Prostate Cancer:

From Screening to Treatment

Philippe Violette, MD, CM; and Wassim Kassouf, MD, FRCSC

Presented at McGill University's Thursday Evening Learning Series, Montreal, Quebec.

The lifetime risk of developing clinically apparent prostate cancer (PCa) is approximately one in seven.[1] Though not all PCa is lethal, it remains the third highest cause of cancer related death among men.[1] The incidence of PCa varies greatly between populations. The highest rates are found among African Americans followed by American Caucasians and Scandinavian men and rates are lowest among Asian men.[2] The two most significant risk factors for PCa are being black (two-fold increase in risk compared to being white) and having a first-degree relative with PCa (two- to three-fold increase in risk).[3] PCa is rare among men < 50-years-of-age (< 0.1% of all patients) and is commonly diagnosed in men > 65-years-of-age.[4]

Diagnosis of PCa

PCa is usually asymptomatic especially in the early stages. Therefore, if one does not look for PCa, it may remain undiagnosed until late stages that are more difficult to treat. When symptoms do occur, they are similar to symptoms of men with benign prostatic hyperplasia (BPH) and may include:

- frequency,
- nocturia,
- decreased urinary stream,
- straining,
- urinary retention,
- incontinence,
- dysuria,
- hematuria, or
- hematospermia.

The basic tools in screening for PCa are the digital rectal exam (DRE) and serum PSA levels. If there is an abnormality among one or both tests, then the patient is counselled for a transrectal ultrasound (TRUS) with prostatic biopsy. DRE alone to identify PCa has a limited sensitivity (56%) and tends to detect cancer at more advanced stages.[5] However, DRE can detect cancers that are present despite a patient having a PSA below the traditional cut-off of 4.0 ng/ml. Adding the PSA measurement to the DRE as a combined screening test greatly increases sensitivity (up 80% in men 50- to 70-years-of-age) and the detection of cancers at an earlier stage.[5] Higher PSA levels have been correlated to risk of PCa (Table 1). TRUS is not a useful screening tool for PCa. The role of TRUS is to provide good sampling of tissue during biopsy of men previously identified as higher risk for PCa on the basis of DRE and PSA screening.

Table 1
Interpretation of PSA values

PSA value	Interpretation
0.5-4	Normal
4-10	20% risk of cancer
> 10	> 50% risk of cancer
Rise > 20% per year	Higher risk of cancer

PSA and screening controversies

There are several criticisms regarding PSA and PCa detection. Firstly, PSA is not a specific test. It can be elevated in the setting of BPH, prostatitis, urinary retention, urinary tract infection, instrumentation to the urethra and tends to increase with patient age. Secondly, the use of PSA as a screening tool can lead to a large number of unnecessary biopsies as 70% to 80% of biopsies performed for PSA 4 ng/dl to 10 ng/dl do not demonstrate malignancy on histologic examination. Furthermore, PSA-driven biopsies can lead to overdiagnosis of clinically insignificant cancers and potential for overtreatment, particularly in the elderly and patients with multiple comorbidities who are at a higher risk of dying from other causes.

Cohort studies have demonstrated that PCa mortality has been reduced by 22% to 40% since the introduction of PSA testing.[6-8] However, there may be many societal reasons that have contributed to this decrease (in addition to PSA screening) including increased awareness, earlier detection and treatment of disease and improvements in treatment modalities. As such, there remains some controversy among published guidelines regarding the use of DRE and PSA for PCa screening. The US Preventive Services Task Force, Canadian Periodic Health Exam Task Force and the Canadian Urological Association guidelines have remained neutral to recommend for or against routine screening for PCa. However, the American Cancer Society (ACS) and the American Urological Association (AUA) recommend that screening be offered to all men > 50-years-of-age and that the risks and benefits of screening be explained to the patient. In agreement with the ACS and AUA, we strongly advocate PCa screening for men > 50-years-of-age. Currently, two large randomized controlled trials are in progress to evaluate the benefit of PCa screening: the Prostate, Lung, Colorectal, and Ovary (PLCO) cancer and the European Randomized Screening for Prostate Cancer (ERSPC) trials expected to publish their results within the next couple of years.

Recommendations for screening

Proponents for PCa screening recommend screening to begin at 50-years-of-age. If the patient has a family history of PCa or is black, screening should start at 40-years-of-age. Screening should include a DRE and PSA annually until 75- to 80-years-of-age. PCa screening is not recommended for patients with multiple comorbidities and a life expectancy of < 10 years.

Indications for biopsy

The indications for TRUS and prostate biopsy are being continually refined. Most would agree that an abnormal DRE alone is an indication for biopsy. However, the optimal PSA cut-off for biopsy has not been identified.

Table 2
Risk of recurrence post treatment

Risk category	DRE	Gleason grade	PSA
Low	Not palpable or less than half of one lobe	2-6	< 10
Intermediate	More than half of one lobe	7	10-20
High	Both lobes involved	8-10	> 20

DRE: Digital rectal exam

Table 3
Selected morbidities associated with prostate cancer treatments

	Surgery	Radiation	Hormonal therapy
Urinary incontinence	√	√	
Bowel urgency		√	
Sexual dysfunction	√	√	√
Urethral injury	√	√	
Bleeding	√	√	
Cystitis		√	
Urinary retention	√	√	
Change in cognitive function			√
Hot flashes			√
Gynecomastia			√
Breast tenderness			√
Osteoporosis			√
Anemia			√
Fatigue			√

Traditionally, a PSA cut-off of 4 ng/dl was used as an indication for biopsy. Unfortunately with this cut-off alone some cancers will be missed and many patients will undergo unnecessary biopsies. Additionally, we know that much of the variability in PSA values can be attributed to benign enlargement of the prostate, which tends to occur in older men. Therefore, many urologists recommend using an age-adjusted PSA cut-off. For example, men in their 40s are expected to have PSA < 2.5 ng/dl; on the other hand, we can tolerate PSA levels of 6 ng/dl in men in their mid 70s who have a normal DRE.[3]

Cohort studies have demonstrated that PCa mortality has been reduced by 22% to 40% since the introduction of PSA testing.

Many other techniques have been developed, such as PSA velocity, to refine the indications and avoid unnecessary biopsies. We expect clinically significant PCa to be associated with a rapid increase in PSA; however, serial PSA measurements can fluctuate significantly. The PSA velocity is a very useful tool that can be used to identify patients at risk of harbouring PCa. It has been shown that a PSA velocity of > 0.75 ng/dl/yr has a specificity of > 90% and a sensitivity of approximately 80% for the diagnosis of PCa.[9] For example, if a 55-year-old

male has a PSA of 1.0 ng/dl which rises to 3.0 ng/dl one year later, he should be referred to urology for further investigation since the PSA velocity is higher than expected despite the current absolute level being within "normal range." Another useful tool is measuring free/total PSA ratio. Measurable PSA is either bound to serum proteins or free in the serum. It has been shown that men with PCa have a higher fraction of bound PSA. This can be especially useful in patients with borderline normal PSA levels. Using a threshold value of free PSA < 25% has been shown to detect 95% of cancers while eliminating 20% of unnecessary biopsies.[10]

Management of PCa

How do we stratify patients that have been diagnosed with PCa?

Once a patient has been diagnosed with PCa, they can be stratified according to their overall health, PSA, DRE and biopsy (Gleason score) results. Using these parameters, patients can be considered as low, intermediate, or high risk of aggressive disease (Table 2). The severity of disease, life expectancy and patient preference are key determinants of the type of treatment a patient will receive.

Dr. Violette is a Resident, Department of Urology, McGill University Health Center, Montreal, Quebec.

Dr. Kassouf is an Assistant Professor and Urologic Oncologist, Department of Surgery, McGill University Health Center, Montreal, Quebec.

What are the treatment options available?

There are many treatment options for patients with PCa. The only established and definitive treatment modalities are surgery (radical prostatectomy) and radiotherapy. Other therapies which are not considered curative include hormonal therapy and chemotherapy. Each therapy should be considered in the context of common morbidities (Table 3). Long-term follow-up after cryotherapy or high intensity focused ultrasound (HIFU) is needed to establish equivocal efficacy in the treatment of localized PCa.

The gold standard treatment for localized PCa is radical prostatectomy (open, laparoscopic, or robotic-assisted). In the hands of an experienced surgeon, 90% to 95% of men recover complete urinary continence. These three approaches of surgical removal of the prostate appear to have similar short/intermediate term cure rates. Laparoscopic prostatectomy has a slightly quicker recovery time but slower recovery of continence compared with the open approach. Robotic surgery is more expensive and less accessible in Canada but has recently gained more popularity in America and Europe.

Radiotherapy is commonly used to treat PCa and includes external beam radiation therapy and brachytherapy. Though it is difficult to directly compare the survival outcome of patients treated with radiotherapy vs. surgical therapy, the PCa mortality appears to be similar. One difference remains in the event of local recurrence: patients treated initially with surgery can receive radiation upon recurrence, whereas patients treated with initial radiation are less likely to undergo salvage prostatectomy

as the complication rate is significantly higher. Approximately half of patients develop erectile dysfunction after radiotherapy for PCa. External beam radiation therapy tends to be associated with higher incidence of rectal injury and proctitis, whereas brachytherapy is associated with higher occurrence of urinary symptoms.

Several PCa therapies are not considered curative, however, may be of benefit in some patient populations. Temporary androgen ablation therapy has been shown to increase survival in patients undergoing radiation therapy for intermediate and high-risk PCa. Hormone therapy is also commonly used to treat patients diagnosed with metastatic PCa. Chemotherapy is reserved for patients who have developed castrate resistant PCa.

Active surveillance is a novel treatment approach which is gaining acceptance and popularity. We know from autopsy data that histologic findings of PCa is present in 50% of men > 50-years-old and 75% of men > 80-years-old. However, the majority of these men will not die of PCa as only one in seven men will develop clinically significant PCa. In other words, not all PCa needs to be cured—the art is to identify which cancer needs treatment and which is indolent so that patients with indolent disease are not subjected to unnecessary morbidity. Patients on active surveillance for PCa do not undergo active therapy unless there are signs of local disease growth. The men are closely followed with serial PSA, DRE and repeated biopsies. Preferred candidates for active surveillance are elderly and asymptomatic patients with low-grade, non-palpable, low volume disease. Dx

Take-home message

- Prostate cancer is very common (1 in 7 lifetime risk)
- Most cancers are slow growing
- Screening PSA has resulted in identification of earlier disease, which may increase the potential for cure
- Gold standard therapy remains radical prostatectomy and radiotherapy
- Active surveillance is feasible in well-selected patients

References

1. Canadian Cancer Society/National Cancer Institute of Canada: Canadian Cancer Statistics 2008, Toronto, Canada, 2008.
2. Parkin DM, Whelan SL, Ferlay J, et al: *Cancer Incidence in Five Continents*. Vol VII. Lyon: IARC Sci Publ, 1997.
3. Wein AJ, Kavoussi LR, Novick AC, et al: *Campbell-Walsh Urology*. Ninth edition. Saunders-Elsevier Inc, Philadelphia, 2007, p.2855.
4. Grönberg H: Prostate Cancer Epidemiology. Lancet 2003; 361(9360):859-64.
5. Schröder FH, van der Maas P, Beemsterboer P, et al: Evaluation Of The Digital Rectal Examination As A Screening Test For Prostate Cancer. Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 1998; 90(23):1817.
6. Bartsch G, Horninger W, Klocker H, et al: Prostate Cancer Mortality After Introduction of Prostate-Specific Antigen Mass Screening in the Federal State of Tyrol, Austria. Urology 2001; 58(3):417-24.
7. Roberts RO, Bergstralh EJ, Katusic SK, et al: Decline In Prostate Cancer Mortality From 1980 To 1997, And An Update On Incidence Trends In Olmsted County, Minnesota. J Urol 1999; 161(2):529-33.
8. Labrie F, Candas B, Dupont A, et al: Screening Decreases Prostate Cancer Death: First Analysis of the 1988 Quebec Prospective Randomized Controlled Trial. Prostate 1999; 38(2):83-91.
9. Carter HB, Pearson JD, Metter EJ, et al: Longitudinal Evaluation Of Prostate Specific Antigen Levels In Men With And Without Prostate Disease. JAMA 1992; 267(16):2215.
10. Catalona WJ, Partin AW, Slawin KM, et al: Use Of The Percentage Of Free Prostate-Specific Antigen To Enhance Differentiation Of Prostate Cancer From Benign Prostatic Disease: A Prospective Multicenter Clinical Trial. JAMA 1998; 279(19):1542.