Published in final edited form as:

Eur Urol Focus. 2015 September ; 1(2): 149–151. doi:10.1016/j.euf.2015.05.001.

Clinical Consultation Guide: How to Optimize the Use of Prostate-specific Antigen in the Current Era

Sigrid Carlsson^{a,b,*}, Hans Lilja^{a,c,d,e,f}, and Andrew Vickers^g

^aDepartment of Surgery (Urology Service), Memorial Sloan-Kettering Cancer Center, New York, USA ^bDepartment of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Göteborg, Sweden ^cDepartments of Laboratory Medicine and Medicine (Genitourinary Oncology), Memorial Sloan-Kettering Cancer Center, New York, USA ^dNuffield Department of Surgical Sciences, University of Oxford, Oxford, UK ^eInstitute of Biomedical Technology, University of Tampere, Tampere, Finland ^fDepartment of Translational Medicine, Lund University, Malmö, Sweden ^gDepartment of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, USA

Keywords

Prostate cancer; Risk stratification; Screening

Accumulating evidence suggests that screening for prostate cancer (PCa) with prostate-specific antigen (PSA) reduces deaths from PCa [1,2] and should no longer be all or nothing but rather a matter of selecting the appropriate candidates for screening and biopsy so that the benefits outweigh the harms. Consequently, screening ought to focus on identifying the

*Corresponding author. Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Göteborg, Sweden. carlsson@mskcc.org.

Author contributions: Sigrid Carlsson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Carlsson, Vickers, Lilja.

Acquisition of data: Carlsson, Vickers, Lilja.

Analysis and interpretation of data: Carlsson, Vickers, Lilja.

Drafting of the manuscript: Carlsson, Vickers, Lilja.

Critical revision of the manuscript for important intellectual content: Carlsson, Vickers, Lilja.

Statistical analysis: None.

Obtaining funding: Carlsson, Vickers, Lilja.

Administrative, technical, or material support: None.

Supervision: None.

Other (specify): None.

Financial disclosures: Sigrid Carlsson certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Hans Lilja holds patents for free prostate-specific antigen (PSA), human kallikrein 2, and intact PSA assays and is named, along with Andrew Vickers, on a patent application for a statistical method to detect prostate cancer; this has been commercialized by Opko Health, and Andrew Vickers and Hans Lilja will receive royalties from any sales of the test. Andrew Vickers is on the advisory board of Opko Health and has Opko stock options.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

limited group of men at highest risk of future life-threatening PCa so that preventive measures can be undertaken. This so-called risk stratification can be achieved in two steps: stratifying screening and stratifying biopsy. In this clinical consultation guide, we provide the scientific background and evidence-based recommendations.

Stratifying screening

Background

Stratifying screening implies identifying men who are likely, versus those who are unlikely, to benefit from being screened [3].

Evidence

First, despite nearly all prostate-specific antigen (PSA) guidelines recommending shared decision making [4], data suggest that one in four primary care physicians orders the PSA test without having this discussion [5].

Second, screening is associated with overdiagnosis of low-risk PCa, and as such, men can be monitored with active surveillance [6].

Third, although men of African American descent and those with family history, particularly early onset, are considered high-risk groups from a clinical perspective, baseline PSA at age 45 yr provides superior risk stratification in terms of high-risk PCa death at age 75 yr compared with both race and family history [7].

Fourth, an increasing number of guideline groups now recommend baseline PSA starting around age 45 yr [4], based on the large body of evidence from several cohorts around the world demonstrating a strong association between PSA levels in midlife and future risk of PCa outcomes [8,9] as well as data showing that starting screening at age 50–55 yr will be too late for some men [10]. The PSA level, in relation to the age median, can then be used to identify groups of men needing less versus more frequent rescreening. There is strong evidence that men with PSA levels below age median at age 60 yr have very low risk of distant metastasis or PCa death up to 25 yr later and thus can be exempted from further screening [8,9]. Similarly, men with PSA levels below median at approximately age 50 yr are also at very low risk of distant metastasis >15 yr later [9,10], and although they cannot be exempted from any later testing, they are unlikely to benefit from more frequent retesting intervals than 5–10 yr. Among men with PSA ≥ 2 ng/ml at age 60 yr, rescreening contributes substantial reduction in PCa mortality at the cost of little overdiagnosis, as opposed to rescreening of men with PSA <2 ng/ml at age 60 yr, which is associated with considerable risk of overdiagnosis but no benefit in terms of reductions in PCa mortality [11].

Fifth, the field of genetics and genomics is rapidly evolving; however, it is currently unknown how to incorporate this information into early detection practices. Genomewide association studies have identified some 100 single-nucleotide polymorphisms associated with PCa risk [12] and changes in blood biomarker levels [13]; however, due to moderate effect size and lack of replication, none have been introduced in routine clinical practice. Mutations in the *BRCA1* and *BRCA2* tumor suppressor genes in sporadic PCa are rare, and

the initial data from the multicenter IMPACT study provided no clear evidence that carriers should be subject to special screening practices [14].

