Prostate Cancer: Update on Early Detection and New Biomarkers

by Robert L. Grubb, III, MD

The future of screening will likely remain PSA-based, but will also involve an increasing use of adjuvant testing to avoid biopsies and minimize overdiagnosis of indolent cancers.

Robert L. Grubb, III, MD, is Associate Professor, Urology, Washington University School of Medicine, St. Louis, Missouri.
Contact: grubbr@musc.edu

Abstract

Screening and early treatment of prostate cancer (PCa) has recently come under scrutiny due to the rates of overdiagnosis of low risk cancer. Randomized trials, including ERSPC and PLCO, have informed our understanding of the survival benefit provided by systematic PCa screening with serum prostate-specific antigen (PSA). To reduce the number of patients diagnosed with indolent disease, new adjuvant risk stratification tests have become available.

Introduction

Prostate cancer (PCa) is the most common cancer diagnosed in males in the United States, with an estimated 161,360 new cases and causing 26,730 deaths in 2017.[1] This high incidence to mortality ratio is strongly linked to the introduction of prostate-specific antigen (PSA) as a screening test in the 1980s, which facilitated detection of PCa over pre-existing methods.[2] Patterns of PSA-based screening have evolved as the results of randomized screening trials have become available, and professional organizations have incorporated these findings into their recommendations. Although a powerful marker for the early detection of cancer, PSA has been associated with the over detection of many indolent cancers. New urine and blood-based biomarkers have been developed to improve the identification of clinically significant cancers, while minimizing the detection of less aggressive cancers. This article will review the current state of PSA-based early detection of PCa, focusing on the seminal screening studies and current guidelines for early detection. Additionally, the use of new urine and blood based early detection biomarkers will be discussed.

PSA Screening

Randomized trials have demonstrated a reduction in PCa-specific mortality rates attributable to PSA-based screening for PCa.[3-5] The largest of these is the European Randomized Study of Screening for Prostate Cancer (ERSPC), which randomized 182,160 men to a screening arm or control group across seven European countries.[3] The screening regimen was not uniform across all centers, but a PSA of 3.0 ng/mL was most commonly used as the threshold for a biopsy. Digital rectal exam was omitted from the screening process. No difference in overall mortality was noted (RR 0.99, 95% CI [0.97-1.01]),[3] but for the pre-defined core group of men aged 55-69 years (n=162,243), there was a 21% reduction in PCa-specific mortality (RR 0.79, 95% CI [0.68-0.91]) at 11-year median follow-up. This corresponded to an absolute mortality risk reduction of 1.07 deaths per 1,000 men. When the ERSPC was updated at 13-year median follow-up, the 20% reduction in PCa-specific mortality was maintained. Importantly, the number needed to screen in order to prevent

one death dropped from over 1,000 to 781.[6] Further, the cumulative risk of metastatic disease at 9 to 11 years of follow-up was 31% to 33% lower in the screened arm compared to the control arm of ERSPC.

Another significant population-based PSA screening trial was performed in Göteborg, Sweden; in this trial, 19,904 men aged 50-64 years were randomized to either a screening or control group.[5] Screening was performed with a PSA every two years, with additional evaluation (consisting of DRE and biopsy) performed for an elevated PSA. The PSA cutoff changed over the course of the study. A PSA cutoff of 3.4 ng/mL was used at the beginning of the study, but this was later lowered to 2.5 ng/mL. After a median follow-up of 14 years, a significant 44% decrease in PCa mortality was noted in the group randomized to screening (RR 0.56, 95% CI [0.39-0.82]), with a 56% risk reduction noted in the group of men who actually attended screening (RR 0.44, 95% CI [0.28-0.68]). Based on the observed risk reduction, in order to prevent one PCa death, the number needed to screen was 293. Even in this strongly positive trial in favor of PSA screening, 1,000 men would need to be screened for 14 years, and 120 men would have been diagnosed and treated, in order to avert 5 PCa deaths.[7]

