The use of PSA, biomarkers, risk calculators and mpMRI in the early detection of prostate cancer.

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Abstract

Prostate cancer (PCa) is the most common cause of cancer in men in the developed world and the fifth leading cause of cancer death among men. In 1991 the use of prostate-specific antigen (PSA) level in serum was described to detect prostate cancer at an early stage, where curative treatment is still possible. To answer the question whether PSA-based screening could reduce PCa-specific mortality, two large randomized controlled trials were set up in 1993 namely; the Prostate, Lung, Colorectal and Ovary (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC). After years of research followed by years of debate, the general consensus is that PSA-based screening can reduce PCa-specific mortality. Unfortunately, purely PSA-based screening results in harms like unnecessary biopsies, overdiagnosis of low-risk prostate cancer and subsequent overtreatment. In a purely PSA-based screening protocol, harms tend to outweigh the benefits. Therefore, further refinement of the screening algorithm is indicated. Risk calculators, contemporary biomarkers and imaging techniques like multi-parametric magnetic resonance imaging (mpMRI) can be used to reduce the harms of PSA-based screening by improving the specificity of the PSA tests. In current practice, PSA tests, in general, are used on patient request. This so-called opportunistic screening is mostly applied in elderly men who benefit least from PCa screening. Hence, further development and implementation of risk calculators, contemporary biomarkers and mpMRI is needed and will undoubtedly lead to a more favorable harm-benefit trade-off for prostate cancer screening. Pilot studies for the implementation of organized PCa screening programs should be started to determine the harm-benefit trade-off of these new modalities and to determine cost-effectiveness. A well-organized contemporary screening program is preferred above the current ineffective opportunistic screening practices.

1 Introduction

Prostate cancer (PCa) is estimated to be the most common cause of cancer in men in the developed world and the second most common cause worldwide.[1] In 2018, it is estimated that worldwide 1.3 million cases of PCa will be diagnosed and that there will be 359,000 PCa associated deaths worldwide, making it the fifth leading cause of cancer death in men.[1] In 2018, an estimated total of 164,690 new prostate cancer cases will be diagnosed in the United States (U.S.).[2] PCa will account for almost 1 of every 5 newly cancer diagnosis.[3] The incidence of PCa has increased mainly due to the increased use of prostate-specific antigen (PSA) screening.[4] Since the late 1980's, the incidence of PCa in the U.S. increased by 44% in the age group 45-74.[4]

PCa is predominantly a slow-growing disease with a potentially long window for curative management, making it suitable for screening. Screening aims to detect cancer at an early stage, where curative treatment is required. However, because PCa is predominantly a slow-growing disease, screening procedures may lead to the over diagnosis of indolent PCa. The described increase in the incidence of PCa was accompanied with a decline in the PCa-specific mortality. In the U.S., the PCa-specific mortality reduced nearly 40% since 1990. This reduce is most likely explained by the improvement in PCa treatment and the increased use of PSA-based screening.[2] In 2011 the U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based screening for all age groups. This recommendation was given due to concerns about the high increase in incidence and overtreatment. The effect of this recommendation is being closely monitored and it appears that in 2012 there was an increase in the diagnosis of advanced stage prostate cancer in the U.S. In 2017 the USPSTF repealed their recommendation against PSA-based screening. Now, the USPSTF recommends an informed and individual decision making on PCa screening.[2]

PSA-based screening remains controversial, however with the increased life-expectancy and associated increased incidence of PCa a thorough understanding of the different sequale associated with PCa screening is demanded. In this narrative review, we will discuss the important considerations that relate to the still controversial issue of PCa screening.[4, 5] Furthermore, we will describe the use of risk calculators, biomarkers and imaging technologies that can be incorporated into clinical decision making regarding the harms associated with PCa screening.

2 Prostate cancer screening

The use of PSA as a screening tool for PCa was reported for the first time in 1991 by Catalona et al[6]. PSA is a kallikrein that is excreted into semen by the prostate to liquefy clotted ejaculate to enhance sperm cell motility.[7] PSA enters the blood circulation, enabling its measurement in the serum. PSA is produced by prostate epithelial cells and is organ-specific.[8] An elevated serum PSA can be an early sign of PCa.[8] Unfortunately, the serum PSA level can also be elevated due to benign prostatic hypertrophy (BPH) or prostatitis.[9] If the

serum PSA level is elevated prostate biopsies are needed to detect or rule out a PCa diagnosis.