Sixth, to the best of our knowledge, the well-cited upper cut-off of 10-yr life expectancy for screening and treatment has never been adequately justified. Older age and comorbidities imply competing risks and, hence, a lower likelihood of screening being effective. There is mounting evidence of excessive PSA screening in elderly men with multiple comorbidities and limited life expectancy who are unlikely to benefit [15,16]. Some guideline groups are moving away from recommending an arbitrary age threshold beyond which screening should not occur and rather emphasize not denying any older man in good health the opportunity to get screened [17].

Recommendations

1. Engage in shared decision making and obtain consent from the man before any screening takes place.
2. Informed decision making should make explicit reference to the possibility that screening will find indolent disease and that active surveillance is an established strategy to manage low-risk PCa.
3. Obtain a baseline PSA level at age 45 yr. Have the same conversation regardless of race and ethnicity.
4. The decision to screen should take into account a man's age and general health status. Do not screen men who are unlikely to benefit.
5. We recommend individualizing the rescreening interval and when to cease PSA screening according to the PSA level for the man's age, following a prespecified algorithm [18].
6. Men with PSA <1 ng/ml at age 60 yr should be exempted from further screening.

Stratifying biopsy

Background

The decision to biopsy should similarly be based on risk assessment. The European Association of Urology guidelines state that "PSA testing should not be considered on its own, but rather as part of a multivariable approach to early detection" [19].

Evidence

First, PSA has low specificity, fluctuations in PSA levels may occur [20], and levels are affected by 5 α -reductase inhibitors. Most men with modestly elevated PSA levels do not have intermediate- or high-risk PCa, and most of these men have no evidence of cancer at biopsy. Consequently, a large number of biopsies, with their inherent risks, are performed unnecessarily.

Second, several risk calculators have been developed for the purpose of guiding the decision to biopsy. Although they may improve predictions of any-grade and high-grade PCa at

biopsy, few studies report model calibration [21], and compliance among urologists is limited [22].

Third, reflex tests based on additional biomarkers can help make biopsy decisions, and some well-documented evidence suggests that they also discriminate between high- and low-grade disease. Today, there are four commercially available reflex tests: free-to-total PSA ratio, 4Kscore, the Prostate Health Index (PHI), and the urine PCA3 test. The 4Kscore predicts an individual's risk of high-grade cancer on biopsy integrated with clinical information, whereas the PHI and PCA3 tests give a dimensionless score associated with risk of any-grade PCa.

Fourth, the role of multiparametric magnetic resonance imaging (mpMRI) in the prediagnostic setting is under study. Several groups of investigators are currently evaluating whether the use of mpMRI could offer important advantages in identifying clinically significant or lethal PCa forms at early, curable stages. Current evidence shows that mpMRI can help find some lesions that would otherwise be missed, with an improved relative sensitivity to high-grade PCa with mpMRI and targeted biopsy compared with transrectal ultrasound with systematic biopsy in men with previous negative biopsy [23]; however, it is not clear whether these cancers would have progressed significantly before being found on subsequent biopsy. There is also evidence that current use of mpMRI and targeted biopsies only for lesions with PI-RADS (Prostate Imaging and Reporting and Data System) scores 3–5, without concurrent systematic biopsy, may miss 9–20% of high-grade tumors [24].

Recommendations

1. Consider prostate biopsy if the PSA level is ≥ 3 ng/ml, but do not biopsy unless you have a compelling reason.
2. Evaluate the PSA level in reference to the man's age, general health, and any previous screening.
3. Evaluate the PSA level in the context of the presence of benign disease, transient elevations, and 5 α -reductase inhibitors. We recommend that the first steps for a physician following up with a man with modestly elevated PSA are to confirm this finding by repeated PSA testing and rule out benign elevation by clinical examination.
4. Consider reflex tests to guide the decision to biopsy.

Conclusions

Optimizing the use of PSA in the current era entails abandoning the “one size fits all” model to optimize the ratio of benefits to harms. This can be achieved through risk stratification and emphasizing the importance of active surveillance for low-risk disease. Avoid screening and biopsy in men only likely to be harmed, and do not delay the opportunity for screening and biopsy in men at high risk of a preventable cancer death.

