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PSA screening—a matter of debate?

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Summary Prostate cancer (PCa) is the most common cancer type in men. Overall, the goal of prostate-specific antigen (PSA)-based screening is to identify early-stage disease that can be treated successfully. However, evidence supporting an overall survival advantage in men undergoing PSA screening is controversial, leading to a lack of consensus on guidelines.
The present review article provides an overview of the most important studies on PSA screening including the latest updates of large trials. In addition, modern concepts in early detection of PCa that can be added to PSA measurement alone such as PSA isoforms or mpMRI are discussed. Lastly, recommendations for PCa screening and early detection from the European and German Societies of Urology issued in 2019 are presented.

Keywords Prostate cancer · PSA · Early detection · PSA isoforms · mpMRI · Guidelines

Introduction

Prostate cancer (PCa) is the most common cancer and remains an important cause of death in males [1]. Overall, PCa is a pleiotropic disease ranging from slow-growing organ-confined tumors to highly aggressive carcinomas associated with metastatic spread inducing significant morbidity and mortality. Although most type of prostate tumors belong to the slow-growing forms, 10–15% of patients are diagnosed in a metastatic stage of disease. Therefore, early detection is important in PCa treatment strategies.

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Prostate-specific antigen (PSA) remains the most used biomarker in the detection of early PCa [2]. In general, PSA is a serine protease produced and released by epithelial cells of the prostate. It is secreted as an inactive proenzyme (proPSA) into seminal fluid and activated by the kallikrein-related peptidase 2 and other endopeptidases produced in the prostate. PSA itself occurs in several different molecular forms in serum: free PSA (fPSA) and complexed PSA (total PSA; [2, 3]).

Although it has been demonstrated in large patient cohorts that regular PSA measurement reduces PCa mortality rates, PSA screening is still a controversial issue in most countries because beside the benefits there are also harms such as overdiagnosis and overtreatment.

Impact of PSA measurement on mortality

The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in 1993 and is the world's largest randomized controlled trial on PSA screening including men aged 55–69 years from eight European countries [4]. Data revealed a 21% reduction of PCa mortality after 11 years of follow-up in screened patients [4]; the 13-year follow-up update also confirmed that mortality was significantly lower in the screened group compared with the control group [5].

Recently, the 16-year follow-up of the ERSPC was published corroborating earlier results that PSA screening significantly reduces PCa mortality. In detail, the study was able to demonstrate a larger benefit with longer follow-up, reporting a rate ratio of PCa mortality of 0.80 (95% confidence interval [CI] 0.72–0.89, $p<0.001$) at 16 years. The difference in absolute PCa mortality increased from 0.14% at 13 years to 0.18% at 16 years. The number of men that had to

be invited for screening to prevent one PCa death was 570 at 16 years compared with 742 at 13 years. The number needed to diagnose was reduced to 18 from 26 at 13 years [6]. In addition, in July 2019 the study group published data excluding differential or better treatment in the screening arm compared with the control arm, which has been commonly suggested to bias PCa mortality in the ERSPC study [7]. However, there is also evidence that ERSPC centers varied by attendance, screening interval, biopsy compliance, contamination in the control arm, as well as treatments. Admittedly, using a microsimulation model, the ERSPC investigators were able to demonstrate that ERSPC would have shown only a slightly larger PCa mortality reduction if all centers had complied with the quality criteria for attendance or biopsy compliance [8]. These data again underline the importance of compliance to PSA testing as well as that biopsy after an elevated PSA substantially influences PCa mortality.

In contrast to the Swedish ERSPC data, the U.S. Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial randomized 76,685 men aged 55–74 years. Both PSA and digital rectal examination were used in the three first annual screens and PSA only (cut-off 4 μg/l) in the last two rounds. In contrast to the Swedish study, the incidence of PCa at 13 years was 108 per 10,000 person-years in the screening arm and 97 in the control arm (RR = 1.12, 95% CI: 1.02–1.17) failing to show any difference in PCa mortality between the screening and control arm [9]. An extended follow-up of the PLCO trial over a median of 15 years continued to indicate no reduction in PCa mortality for the intervention arm versus the control arm [10].

