Prostate cancer screening: Canadian guidelines 2011

Jonathan I. Izawa, MD, FRCSC;* Laurence Klotz, MD, FRCSC;† D. Robert Siemens, MD, FRCSC;§
Wassim Kassouf, MD, FRCSC;‡ Alan So, MD, FRCSC;± John Jordan, CCFP, FCFP, MSc;¥
Michael Chetner, MD, FRCSC;¶ Alla E. Iansavichene, MD**

*Departments of Surgery & Oncology, Divisions of Urology & Surgical Oncology, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON; †Department of Surgery, Division of Urology, University of Toronto, Toronto, ON; §Department of Urology, Queen's University, Kingston, ON; ‡Department of Surgery, Division of Urology, McGill University, Montreal, QC; ±Department of Urological Sciences, University of British Columbia, Vancouver, BC; ¥Department of Family Medicine, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON; ¶Department of Urology, University of Alberta, Edmonton, AB; **Departments of Medicine & Surgery, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON

Methods and data collection

A systematic literature search was conducted in the following electronic bibliographic databases: MEDLINE, including PreMedline (2004 to November 2010), EMBASE (2004 to Week 44, 2010) and the Cochrane Central Register of Controlled Trials (2010, 4th Quarter). This search was restricted to studies published in English.

The search queries were based on a combination of exploded and non-exploded subject headings and free-text keywords. These terms included prostate cancer, prostatic neoplasms, prostate tumour, prostate-specific antigen (PSA), digital rectal examination (DRE), DRE, mass screening, screening test, early detection of cancer, cancer screening, screening, PSA, transrectal ultrasound (TRUS), TRUS, randomized, false-negative and false-positive; we used alternative word spellings and endings.

The search strategy was modified for each database using database-specific thesaurus terms, syntax and search fields. We excluded case reports, editorials, news and letters. To identify additional relevant studies, we also examined bibliographies of the relevant articles and selected reviews.

We compiled 1938 unique citations and, after removing the duplicates, 1036 citations were assessed for relevance. The screening process yielded 49 articles for a full-text review.

Introduction

The goal of prostate cancer (PCa) screening is to reduce the morbidity and mortality from this disease through early detection. There has been a steady decline in PCa mortality following the introduction of PSA testing in the late 1980s.[1] However, phase III trials on PCa screening have demonstrated a high number needed to treat, suggesting many PCas diagnosed were not destined to have an impact on a patient's overall survival.[2,3] **(Level 1 Evidence.)** We review the literature on PCa screening and describe what contemporary screening entails. We offer guidelines to facilitate the discussion of the risks and benefits of PCa screening. These guidelines are recommendations; they are not a standard of care for all patients and should not pre-empt a physician's clinical judgment.

Epidemiology

Prostate cancer remains the third leading cause of cancer death in men in Canada.[4] The lifetime risk of death from PCa is 3.7% and the lifetime risk of PCa diagnosis is 13.6%.[4] A Canadian male has a 1 in 7 chance of being diagnosed with PCa and a 1 in 27 chance of dying of PCa.[4] The incidence of PCa at autopsy in men over 50 years of age dying of other causes ranges from 33% to 46%.[5-7] The chance that a man over 55 years of age will be diagnosed with PCa with a standard biopsy is 25%.[8] It is evident from the epidemiologic data alone that most men with histologic PCa are not destined to die from PCa.

Prostate cancer screening tests

Digital rectal examination and PSA are the first-line PCa screening tests. **(Level 2 Evidence, Grade A Recommendation.)**

a) Digital rectal exam

Digital rectal examination and PSA have different sensitivities and specificities for PCa detection; a DRE may identify PCas that would not necessarily be picked up on PSA alone.[9] However, the European Randomized Study of Screening for