Acknowledgments

Funding/Support and role of the sponsor: Sigrid Carlsson is supported by grants from AFA Insurance, the Swedish Cancer Society, the Swedish Prostate Cancer Foundation, the Research Foundation at the Department of Urology Sahlgrenska University Hospital Gothenburg Sweden, the Sweden America Foundation, the Swedish Council for Working Life and Social Research and the Swedish Society for Medical Research. Other grant support was received from David H. Koch provided through the Prostate Cancer Foundation, the Sidney Kimmel Center for Prostate and Urologic Cancers, P50-CA92629 SPORE grant from the National Cancer Institute to Dr. H. Scher, and the P30-CA008748 NIH/NCI Cancer Center Support Grant to MSKCC, R01 CA160816 award from the NIH/ National Cancer Institute; the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Program; the Swedish Cancer Society (Cancerfonden project no. 14-0722); a FiDiPro-program award from TEKES, Finland; and Fundacion Federico SA.

References

1. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014; 384:2027–35. [PubMed: 25108889]
2. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*. 2010; 11:725–32. [PubMed: 20598634]
3. Carlsson S, Vickers AJ, Roobol M, et al. Prostate cancer screening: facts, statistics, and interpretation in response to the US Preventive Services Task Force review. *J Clin Oncol*. 2012; 30:2581–4. [PubMed: 22711853]
4. Loeb S. Guideline of guidelines: prostate cancer screening. *BJU Int*. 2014; 114:323–5. [PubMed: 24981126]
5. Volk RJ, Linder SK, Kallen MA, et al. Primary care physicians' use of an informed decision-making process for prostate cancer screening. *Ann Fam Med*. 2013; 11:67–74. [PubMed: 23319508]
6. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015; 33:272–7. [PubMed: 25512465]
7. Vertosick EA, Poon BY, Vickers AJ. Relative value of race, family history and prostate specific antigen as indications for early initiation of prostate cancer screening. *J Urol*. 2014; 192:724–8. [PubMed: 24641912]
8. Vickers AJ, Cronin AM, Björk T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. *BMJ*. 2010; 341:c4521. [PubMed: 20843935]
9. Stattin P, Vickers AJ, Sjöberg DD, et al. Improving the specificity of screening for lethal prostate cancer using prostate-specific antigen and a panel of kallikrein markers: a nested case-control study. *Eur Urol*. In press.
10. Vickers AJ, Ulmert D, Sjöberg DD, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40–55 and long term risk of metastasis: case-control study. *BMJ*. 2013; 346:f2023. [PubMed: 23596126]
11. Carlsson S, Assel M, Sjöberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. *BMJ*. 2014; 348:g2296. [PubMed: 24682399]
12. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet*. 2014; 46:1103–9. [PubMed: 25217961]
13. Klein RJ, Halldén C, Cronin AM, et al. Blood biomarker levels to aid discovery of cancer-related single-nucleotide polymorphisms: kallikreins and prostate cancer. *Cancer Prev Res*. 2010; 3:611–9.
14. Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. *Eur Urol*. 2014; 66:489–99. [PubMed: 24484606]
15. Drazer MW, Huo D, Schonberg MA, Razmaria A, Eggener SE. Population-based patterns and predictors of prostate-specific antigen screening among older men in the United States. *J Clin Oncol*. 2011; 29:1736–43. [PubMed: 21444863]

16. Sima CS, Panageas KS, Schrag D. Cancer screening among patients with advanced cancer. *JAMA*. 2010; 304:1584–91. [PubMed: 20940384]
17. Murphy DG, Ahlering T, Catalona WJ, et al. The Melbourne Consensus Statement on the early detection of prostate cancer. *BJU Int*. 2014; 113:186–8. [PubMed: 24206066]
18. Prostate cancer: screening guidelines. Memorial Sloan Kettering Cancer Center Web site. <http://www.mskcc.org/cancer-care/adult/prostate/screening-guidelines-prostate>
19. Heidenreich A, Abrahamsson PA, Artibani W, et al. Early detection of prostate cancer: European Association of Urology recommendation. *Eur Urol*. 2013; 64:347–54. [PubMed: 23856038]
20. 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. [PubMed: 12771116]
21. Louie KS, Seigneurin A, Cathcart P, Sasieni P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. *Ann Oncol*. 2015; 26:848–64. [PubMed: 25403590]
22. van Vugt HA, Roobol MJ, Busstra M, et al. Compliance with biopsy recommendations of a prostate cancer risk calculator. *BJU Int*. 2012; 109:1480–8. [PubMed: 21933335]
23. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol*. 2015; 67:627–36. [PubMed: 25511988]
24. Bjurlin MA, Carter HB, Schellhammer P, et al. Optimization of initial prostate biopsy in clinical practice: sampling, labeling and specimen processing. *J Urol*. 2013; 189:2039–46. [PubMed: 23485507]

Take-home message

Optimizing the benefits versus harms of prostate-specific antigen screening can be achieved through stratifying screening and biopsy. This clinical consultation guide provides the scientific background and evidence-based recommendations.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript