Men should be followed with PSA every 6-12 months until year 5 after treatment, then annually thereafter. A digital rectal exam should be done at least annually for surveillance. Monitoring should be coordinated between the oncologist, urologist and family doctor.

Intent of follow-up: detect recurrence and monitor for side effects

4. Biochemical Failure (rising PSA in an asymptomatic patient)

Over time, you will see some patients with a rising PSA. This indicates that the cancer has returned or is persistent. What treatment and when to treat are questions that are still being answered. Possible treatment considerations based on whether the failure is local or distant are listed below.

Post Prostatectomy

Isolated local failure likely:

- Nadir PSA after prostatectomy <0.2
- Slow rise more than 12 months post prostatectomy
- PSA <2-3
- Risk factors at time of prostatectomy (T3 or positive/close margin)

Salvage prostate bed radiotherapy can be considered

Isolated local failure unlikely:
- Nadir PSA after prostatectomy >0.2
- Rapid or early (<12 months) rise in PSA post prostatectomy
- PSA > 2
- Salvage with prostate bed radiotherapy alone unlikely

Consider hormones +/- radiotherapy

Post Radiotherapy
Isolated local failure likely:
- Initial low or intermediate risk prostate cancer
- Repeat bone scan and CT scan abdomen and pelvis negative
- Biopsy proven persistent disease within the prostate
- Lower PSA (<5) at time of salvage therapy

Consider for cryotherapy or observation or hormones. Selected patients may be suitable for salvage prostatectomy.

Systemic failure likely
- Initial high risk prostate cancer
- Positive bone scan
- Rapid rise in PSA (rising <12 mo. post radiotherapy or doubling time <12 mo.)
- Negative prostate biopsy and/or higher PSA (>5) at time of salvage therapy

Consider for hormones for salvage or observe until symptomatic metastasis develop

5. Metastatic Prostate Cancer

Metastatic prostate cancer is **not** curable but most men have improved symptoms and a period of disease control with hormonal therapy ranging from 24-36 months on average. Higher PSA, rapidly doubling time of PSA, higher PSA nadir on hormones; extensive bone metastasis or cytopenias generally predict a shorter time to progression on hormones. Hormone refractory disease is usually indicated by increasing symptoms and/or PSA while on hormone therapy.

Initial Treatment
Hormonal monotherapy (orchidectomy or LHRH agonist such as leuprolide/buserelin/goserelin) is recommended. The benefit of adding an antiandrogen (bicalutamide) to orchidectomy/LHRH agonist has not been proven by recent randomized controlled trials but can be considered for those with incompletely suppressed testosterone on monotherapy and during the first 6-8 weeks of LHRH agonist therapy to prevent tumor flare. Palliative radiotherapy to

symptomatic metastatic sites can be considered in addition to hormone therapy.

Treatment of Castrate Resistant Prostate Cancer (CRPC)

CRPC is defined by rising PSA or worsening symptoms while under hormonal therapy. Castrate testosterone levels should be confirmed and effective gonadal androgen ablation implemented if not the case. Addition of antiandrogen (bicalutamide) to orchiectomy or LHRH agonist may be tried. Discontinuation of long-term antiandrogen (bicalutamide) may produce a withdrawal response in about 20% of men who have been on this medication long term thus antiandrogens should be stopped if there is clear progression while on this medication. Symptom control should be optimized, especially analgesic therapy. Recent randomized trials have suggested a benefit to the prophylactic use of **bisphosphonates** in reducing adverse skeletal events (fracture, spinal cord compression) in patients with symptomatic bone metastases

The use of **chemotherapy** has been suggested to provide a modest survival advantage over secondary hormonal treatments in men with hormone refractory disease. Hormone refractory prostate cancer does not have a high objective response rate (tumour shrinkage, PSA decline) however clinical trials have indicated the following:

- Comparing prednisone 5 mg bid alone vs. prednisone plus Mitoxantrone: improved quality of life in the combination arm
- Comparing Mitoxantrone plus prednisone vs Docetaxel plus prednisone (Tannock et al): improved quality of life, pain control, and a small survival advantage (<8 weeks) in favour of Docetaxel/prednisone. This is now the standard for fit patients with HRPC.

Other interventions aimed at improving symptomatology may include:

- Systemic radionuclide (See below)
- Local field radiotherapy (helpful if 1 or 2 dominant symptomatic sites)
- Low dose steroid (i.e., prednisone 5-10 mg/day or decadron 1-2 mg/day)
- Bisphosphonate therapy