available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission

Hendrik Van Poppel [a,†,*], *Renée Hogenhout* [b,†], *Peter Albers* [c,d], *Roderick C.N. van den Bergh* [e], *Jelle O. Barentsz* [f,‡], *Monique J. Roobol* [b,‡]

[a] *Department of Development and Regeneration, University Hospital KU Leuven, Leuven, Belgium;* [b] *Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [c] *Department of Urology, Heinrich-Heine University Medical Faculty, Düsseldorf, Germany;* [d] *Division of Personalized Early Detection of Prostate Cancer, German Cancer Research Center, Heidelberg, Germany;* [e] *Department of Urology, St. Antonius Hospital, Utrecht, The Netherlands;* [f] *Department of Medical Imaging, Radboudumc, Nijmegen, The Netherlands*

The general prevailing motives for not implementing a prostate-specific antigen (PSA)-based population screening program for prostate cancer (PCa) arise from its overdiagnosis and eventual subsequent overtreatment of indolent PCa. However, this has been overthrown by the availability of increased knowledge on the natural course of different risk groups, new technologies such as multivariable risk prediction models, and magnetic resonance imaging (MRI) [1,2]. The harms of screening can now be reduced by risk-adapted and personalized strategies, while maintaining the reduction in metastasis and death.

The US Preventive Services Task Force recommendations against PSA-based screening in 2008 resulted in a rise in diagnoses of advanced metastatic stages of PCa, which still continues [3]. In Europe, PCa has now become the most frequently diagnosed cancer among men and the second leading cause of male cancer death [4]. Furthermore, we are currently in a situation in which wide-scale PCa screening occurs in an opportunistic setting, with rates varying by region and socioeconomic status. Opportunistic screening has proven to be ineffective, with no mortality reduction but considerable overdiagnosis [5,6]. These figures portray PCa as a significant health problem, with available screening tools applied inefficiently. It is time that the European Commission considers modern risk-stratified early detection of PCa.

The classic, organized screening pathway—which dates from the early 1990s—has already proven to be effective in terms of disease-specific mortality reduction [7]. Addition of the risk stratification tools (multivariable risk prediction models and MRI) that have meanwhile emerged results in a more favorable balance between the harms and benefits of early detection. This enhanced pathway reduces unnecessary testing and overdiagnosis, while maintaining the reduction in incidence of advanced, sometimes symptomatic PCa with the accompanying aggressive and expensive treatment, resulting in a higher net benefit for quality of life and costs. In anticipation of level 1 evidence, we present a contemporary intelligible algorithm for early detection of PCa that balances these risks and benefits: PCa Screening 2.0.

Table 1 presents the results, in terms of both harms and benefits, of ongoing opportunistic screening and the European Randomized Study of Screening for Prostate Cancer (ERSPC) algorithm, together with empirical and modeling data when introducing risk stratification and MRI into the screening algorithm [7–10].

Our proposed early detection algorithm for PCa starts by counseling of men on the potential harms and benefits of early detection. The European Association of Urology guidelines on PCa have been used to define the age ranges and further actions after initial PSA testing, as presented in Fig. 1A [11].

* Corresponding author. Department of Development and Regeneration, University Hospital KU Leuven, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.
E-mail address: hendrik.vanpoppel@kuleuven.be (H. Van Poppel).
† These authors contributed equally to this work.
‡ These authors contributed equally to this work.

https://doi.org/10.1016/j.eururo.2020.12.010

Please cite this article in press as: Van Poppel H, et al. Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.12.010

Table 1 – Expected harm and benefit of various hypothetical screening strategies.

	Overdiagnosis	Overtreatment	PCa mortality reduction	LYs[a]	QALYs[a]
Opportunistic screening: unorganized.	Significant	Significant	No	–	–
Organized PSA-based screening program (ERSPC): fixed PSA threshold for biopsy indication, treatment for all diagnoses.	Significant	Significant	Yes	73	56
Organized HR-based screening program, inviting only high-risk cases (eg, *BRCA2* mutation, positive family history, African descent).[b]	Lower (fewer men invited)	Lower (fewer men invited)	Yes, but only for invited HR subgroup	73	56
Screening 2.0: risk-based screening interval, risk-based biopsy indication using RCs and MRI, encourage AS in patients with low- and favorable intermediate-risk PCa.	Lower	Lower	Yes	73	>74 [10]

PCa = prostate cancer; PSA = prostate-specific antigen; AS = active surveillance; ERSPC = European Randomized Study of Screening for Prostate Cancer; HR = high risk; LYs = life-years; QALYs = quality-adjusted life-years; RCs = risk calculators; MRI = magnetic resonance imaging.
[a] Based on Carlsson et al [9]. The numbers refer to QALYs gained over a population of 1000 men.
[b] If the lifetime risk of diagnosis and death are both twice as high, the harm-to-benefit ratio of screening will remain unchanged [8].

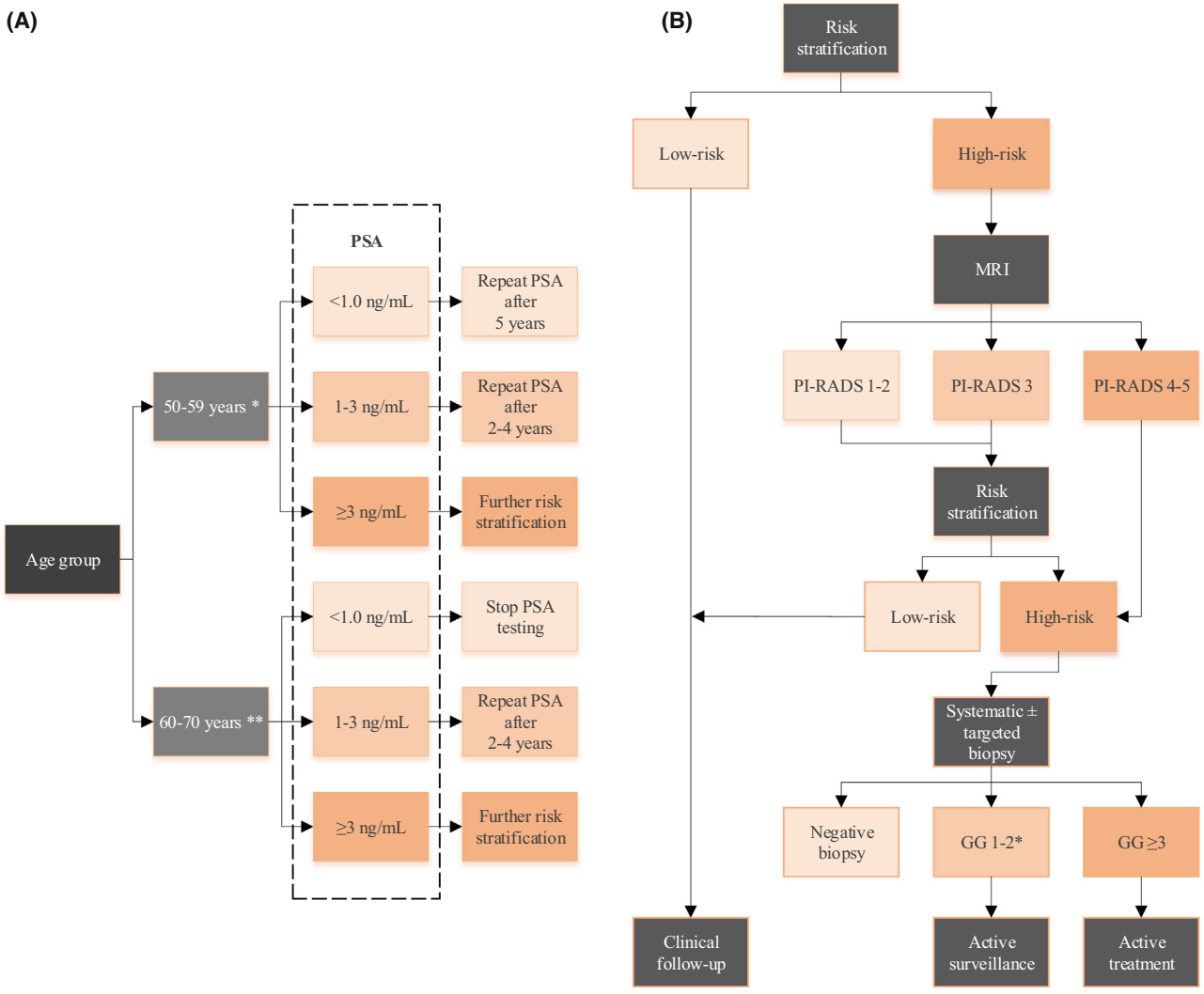

Fig. 1 – (A) Flow chart for PSA interval testing in different age groups. PSA = prostate-specific antigen. *Follow the same schedule for men aged >45 yr with a family history of prostate cancer or African descent and for men aged >40 yr who carry *BRCA2* mutations [11]. **Follow the same schedule for men aged >70 yr with good performance status and life expectancy of at least 10–15 yr [11]. (B) Algorithm for a risk-stratified early detection strategy for prostate cancer in men with elevated PSA. MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; GG = Gleason grade group. *Only favorable intermediate-risk prostate cancer.

Please cite this article in press as: Van Poppel H, et al. Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.12.010

Multiple analyses on the optimal screening interval are available and, although not conclusive, agree that annual screening for all participants is redundant. The testing intervals presented in Fig. 1A, based on a baseline PSA level, represent a conservative compromise of these estimates [11].

Further risk stratification for prostate biopsy with multivariable risk prediction models, so-called risk calculators, and/or multiparametric (mp)MRI will provide an individualized assessment of the potential risk of having a biopsy-detectable cancer. The aim is also to distinguish clinically significant from insignificant PCa [12,13]. Fig. 1B presents a diagnostic pathway that is generally applicable in a routine early detection program for PCa. Unnecessary MRI scans can be avoided in men for whom the risk of finding PCa is low according to a risk calculator. In general, prostate biopsy is offered to men with suspicious mpMRI Prostate Imaging-Reporting and Data System (PI-RADS) scores of 3–5. Increasing evidence shows that biopsy can be safely avoided in men with equivocal (PI-RADS 3) lesions when PSA density (PSAD) is <0.15 ng/mL/cm^3 [14]. However, other important clinical predictive parameters for finding (clinically significant) PCa, such as age, family history, PSA, and digital rectal examination, should also be taken into account. Underdiagnosis in men with equivocal lesions, as well as in MRI-negative men, could therefore be limited by applying risk stratification after performing MRI. This could be done, for example, by integrating the MRI results with clinical parameters, including PSAD as a continuous variable, in a risk calculator [12]. Thus, for men with negative MRI (PI-RADS 1–2) but for whom the risk of having PCa remains high based on the calculated risk, systematic biopsy should not be avoided. Men with PI-RADS 3 lesions may be excluded from biopsy if their calculated risk is low. Men with PI-RADS 4–5 lesions are advised to undergo systematic plus targeted biopsy.

Men with a negative biopsy need to be monitored using repeat PSA measurements and, if indicated, repeat mpMRI as a safety net. The algorithm can be run again, taking into account the previous negative prostate-biopsy status.

After diagnosis, overtreatment can be reduced with active surveillance. This treatment strategy will be applicable to a growing proportion of PCa patients because of our increasing knowledge of the biology of indolent cancers and improved sampling using imaging. When curative therapy is indicated, new-generation surgical and radiation techniques that have less functional side effects are now available, reducing the impact on quality of life.

In summary, the currently proposed algorithm exploits the knowledge gathered on PCa screening and novel technologies over the past decades, which reduce the harms and may be able to increase the benefits of the classic screening strategy. With the increasing burden of PCa on the society and the widespread ongoing application of harmful opportunistic screening practices, we feel that the time has come to start implementing organized, risk-stratified early detection of PCa for well-informed men throughout the European Union. The European Commission should endorse such a strategy so that the EU member states can incorporate it in their national cancer plans.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: The authors acknowledge Europa Uomo.

References

[1] Osses DF, Roobol MJ, Schoots IG. Prediction medicine: biomarkers, risk calculators and magnetic resonance imaging as risk stratification tools in prostate cancer diagnosis. Int J Mol Sci 2019;20:1637.
[2] Schoots IG, Padhani AR, Rouvière O, Barentsz JO, Richenberg J. Analysis of magnetic resonance imaging-directed biopsy strategies for changing the paradigm of prostate cancer diagnosis. Eur Urol Oncol 2020;3:32–41.
[3] Jemal A., Culp M.B., Ma J., Islami F., Fedewa S.A. Prostate cancer incidence 5 years after US Preventive Services Task Force recommendations against screening. J Natl Cancer Inst. In press. https://doi.org/10.1093/jnci/djaa068.
[4] Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53.
[5] Arnsrud Godtman R, Holmberg E, Lilja H, Stranne J, Hugosson J. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. Eur Urol 2015;68:354–60.
[6] Roobol MJ. Screening for prostate cancer: are organized screening programs necessary? Transl Androl Urol 2018;7:4–11.
[7] Hugosson J, Roobol MJ, Mansson M, et al. A 16-yr follow-up of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2019;76:43–51.
[8] Bokhorst LP, Roobol MJ. Ethnicity and prostate cancer: the way to solve the screening problem? BMC Med 2015;13:179.
[9] Carlsson SV, de Carvalho TM, Roobol MJ, et al. Estimating the harms and benefits of prostate cancer screening as used in common practice versus recommended good practice: a microsimulation screening analysis. Cancer 2016;122:3386–93.
[10] de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JP. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. Eur Urol 2014;66:430–6.
[11] Mottet N, Bellmunt J, Briers E, et al. EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2020.
[12] Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging: improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk calculators. Eur Urol 2019;75:310–8.
[13] van der Leest M, Cornel E, Israel B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naive men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019;75:570–8.
[14] Brizmohun Appayya M, Adshead J, Ahmed HU, et al. National implementation of multi-parametric magnetic resonance imaging for prostate cancer detection – recommendations from a UK consensus meeting. BJU Int 2018;122:13–25.