Besides the U.S. and the Swedish study, PSA testing was also introduced in Tyrol (Austria) in 1988, and since 1993 it has been offered cost free in an organized form to men aged between 45 and 74 years. In line with the ERSPC data, survival analyses revealed a significant reduction in PCa mortality with a risk ratio of 0.70 (95% CI: 0.57–0.87) for Tyrol compared with the mortality rate in the period from 1989 to 1993 in Austria [11, 12]. However, a significant problem of the Tyrol study was that more than 50% of diagnosed cancers were low risk, opening the discussion of overdiagnosis and overtreatment [13]. Thus, we recently evaluated the age-dependent PSA cut-offs used since 1995 in our early detection program in order to reduce the number of unnecessary biopsies in patients with benign disease, but without missing PCa, in particular without missing significant PCa [13]. With "new," fine-tuned PSA cut-offs, we detect all relevant PCa with a significant reduction of biopsies compared with the "old" cut-off values, which is one step toward a smarter strategy in the Tyrol PCa Early Detection Program.

Additional parameters beyond PSA for PCa diagnosis

Molecular markers

A main limitation of PSA-based early PCa detection is its low specificity associated with a high proportion of men detected with nonmalignant findings at the first or subsequent prostate biopsy. Thus, several concepts to optimize PSA rating such as PSA density (PSA/prostate volume), PSA kinetics (velocity, doubling time), and age- or race-specific reference ranges have been described to reduce the false-negative and false-positive rates of PCa detection.

Moreover, one has to consider that 10–30% of PSA is present in an uncomplexed form, whose implementation in PSA measurement has further improved the accuracy of cancer detection compared with PSA alone [14]. For example, the use of percentage of free PSA (fPSA%) has been successfully demonstrated in numerous studies to improve the accuracy of PCa detection compared with PSA measurement alone. To summarize, studies revealed a lower ratio of fPSA/PSA in PCa patients compared with patients with benign prostate hyperplasia (reviewed in [15]). In addition, several studies identified the PSA isoform proPSA as a predictor of significant PCa [16–18]. Thereby studies including our own research were able to demonstrate that a high amount of proPSA is associated with aggressive forms of PCa [18–21].

Besides fPSA and proPSA, several concepts combining total PSA values with PSA isoforms have been developed to reduce the false-negative and false-positive rates of PCa detection. By way of example, prostate health index (PHI) calculation combines PSA, fPSA, and proPSA and now plays an important role in discriminating the presence of PCa from non-cancerous prostatic diseases [22, 23]. Incrementally, our own data described the PHI index as a marker of cancer aggressiveness and as a predictor of disease progression in patients undergoing active surveillance [21].

Secondary, multivariate prediction models, such as nomograms have been developed providing a more accurate method for prospectively determining the risk of a positive biopsy. Lastly, apart from PSA, numerous studies investigated new biomarkers for PCa detection among them some—for example, PCA3, 4KScore, or TMPRSS2-ERG—are highly promising; however, this topic is beyond the scope of this mini review article.

Multiparametric magnetic resonance imaging

Multiparametric magnetic resonance imaging (mpMRI) of the prostate is a novel promising tool for the diagnosis of PCa that might help to reduce overdiagnosis of insignificant cancer types.

According the current guidelines of the European Society of Urology (EAU), mpMRI should be used

Table 1 Recommendation of the European Society of Urology (updated March 2019) for PCa screening and early detection (www.uroweb.org)

Recommendations	Strength rating
Do not subject men to PSA testing without counselling them on the potential risks and benefits	Strong
Offer an individualized risk-adapted strategy for early detection to a well-informed man with a good performance status and a life expectancy of at least 10–15 years	Strong
Offer early PSA testing in well-informed men at elevated risk of having PCa: Men >50 years of age Men >45 years of age and a family history of PCa African-Americans >45 years of age	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: Men with a PSA level of >1 ng/ml at 40 years of age Men with a PSA level of >2 ng/ml at 60 years of age Postpone follow-up to 8 years in those not at risk	Weak
Stop early diagnosis of PCa based on life expectancy and PS; men who have a life-expectancy of <15 years are unlikely to benefit	Strong

Table 2 Recommendation of the German Society of Urology (updated May 2019) for PCa screening and early detection (www.leitlinienprogramm-onkologie.de)