Prostate Cancer (ERSPC) showed that a DRE did not provide any additive information beyond PSA.[10] **(Level 1 Evidence.)** The DRE can be normal or show findings consistent with benign prostatic hyperplasia (BPH), such as symmetrical enlargement. Findings associated with PCa include induration or hard nodules. Controversy exists regarding asymmetry alone as a predictor of PCa. The positive predictive value of the DRE increases as the PSA increases.[11,12] Prostate cancers identified by DRE are pathologically advanced in over 50% of men.[12] **(Level 3 Evidence.)**

b) Prostate-specific antigen

Prostate-specific antigen is a glycoprotein produced primarily by the prostate epithelial cells that line the ducts and acini of the prostate. It is thought that the disruption of the normal prostate glandular architecture facilitates PSA's access to the systemic circulation. Conditions that increase PSA include BPH, prostatitis, urethral instrumentation, prostate biopsy and PCa. Inconsistent causes of PSA elevation include a vigorous DRE and recent ejaculation. 5-alpha reductase inhibitors (5aRIs) reduce the PSA by about 50% by 6 months and is non dose-dependent.[13] Patients on 5aRIs who have reached their nadir should have a baseline level after 6 months of medication. Any sustained rise should raise concerns for biologically significant PCa.[14]

A PSA cut point of 4 ng/mL was originally chosen to differentiate normal PSA levels from pathological elevation. In contemporary series, a PSA level of 4 ng/mL has a sensitivity of 20% in detecting PCa.[15] To improve upon PSA sensitivity in younger men and increase specificity in older men, PSA age-specific reference ranges have been used.[16] However, the Prostate Cancer Prevention Trial (PCPT) demonstrated that the relationship between PSA and PCa incidence is continuous (i.e., the higher the PSA, the greater the risk). **(Level 1 Evidence.)** There is no single justifiable cut point, regardless of age.[8]

Since PSA levels may fluctuate from causes other than PCa, a single PSA value is not sufficient. Decisions regarding whether a prostate biopsy should be recommended should be based on more than a single PSA.[17] The variation between laboratories is 20% to 25%; therefore using the same laboratory may reduce variability.[18,19] If the PSA level is below 1.0 ng/mL, biologically significant PCa is very unlikely to develop over the next 7 years.[11] **(Level 2 Evidence.)**

Prostate-specific antigen velocity (PSAV) may improve the sensitivity of PSA. To calculate PSAV, at least 3 PSA determinations must be used over a time period of 18 months.[20,21] A PSAV rise of greater than 0.75 ng/mL/year when the PSA is between 4 ng/mL and 10 ng/ml may indicate a higher risk of PCa.[21] However, for PSA levels less than 4 ng/mL, PSAV increases of 0.4 ng/mL/year appear to denote a higher risk of PCa.[20,22,23] Age-specific PSAV with cut points of 0.25, 0.5 and 0.75 ng/mL/year in men aged 40-59, 60-69 and over 70 years, respectively, has been described to improve the sensitivity of PCa detection.[23] **(Level 3 Evidence.)** It is important to note that in phase III trials, the PSAV has not been shown to be an independent predictor of a positive biopsy over PSA alone.[19,24] Prostate-specific antigen velocity alone should not be the basis for a decision to biopsy.

Prostate-specific antigen densities (PSAD) may improve the specificity in detecting PCa.[25] Prostate-specific antigen densities greater than 0.15 ng/mL may indicate a greater risk of PCa. However, not all studies confirm the utility of PSAD. Measuring the PSAD for the transition zone only may also be used, as the transition zone usually accounts for the PSA production by the BPH component.[25] For these volume/density measurements, a TRUS is required. A TRUS imposes additional costs and has not been shown to improve PCa screening; it also has variable interoperator reproducibility.[26,27] **(Level 3 Evidence.)**

Prostate-specific antigen isoforms can also improve PCa detection, while improving the sensitivity of prostate biopsies. Most circulating PSA bind to alpha-1 antichymotripsin (ACT) and alpha-2 macroglobulin (AMG), while the remainder is free in the serum.[28] In normal prostatic acini, PSA is processed by enzymatic nicking of a 7 kD segment, followed by back diffusion into the serum. In PCa acini, loss of polarity results in direct secretion into the serum with no enzymatic nicking. This results in greater avidity between ACT and PSA, thus less free PSA. The lower the free to total PSA ratio, the greater the risk of PCa. There is no known optimal cut point. Like total PSA, the free to total ratio presents a continuum of PCa risk. Using the free to total PSA ratio improves specificity and will reduce the number of negative prostate biopsies.[29] **(Level 3 Evidence.)** Hemodialysis and peritoneal dialysis do not affect the total serum PSA levels, but may affect the free PSA levels.[30]

Measured complexed PSA levels may improve the specificity of PSA screening, but the data on complexed PSA is limited and this isoform is not commonly utilized.[31] Biomarkers, such as PCA3, may play a more significant role in PCa screening, but the data supporting its use for routine screening is limited.[32]

Transrectal ultrasound-guided prostate biopsy

Once the PCa screening evaluation determines that a man is at increased risk of PCa, a TRUS guided prostate biopsy is required to obtain the histologic diagnosis. The biopsy provides important data, including the grade and volume of PCa and the presence of extraprostatic disease. No single biopsy template is optimal for all men. A 10 to 12 core biopsy template is standard and should incorporate tissue from the peripheral zones and anterior horns.[33,34] **(Level 3 Evidence, Grade B Recommendation.)** Transition zone biopsies are

not necessary with initial prostate biopsies unless there is a suspicious lesion identified on the TRUS.[34]

Nomograms incorporating prostate volume and age may be useful to determine the number of biopsies cores to optimize detection rates.[35] Despite the critical data biopsies provide, morbidity and rising post-biopsy sepsis rates have to be taken into consideration as a significant risk of PCa screening.[36]

Biologically significant prostate cancer

There are no clinical parameters that afford unequivocal prediction of the biologic significance of a patient's detected PCa. At the extremes of disease where a man has metastatic PCa or low volume, low-grade disease, PCa biology is easier to predict. For men with organ-confined PCa in the absence of high-grade and high-volume disease, predicting the risk of morbidity and mortality relative to other medical comorbidities can be challenging. The clinical data most commonly used to predict disease biology include PSA, histologic grade, clinical or pathologic stage and cancer volume. The number of biopsy cores containing cancer and the extent of cancer involvement of each core provides an estimate of cancer volume.[37-39]

Based on autopsy data, biologically insignificant PCa has been defined as tumour volume <0.5 cc with a Gleason score 6 or less. Histologic criteria for biologically insignificant PCa is based on core biopsies and include PSA density <0.15, no Gleason grade 4 or 5, involvement of <3 needle biopsy cores (on sextant biopsies) and involvement of <3 mm of tissue in any one biopsy core.[39] **(Level 3 Evidence.)** It is important to note that a "biologically significant" PCa may be present in up to 24% of patients using these criteria.[40] A caveat is that the biologic significance of grade 3 cancer >0.5 cc has never been established.

Standard radiologic imaging has not allowed for better local tumour volume assessment.[41] Multiparametric magnetic resonance imaging may have an emerging role in assessing tumour volume and improving biopsy accuracy.[42] Nomograms are available that combine many clinical variables to try to determine which PCas are biologically insignificant.[43] Inaccuracies range from 10% to 20%. **(Level 3 Evidence.)**

Active surveillance

Many men diagnosed with screen-detected PCa will have disease that is not destined to affect their overall survival. Watchful waiting is a strategy whereby there is no therapy until the patient develops symptoms secondary to advanced PCa. Treatment usually involves androgen deprivation for metastatic disease. This approach does not offer an opportunity for cure in men with more aggressive disease.[44] Active surveillance entails close follow-up on patients diagnosed with early stage, low-risk PCa. Therapy is recommended at a time when cure is deemed possible and when disease progression occurs as defined by a rapid PSA doubling time, clinical progression on DRE, grade progression or tumour volume progression on repeat TRUS-guided prostate biopsies.

Active surveillance appears to be safe, as demonstrated in 7 studies.[45-51] **(Level 3 Evidence.)** The total number of patients in these studies is 2365 with a median follow-up ranging from 22 to 73 months. Overall survival ranges from 82% 100%. Prostate cancer survival ranges from 97% to 100%. Patients remaining on active surveillance range from 50% to 92%. The main limitation of these studies is their lack of long-term follow-up. An international, prospective, randomized, phase III trial (Surveillance Therapy Against Radical Treatment [START]) randomized men with low-risk PCa to active surveillance or immediate curative therapy; START is now accruing patients. Until the START trial is completed, active surveillance with possible delayed curative intervention seems to be a reasonable option for men with favourable risk, screen-detected PCa.