In contrast to the ERSPC and the Göteborg trial, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial did not show improved PCa-specific mortality with PSA-based screening.[4] In the PLCO trial, 76,685 men were randomized to screening or usual medical care across ten sites in the United States. The screening regimen consisted of an annual PSA for six years and an annual DRE for four years. All screened men and their primary care providers received PSA results; those with a PSA above 4.0 ng/mL were advised to seek further diagnostic evaluation. After 13 years of follow-up, no difference in PCa-specific mortality (RR 1.09, 95% CI [0.87-1.36]) was observed between the groups. In the updated 15-year follow-up results, there is still no significant difference in PCa-specific mortality between the intervention (screened) and control groups.[8]

Criticisms of the PLCO study are well-documented, mainly relating to the high rates of PSA screening that occurred in the control group (3 in 4 men underwent at least one test), as well as the level of PSA screening prior to trial enrollment (up to 40%).[9] A recent evaluation of PLCO data suggested that men in the control group underwent more intense PSA screening through the follow-up period (study years 6-12).[10] Although these findings have been refuted by PLCO investigators, as the incidence of PCa was higher in the intervention group,[11] the above mentioned study limitations and the fact that only 85% of men in the intervention group underwent PSA screening may have affected the power of the trial to detect a beneficial effect from PSA screening.[12] While the PLCO trial failed to demonstrate a survival benefit to screening as a whole, a secondary analysis of men with minimal comorbidity found a 44% reduction in PCa-specific mortality (hazard ratio [HR], 0.56, 95% CI [0.33-0.95], p=0.03).[13] Moreover, the number needed to treat to prevent one PCa death at ten years in this subgroup was five. This analysis demonstrates the importance of clinical judgement and weighing competing risks of mortality when considering PSA screening and PCa management.

Taken together, the results of these large randomized screening trials demonstrate that PSA screening confers a modest reduction in PCa-specific mortality at the cost of significant overdiagnosis and overtreatment, with attendant economic and quality of life costs. As a result, many organizations have changed their PSA screening guidelines to emphasize the importance of a discussion of these risks.[14]

Current Guidelines in Early Detection

The American Urologic Association (AUA), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) have modified their guidelines to reflect the limitations of PSA screening and provide a rational basis of screening that minimizes overdiagnosis.[14,15] The AUA, EAU and NCCN recommend shared decision-making, counselling men on potential risks and benefits of PSA screening. All three organizations recommend screening only men in the 45-75 year age group (AUA and EAU use 70 years as routine upper age limit); the AUA and EAU also limit screening to men with life expectancy > 10-15 years. Screening intervals of two or more years are also suggested as a way to decrease the risks of overdiagnosis. The EAU provides risk stratification and interval adjustment based on PSA levels, while the AUA does not provide any specific criteria on who may be offered an extended screening interval. Neither organization recommends PSA testing in men younger than 40 years of age. However, the EAU does imply that a baseline PSA at age 40 can be used to risk stratify those who should begin earlier routine screening (men with PSA >1.0 ng/mL at age 40).[16,17]

Use of Adjuvant Risk Stratification Tests

The NCCN guidelines were among the first to incorporate adjuvant testing into their screening recommendations. Men with persistently elevated PSA are

recommended to undergo adjuvant testing: blood tests such as percent free PSA, the 4K score (GenPath, Elmwood Park, NJ), and prostate health index (PHI) (Beckman Coulter, Brea, CA), or urine tests such as prostate cancer antigen-3 and Select MDx (MDx Health, Irvine CA). These adjuvant tests are designed to help reduce overdiagnosis by avoiding potentially unnecessary biopsies. As an example, using a PHI score of 24 as a cutoff for biopsy would avoid 36% of biopsies with no cancer and 24% of biopsies with indolent cancer; this strategy would miss only 4% of clinically significant PCa.[18] The 4K score uses a panel of four prostate specific kallikrein proteins related to PSA to improve the accuracy of diagnosis. As an example, using the 4K score with a cutoff of 6% risk of high grade PCa among participants in the PLCO trial would have eliminated unnecessary biopsies in 42% of men, while detecting 88% of high grade cancers.[19] While PHI and 4K score are blood tests, urine based diagnostics are also available to help improve PCa diagnostic accuracy. One such example is the Select MDx test, which measures the mRNA levels of HoxC6 and DLX1 in the urine and incorporates traditional clinical variables into a predictive model. In a testing and validation cohort study, Van Neste et al. determined that the Select MDx test could avoid 30% of negative biopsies while only missing 2% of aggressive cancers.[20]