Recommendations	Strength rating
Men over 45 years of age with a life expectancy of more than 10 years should be informed about the possibility of early detection. In men at risk for prostate cancer, this age limit may be brought forward by 5 years	B
Men should be informed about the advantages and disadvantages of early detection measures, in particular about the validity of positive and negative test results as well as any further measures that may be required	A
Men who wish to undergo a screening test after the investigation should be offered the determination of the PSA value as an examination method	A
In addition, a digital rectal examination should be recommended	B
An increased PSA value should be controlled taking into account influencing factors	A
For men who wish to continue a PSA screening, the follow-up interval should be based on the current PSA value and on the age of the patient, unless indicated for biopsy. Age group from 45 years and a life expectancy >10 years – PSA <1 ng/ml: interval every 4 years – PSA 1–2 ng/ml: interval every 2 years – PSA >2 ng/ml: interval every year For men over 70 years of age and PSA <1 ng/ml, further PSA-assisted screening is not recommended	B
In the context of early detection, a prostate biopsy should be recommended if at least one of the following criteria is met: – Controlled PSA value of ≥4 ng/ml at the initial early detection consultation, taking into account influencing factors – Carcinoma suspected results in digital rectal examination – Noticeable PSA increase (without change of determination method)	A
Recommendation grade: *A* strong recommendation, *B* recommendation	

for patients with a previous negative prostate biopsy; however, the role of a mpMRI in biopsy-naive men remains conflicting. For example, it has been shown that in men with clinical suspicion of PCa, a subsequent positive MRI did not differ regarding overall PCa detection [24]. By contrast, the PROMIS trial showed that mpMRI-targeted biopsy had greater sensitivity than transrectal ultrasound(TRUS)-guided biopsy (87% vs. 60%) and a higher negative predictive value (NPV (72% vs. 65%) for detecting significant PCa [25].

Several studies are ongoing, or have been terminated, to investigate PCa prediction rates by combing mpMRI with PSA; among them, PSA density and PHI are the most commonly studied. For instance, Washino et al. reviewed 288 biopsy-naive patients who underwent mpMRI-guided prostate biopsy for suspected PCa for whom PSA density values were available and found that a high PI-RADS score in combination with a high PSA density (PI-RADS score ≥4 plus PSA density ≥0.15 ng/ml/ml, or PI-RADS score 3 plus PSA density ≥0.30 ng/ml/ml) yielded high PCa detection rates [26]. Druskin et al. showed that the addition of PHI to a multivariate model including age, biopsy history, and Prostate Imaging Reporting and Data System (PI-RADS) score increased the area under the curve for clinically significant PCa detection from 0.83 to 0.90 in a cohort of 109 patients [27].

Guideline recommendations—who to screen? When to start?

As not all large randomized clinical trials proved uniform survival advantages, screening for PCa is one of the most controversial topics in the urological literature. Based on this, there exist no consistent guidelines concerning PSA measurement. Overall, an individualized risk-adapted strategy for early detection might be offered to a well-informed man with at least 10–15 years of life expectancy. In addition, care should be taken to carefully identify the patient, taking into account the potential benefits and harms involved

such as overdiagnosis and overtreatment of low-risk PCa.

An overview of the recommendations for PCa screening and early detection of the European (Table 1) and German Societies of Urology (Table 2) updated in 2019 are illustrated in Tables 1 and 2.

Conclusion

PCa is the most common cancer type in men. Overall, the goal of PSA-based screening is to identify early-stage disease. However, not all clinical trials were able to demonstrate a survival advantage in men undergoing PSA screening, thereby leading to a lack of consensus on guidelines. Thus, an individualized risk-adapted strategy should be pursued to balance the advantages and harms of PSA measurement.

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Conflict of interest I. Heidegger declares that she has no competing interests regarding this manuscript.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. Ca Cancer J Clin. 2017;67(1):7–30.
2. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987;317(15):909–16.
3. Haese A, Graefen M, Huland H, Lilja H. Prostate-specific antigen and related isoforms in the diagnosis and management of prostate cancer. Curr Urol Rep. 2004;5(3):231–40.
4. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012;366(11):981–90.
5. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, 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):2027–35.
6. Hugosson J, Roobol MJ, Mansson M, Tammela TLJ, Zappa M, Nelen V, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. Eur Urol. 2019;76(1):43–51.
7. Carlsson SV, Mansson M, Moss S, Kwiatkowski M, Recker F, Tammela TLJ, et al. Could differences in treatment between trial arms explain the reduction in prostate cancer mortality in the European randomized study of screening for prostate cancer? Eur Urol. 2019;75(6):1015–22.
8. Heijnsdijk EAM, Adolfsson J, Auvinen A, Roobol MJ, Hugosson J, de Koning HJ. The impact of design and performance in prostate-specific antigen screening: differences between ERSPC centers. Eur Urol. 2019; 76(3):276–9. https://doi.org/10.1016/j.eururo.2019.04.007
9. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al. Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012;104(2):125–32.
10. Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2017;123(4):592–9.
11. Bartsch G, Horninger W, Klocker H, Pelzer A, Bektic J, Oberaigner W, et al. Tyrol prostate cancer demonstration project: early detection, treatment, outcome, incidence and mortality. BJU Int. 2008;101(7):809–16.
12. Oberaigner W, Siebert U, Horninger W, Klocker H, Bektic J, Schafer G, et al. Prostate-specific antigen testing in Tyrol, Austria: prostate cancer mortality reduction was supported by an update with mortality data up to 2008. Int J Public Health. 2012;57(1):57–62.
13. Heidegger I, Fritz J, Klocker H, Pichler R, Bektic J, Horninger W. Age-adjusted PSA levels in prostate cancer prediction: updated results of the tyrol prostate cancer early detection program. PLoS ONE. 2015;10(7):e134134.
14. Catalona WJ, Partin AW, Finlay JA, Chan DW, Rittenhouse HG, Wolfert RL, et al. Use of percentage of free prostate-specific antigen to identify men at high risk of prostate cancer when PSA levels are 2.51 to 4 ng/mL and digital rectal examination is not suspicious for prostate cancer: an alternative model. Urology. 1999;54(2):220–4.
15. Stephan C, Jung K, Lein M, Sinha P, Schnorr D, Loening SA. Molecular forms of prostate-specific antigen and human kallikrein 2 as promising tools for early diagnosis of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2000;9(11):1133–47.
16. Hori S, Blanchet JS, McLoughlin J. From prostate-specific antigen (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer. BJU Int. 2013;112(6):717–28.
17. Mikolajczyk SD, Rittenhouse HG. Pro PSA: a more cancer specific form of prostate specific antigen for the early detection of prostate cancer. Keio J Med. 2003;52(2):86–91.
18. Sokoll LJ, Sanda MG, Feng Z, Kagan J, Mizrahi IA, Broyles DL, et al. A prospective, multicenter, National Cancer Institute Early Detection Research Network study of [–2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. Cancer Epidemiol Biomarkers Prev. 2010;19(5):1193–200.
19. Heidegger I, Klocker H, Steiner E, Skradski V, Ladurner M, Pichler R, et al. 2]proPSA is an early marker for prostate cancer aggressiveness. Prostate Cancer Prostatic Dis. 2014;17(1):70–4.
20. Chiu PK, Lai FM, Teoh JY, Lee WM, Yee CH, Chan ES, et al. Prostate health index and %p2PSA predict aggressive prostate cancer pathology in Chinese patients undergoing radical prostatectomy. Ann Surg Oncol. 2016;23(8):2707–14.
21. Heidegger I, Klocker H, Pichler R, Pircher A, Prokop W, Steiner E, et al. ProPSA and the Prostate Health Index as predictive markers for aggressiveness in low-risk prostate cancer-results from an international multicenter study. Prostate Cancer Prostatic Dis. 2017;20(3):271–5.
22. Loeb S, Sokoll LJ, Broyles DL, Bangma CH, van Schaik RH, Klee GG, et al. Prospective multicenter evaluation of the Beckman Coulter Prostate Health Index using WHO calibration. J Urol. 2013;189(5):1702–6.

23. Loeb S, Catalona WJ. The Prostate Health Index: a new test for the detection of prostate cancer. Ther Adv Urol. 2014;6(2):74–7.
24. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol. 2015;68(3):438–50.
25. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multiparametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389(10071):815–22.
26. Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, et al. A multicenter study of [–2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. J Urol. 2011;185(5):1650–5.
27. Druskin SC, Tosoian JJ, Young A, Collica S, Srivastava A, Ghabili K, et al. Combining Prostate Health Index density, magnetic resonance imaging and prior negative biopsy status to improve the detection of clinically significant prostate cancer. BJU Int. 2018;121(4):619–26.