Curative therapies

For any cancer-screening program to be effective, there must be curative therapies. Of all the potentially curative therapies for organ-confined PCa, phase III data on 695 patients comparing curative therapy to watchful waiting exists only for radical prostatectomy.[52] It was shown that there was an overall and disease-specific survival advantage for men undergoing radical prostatectomy. **(Level 1 Evidence.)** However, one needed to treat 17 men to save 1 life from PCa and this study was in the pre-PSA era. In a separate evaluation of the same study with a longer median follow-up of 10.8 years, overall survival was not different, but PCa mortality and risk of metastases were reduced significantly by radical prostatectomy.[53]

Phase III survival data also exist for postoperative radiotherapy, conferring a survival benefit for men at higher risk for disease recurrence post-radical prostatectomy.[54,55] **(Level 1 Evidence.)** There are local therapies that do provide a survival benefit for patients, although given the early follow-up of these studies relative to the prolonged natural history of localized PCa, the overall benefit compared to harm is yet to be fully elucidated.

Level 1 evidence for screening

The initial 2 multicentre, randomized, prospective PCa screening studies have been recently published (Table 1).[2,3] There were limitations associated with the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial that had a significant impact on the results and may reduce gen-

Table 1. Comparisons between the PLCO, ERPSC and Goteborg studies

	PLCO[3]		ERSPC[2]		Goteborg[56]	
Period	1993-2001		1994-2006		1995-2008	
No.	76 693		162 243		20 000	
Age	55-74 (13% >70)		55-69		50-64	
Site	Multiple centres (United States)		7 countries		1 city (Goteborg, Sweden)	
Methods	PSA >4 ng/mL		PSA >3 ng/mL		PSA >2.5 ng/mL (From 2005 on)	
	Abnormal DRE		Abnormal DRE		PSA >2.9 ng/mL (From 1999-2004) PSA >3.4 ng/mL (From 1995-98)	
Follow-up	Every 1 year × 6 11 years median follow-up		Every 4 years 9 years (complete)		Every 2 years 78% had 14-year follow-up	
Compliance	85%		82%		76%	
Contamination	52%		Not known		3%	
	Control	Screened	Control	Screened	Control	Screened
Prostate cancers	7.3%	6%	8.2%	4.8%	7.2%	11.4%
Prostate cancer Deaths	50	44	326	214	78	44
Risk ratio	NS		20% (*p* = 0.04)		44% (*p* = 0.002)	
NNS			1:1410		1:293	
NNT			1:48		1:12	

PLCO: Prostate, Lung, Colorectal, and Ovarian screening trial; ERSPC: European Randomized Study of Screening for Prostate Cancer trial; PSA: prostate-specific antigen; DRE: digital rectal examination; NNS: number needed to screen; NNT: number needed to treat.

eralizability. Firstly, only a PSA cut point of 4 ng/mL was used to determine if a biopsy was required. Only 67% of patients in this study had 10-year data, so the study had insufficient follow-up given the prolonged natural history of screen detected PCa. The short follow-up period also had an impact on the low level of events or deaths from PCa in the trial. Contamination of PSA screening in the control arm was high (52%). Thus, this study compared a group of men who were more closely screened to a group undergoing less screening, as opposed to a group that was unscreened.

A third phase III trial randomizing men to PSA screening versus no screening was recently published.[56] In this study from Sweden, men were randomized prior to receiving information regarding the screening protocol. Results relative to the 2 aforementioned screening trials were significantly different in favour of PCa screening. The numbers needed to screen and numbers needed to be diagnosed to save 1 life from PCa were 293 and 12, respectively. Potential explanations for the differences are as follows: men were younger (median age 56 at baseline), the PSA cut point was lower (2.5-3.4 ng/mL), contamination was lower (3% of patients received PSA testing prior to the study), not all patients underwent immediate curative therapy and there was longer follow-up (median 14 years).

Although the ERSPC[2] and Swedish[56] studies did demonstrate a difference in favour of the more intensely screened population, the number of patients needed to screen and treat to save 1 life from PCa indicates that there are men who undergo treatment (and experience the associated morbidity) who were not destined to die from their PCa. These figures are similar to breast cancer;[57] however, the quality of life issues specific to PCa therapies make comparisons difficult.

Contemporary screening

Contemporary PCa screening for men with at least a 10-year life expectancy now involves more than just a DRE and PSA. No single PSA value should be the only determinant of whether or not to biopsy a patient. The PSAV, PSAD and PSA free to total ratio may improve PSA sensitivity and specificity. **(Level 2 Evidence, Grade B Recommendation.)** Furthermore, nomograms and mathematical models may guide a clinician by combining multiple clinical variables, such as DRE, PSA, PSAV, PSA isoforms, age, race, family history of PCa and genetic data to determine the risk of PCa and the risk of biologically significant disease.[58-60] **(Level 3 Evidence, Grade B Recommendation.)**

Some guidelines recommend PCa screening at age 40, particularly for those at higher risk.[61] **(Level 3 Evidence, Grade B Recommendation.)** There is evidence that a baseline PSA at such an early age may also be a predictor for future risk of PCa and allow a risk-stratified approach for timing and intensity of PCa screening.[62-65]

Men with a PSA lower than 0.5 ng/mL are at lower risk of PCa and may benefit from PSA screening every few years, as was standard in the ERSPC trial.[2,62-65] It is important to realize that opening PSA testing to all men at age 40 poses increased risks of further testing and therapy; the data sup-

porting earlier testing are limited and does not offer supportive outcome data.[62-65]

The benefits of screening also decline with age due to competing causes of death, the long natural history of PCa and the lead time bias of PSA screening.[44,66,67] The U.S. Preventative Services Task Force recommends against screening once a man reaches age 75.[68] (**Level 3 Evidence, Grade C Recommendation.**) Strong consideration should be given to discontinuing PSA screening for Canadian men over 75 years of age.

Conclusions

Prostate cancer screening allows the detection of potentially lethal cancer at a point in time when it is more likely to be curable. This comes at the expense of many patients being treated when their cancer poses no threat to their life. Therefore, the harms and benefits of PCa screening must be explained to each patient so they understand all the factors to be considered in the shared decision-making about screening. Prostate cancer screening should be offered to all men 50 years of age with at least a 10-year life expectancy. Annual screening has been the standard; however, two screening studies demonstrate that screening is beneficial every 2 to 4 years. If there is a higher risk of PCa, such as family history of PCa or if the patient is of African descent, screening should be offered at age 40 years. Furthermore, there may be benefit in offering a baseline PSA for men 40 to 49 years of age to establish future PCa risk. Initial screening should include DRE and PSA. Prostate-specific antigen and PSA free/total ratio are currently the most reliable serum markers. Both markers offer a continuum of PCa risk. No strict cut point should be used for all patients. The lowest cut point used in phase III trials (which demonstrates a benefit to screening) was 2.5 ng/mL. Many other factors may be used beyond the initial screening tests. If a biopsy is indicated, a 10- to 12-core TRUS-guided peripheral zone prostate biopsy incorporating the anterior horn area should be performed. For men diagnosed with screen-detected PCa, tumour volume, grade, DRE and PSA results direct management. Selectively treating patients with favourable risk PCa may significantly improve screening outcomes.

Competing interests: None declared.

This paper has been peer-reviewed.

References

1. Ries LA, Melbert D, Krapcho M et al. SEER Cancer Statistics Review, 1975-2005. Bethesda: NCI. http://seer.cancer.gov/csr/1975_2005/. Accessed July 5, 2011.

2. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-8.

3. Andriole GL, Grubb RL, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310-9.

4. Canadian Cancer Society's Steering Committee: Canadian Cancer Statistics 2009. Toronto: Canadian Cancer Society, 2009.

5. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early- stage prostate cancer: a review of literature. *Cancer* 2008;112:1650-9.

6. Yin M, Bastacky S, Chandran U, et al. Prevalence of incidental prostate cancer in the general population: a study of healthy organ donors. *J Urol* 2008;179:892-5; discussion 895. Epub 2008 Jan 22.

7. Yatani R, Chagusi I, Akazaki K, et al. Geographic pathology of latent prostatic carcinoma. *Int J Cancer* 1982;29:611-6.

8. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. *N Engl J Med* 2004;350:2239-46. Erratum in: *N Engl J Med* 2004;351:1470.