Another major tool that has been increasingly utilized to improve diagnostic accuracy for PCa is multiparametric magnetic resonance imaging (MRI). MRI has most commonly been used for patients who have had at least one prior negative biopsy. When combined with ultrasound fusion biopsy technologies, MRI improves the diagnosis of high grade PCa without an increase in overdiagnosis of more indolent cancers. Prostate MRI is discussed in greater detail elsewhere in this issue.

Conclusions

PSA remains the most sensitive screening test available for the early detection of PCa. However, screening of all men has been shown to have only a modest benefit in PCa-specific mortality reduction, while introducing significant potential harms. While the ESRPC and PLCO trial did not provide a clear resolution to the issue of PSA screening, they more clearly defined its benefits and limitations. As a result, national and international organizations have altered their guidelines in recognition of the nuances of PSA screening in order to try to maximize the benefits while minimizing the harms. The future of screening will likely remain PSA based, but will also involve an increasing use of adjuvant testing to avoid biopsies and minimize overdiagnosis of indolent cancers. The exact role and sequence of adjuvant blood, urine, and imaging tests continues to evolve.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
2. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med. 1991;324(17):1156-1161.
3. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360(13):1320-1328.
4. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360(13):1310-1319.
5. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010;11(8):725-732.
6. Schroder 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(9959):2027-2035.
7. Carroll PR, Whitson JM, Cooperberg MR. Serum prostate-specific antigen for the early detection of prostate cancer: always, never, or only sometimes? J Clin Oncol. 2011;29(4):345-347.
8. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2017;123(4):592-599.
9. Pinsky PF, Blacka A, Kramer BS, Miller A, Prorok PC, Berg C. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Clin Trials. 2010;7(4):303-311.
10. Shoag JE, Mittal S, Hu JC. Reevaluating PSA Testing Rates in the PLCO Trial. N Engl J Med. 2016;374(18):1795-1796.
11. Pinsky P, Prorok P. More on Reevaluating PSA Testing Rates in the PLCO Trial. N Engl J Med. 2016;375(15):1500-1501.
12. Gulati R, Tsodikov A, Wever EM, et al. The impact of PLCO control arm contamination on perceived PSA screening efficacy. Cancer Causes Control. 2012;23(6):827-835.
13. Crawford ED, Grubb R, 3rd, Black A, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol. 2011;29(4):355-361.
14. Kim EH, Andriole GL. Prostate-specific antigen-based screening: controversy and guidelines. BMC Medicine 2015; 13: 61.
15. van Leeuwen PJ, Connolly D, Tammela TL, et al. Balancing the harms and benefits of early detection of prostate cancer. Cancer. 2010;116(20):4857-4865.
16. Lilja H, Cronin AM, Dahlin A, et al. PRediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. Cancer 2011; 117: 1210-1219.
17. Preston MA, Batista JL, Wilson KM, et al. Baseline Prostate-Specific Antigen Levels in Midlife Predict Lethal Prostate Cancer. J Clin Oncol. 2016;34(23):2705-2711.
18. de la Calle C, Patil D, Wei JT, et al. Multicenter Evaluation of the Prostate Health Index to Detect Aggressive Prostate Cancer in Biopsy Naive Men. J Urol. 2015;194(1):65-72.
19. Kim EH, Andriole GL, Crawford ED, et al. Detection of High Grade Prostate Cancer among PLCO Participants Using a Prespecified 4-Kallikrein Marker Panel. J Urol. 2017;197(4):1041-1047.
20. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. Eur Urol. 2016;70(5):740-748.

Disclosure

None reported.

MM