9. Richie JP, Kavoussi LR, Ho GT, et al. Prostate cancer screening: role of the digital rectal examination and prostate-specific antigen. *Ann Surg Oncol* 1994;1:117-20.

10. Gosselaar C, Roobol MJ, Roemeling S, et al. Screening for prostate cancer without digital rectal examination and transrectal ultrasound: results after four years in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. *Prostate* 2006;66:625-31.

11. Schroder 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;90:1817-23.

12. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of non-palpable (stage T1C) prostate cancer. *JAMA* 1994;271:368-74.

13. Loeb S, Gonzalez CM, Roehl KA, et al. Pathological characteristics of prostate cancer detected through prostate specific antigen based screening. *J Urol* 2006;175:902-6.

14. Andriole GL, Bostwick D, Brawley OW, et al. The effect of dutasteride on the usefulness of prostate specific antigen for the diagnosis of high grade and clinically relevant prostate cancer in men with a previous negative biopsy: results from the REDUCE study. *J Urol* 2011;185:126-31. Epub 2010 Nov 12.

15. Thompson IM, Ankerst DP, Weiss NS, et al. Operation characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. *JAMA* 2005;294:66-70.

16. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993;270:860-4.

17. Eastham JA, Riedel E, Scardino PT, et al. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. *JAMA* 2003;289:2695-700.

18. Slev PR, La'ulu SL, Roberts WL. Intermethod differences in results for total PSA, free PSA, and percentage of free PSA. *Am J Clin Pathol* 2008;129:952-8.

19. Etzioni RD, Ankerst DP, Weiss NS, et al. Is prostate-specific antigen velocity useful in early detection of prostate cancer? A critical appraisal of the evidence. J Natl Cancer Inst 2007; 99: 1510-5.

20. D'Amico AV, Chen MH, Roehl KA, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351:125-35.

21. Carter HB, Person JD, Metter J, et al. Longitudinal evaluation of prostate specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215-20.

22. Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst* 2006;98:1521-7.

23. Moul JW, Sun L, Hotaling JM, et al. Age adjusted prostate specific antigen and prostate specific antigen velocity cut points in prostate cancer screening. *J Urol* 2007;177:499-503; discussion 503-4.

24. Vickers AJ, Savage C, O'Brien MF, et al. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *J Clin Oncol* 2009;27:398-403.

25. Djavan B, Remzi M, Zlotta AR, et al. Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to- total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial. *Urology* 2002;60:(4 Suppl 1):4-9.

26. Augustin H, Graefen M, Palisaar J, et al. Prognostic significance of visible lesions on transrectal ultrasound in impalpable prostate cancers: Implications for staging. *J Clin Oncol* 2003;21:2860-8.

27. Resnick MI, Smith JA Jr, Scardino PT, et al. Transrectal prostate ultrasonography: Variability of interpretation. *J Urol* 1997;158:856-60.

28. Becker C, Lilja H. Individual prostate-specific antigen (PSA) forms as prostate tumor markers. *Clin Chim Acta* 1997;257:117-32.

29. 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. *JAMA* 1998;279:1542-7.

30. Tzanakis I, Kazoulis S, Girousis N, et al. Prostate-specific antigen in hemodialysis patients and the influence of dialysis in its levels. *Nephron* 2002;90:230-3.

31. Mitchell ID, Croal BL, Dickie A, et al. A prospective study to evaluate the role of complexed prostate-specific antigen and free/total prostate- specific antigen ratio for the diagnosis of prostate cancer. *J Urol* 2001;165:1549-53.
32. Roobol MJ, Schröder FH, van Leeuwen P, et al. Performance of the prostate cancer antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: exploring the value of PCA3 for a first-line diagnostic test. *Eur Urol* 2010;58:475-81.
33. Babaian RJ, Toi A, Kamoi K, et al. A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. *J Urol* 2000;163:152-7.
34. Scattoni V, Maccagnano C, Zanni G, et al. Is extended and saturation biopsy necessary? *Int J Urol* 2010;17:432-47.
35. Remzi M, Fong YK, Dobrovits M, et al. The Vienna nomogram: validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. *J Urol* 2005;174:1256-60.
36. Nam RK, Saskin R, Lee Y, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol* 2010;183:963-8.
37. Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathologic stage of localized prostate cancer. A multi-institutional update. *JAMA* 1997;277:1445-51. Erratum in: *JAMA* 1997;278:118.
38. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 1999;17:1499-507.
39. Epstein JI, Walsh PC, Carmichael M, et al. Pathological and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994;271:368-74.
40. Jeldres C, Suardi N, Walz J, et al. Validation of the contemporary Epstein criteria for insignificant prostate cancer in European men. *Eur Urol* 2008;54:1306-13.
41. Abuzallouf S, Dayes I, Lukka H. Baseline staging of newly diagnosed prostate cancer: a summary of the literature. *J Urol* 2004;171:2122-7.
42. Turkbey B, Pinto PA, Mani H, et al. Prostate cancer: value of multiparametric MR imaging at 3 T for detection–histopathologic correlation. *Radiology* 2010;255:89-99.
43. Chun FK, Haese A, Ahyai SA, et al. Critical assessment of tools to predict clinically insignificant prostate cancer at radical prostatectomy in contemporary men. *Cancer* 2008;113:701-9.
44. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005;293:2095-101.
45. Van As NJ, Parker CC. Active surveillance with selective radical treatment for localized prostate cancer. *Cancer* 2007;13:289-94.
46. Carter HB, Ketterman A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the John's Hopkins experience. *J Urol* 2007;178:2359-64.
47. Soloway MS, Soloway CT, Williams S, et al. Active surveillance: a reasonable management alternative for patients with prostate cancer: the Miami experience. *BJU Int* 2008;101:165-9.
48. Roemeling S, Roobol MJ, de Vries SH, et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. *Eur Urol* 2007;51:1244-50.
49. Van den Bergh RC, Roemeling S, Roobol MJ, et al. Prostate-specific antigen kinetics in clinical decision-making during active surveillance for early prostate cancer–a review. *BJU Int* 2009;54:505-16.
50. Khatami A, Aus G, Damber JE, et al. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *Int J Cancer* 2007;120:170-4.
51. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010;28:126-31.
52. Bill-Axelson A, Holmberg L, Ruutu M et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352:1977-84.
53. Bill-Axelson A, Holmberg L, Filen F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *J Natl Cancer Inst* 2008;100:1144-54.
54. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomized controlled trial (EORTC Trial 22911). *Lancet* 2005;366:572-8.
55. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces the risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009;181:956-62.
56. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomized population-based prostate-cancer screening trial. *Lancet Oncol* 2010;11:725-32.
57. Humphrey LL, Helfand M, Chan BK, et al. Breast cancer screening: a summary of the evidence for the US Preventative Services Task Force. *Annals Int Med* 2002;137:347-60.
58. Nam RK, Zhang WW, Trachtenberg J, et al. Utility of incorporating genetic variants for the early detection of prostate cancer. *Clin Cancer Res* 2009;15:1787-93.
59. Roobol MJ, Steyerberg EW, Kranse R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol* 2010;57:79-85.
60. Herman MP, Dorsey P, John M, et al. Techniques and predictive models to improve prostate cancer detection. *Cancer* 2009;115(13 Suppl):3085-99.
61. Greene KL, Albertsen PC, Babaian RJ, et al. Prostate specific antigen best practice statement: 2009 Update. *J Urol* 2009;182:2232-41.
62. Fang J, Metter EJ, Landis P, et al. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. *Urology* 2001;58:411-6.
63. Loeb S, Roehl KA, Antenor JAV, et al. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology* 2006;67:316-20.
64. Lilja H, Ulmert D, Bjork T, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. *J Clin Oncol* 2007;25:431-6.
65. Ulmert D, Cronin AM, Bjork T, et al. Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: A case-control study. *BMC Med* 2008;6:6.
66. Ross KS, Guess HA, Carter HB. Estimation of treatment benefits when PSA screening for prostate cancer is discontinued at different ages. *Urology* 2005;66:1038-42.
67. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;101:374-83.
68. Screening for prostate cancer: U.S. Preventative Services Task Force recommendation statement. *Ann Int Med* 2008;149:185-91.

Correspondence: Dr. Jonathan Izawa, Victoria Hospital, 800 Commissioners Rd East, London, ON N6A 4G5; jonathan.izawa@lhsc.on.ca