In 1993 two large randomized controlled trials the Prostate, Lung, Colorectal and Ovary (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial were designed to answer the question whether PSA-based screening could reduce PCa-specific mortality.[10, 11]

In the PLCO trial 76,693 men, aged 55-74 were randomly assigned to either a screening or control arm. The screening arm received annual PSA tests for six years and annual DRE for four years. The control arm received usual care.[12] At a complete follow-up period of seven years, the PLCO trial reported no difference in the PCa-specific mortality between the two arms. In addition, with 67% of the data completed, the 10-year follow-up showed no difference in PCa-specific mortality either.[12]

In the ERSPC trial, 162,234 men aged 55-69 were randomly assigned to either an intervention or a control arm. The intervention arm was provided PSA screening every two to four years. No PSA screening was provided to the control arm.[13] In contrast to the PLCO trial, the ERSPC trial reported a significant reduction in PCa-specific mortality of 20% in favour of screening at a median follow-up of nine years.[13] The reduction of PCa-specific mortality in the screening arm coincided with the detection of early-stage disease. There was a 24.4% reduction in the detection of advanced PCa.[14, 15]

Hence, after years of intensive research, the two randomized controlled trials reported conflicting results. The main differences in study design of PLCO and ERSPC were the screening interval that was used in the intervention arms of each trial (annual versus every 2 to 4 year respectively) and the PSA threshold for biopsy referral (4.0 mg/mL versus 3.0 mg/mL). More importantly, the PLCO trial was carried out in the U.S. and the ERSPC in Europe. In 1993, PSA-based screening had already been incorporated as an integral part of clinical urological practice in the U.S. while PSA-based screening was unusual in Europe.[16] When entering the PLCO trial approximately 45% of the trial participants had a history of PSA screening and participants in the control arm received a mean number of 2.7 PSA tests during the study period.[17, 18] Moreover, compliance with biopsy indication in the screening arm was low, at best 40%. This reduced the power of the PLCO trial considerably, questioning the ability of the trial to answer the proposed research question.[19, 20]

The number of participants in the ERSPC trial with a history of PSA based screening is not assessed, but likely to be lower than in the PLCO trial because the trial was carried out in Europe.[20] The level of contamination in the control group was low, especially in the first few years of the study with an estimated contamination level below 15%.[16] In addition, the biopsy procedure that was part of the study led to a high biopsy compliance rate of nearly 86%.[13] Looking at the Rotterdam section of the ERSPC trial, the level of PSA contamination and effective PSA contamination, defined as when

opportunistic PSA test results were ≥ 3 ng/ml and followed by biopsy, was 28% and 8% respectively. The power calculation used for the ERSPC trial sample size calculation assumed an effective PSA contamination of 20%, implying that the ERSPC trial was sufficiently powered to answer the main research question.[21, 22]

Although insufficiently powered, the PLCO trial does provide very valuable data to improve our knowledge of the behavior of PCa.[17-20] Investigators of both the PLCO and ERSPC trials recently collaborated to determine the effect of PSA-based screening compared to no screening.[23] The investigators concluded that both trials provide compatible evidence that PSA-based screening reduces PCa-specific mortality. [23] After years of debate, the general consensus is that PSA-based screening can reduce PCa-specific mortality, but the benefits have to be weighed against the harms before population-based screening should be initiated.

The ERSPC trial reported a 20% reduction of PCa-specific mortality due to PSA-based screening.[13] Translated into clinical practice, 781 men needed to be invited for screening (NNI) and 27 men were diagnosed (NND) to prevent one PCa-specific death at a median follow up op 13 years (Table 1).[15] These results are diluted by non-compliance in the screening arm and contamination in the control arm. After correction for both non-compliance and contamination, the effect of PSA-based screening on PCa-specific mortality in the ERSPC trial increased from 20% to 31%.[24] The Rotterdam section of the ERSPC trial consisted of 34,833 men between the ages of 55 and 69. After correction for non-compliance and contamination, defined as both PSA and biopsy use in the control arm, the Rotterdam section showed a 51% risk reduction of prostate-cancer-specific mortality after a median follow up of 13 years.[25] The above-mentioned NNI and NND will most likely decline further with increased follow up as reported by the Göteborg trial. The Göteborg randomized population-based prostate-cancer screening trial forms part of the ERSPC trial. It was initiated independently to assess the effect of biannual PSA-based screening versus no screening. 20,000 men were included and randomized in 1994.[26] Results showed a NNI of 231 and a NND of 10 to prevent one PCa-specific death after a follow-up of 18 years.[27]

Table 1 Prostate cancer screening trials and their effect.

RCT	Total participants	Absolute effect	NNI	NND
ERSPC	162,243	1.28 less PCa deaths per 1000 men invited (FU 13 ys)	781	27
PLCO	76,693	No reduction in PCa deaths, relative risk in favor of controle arm, 1.09 (0.87 to 1.36)		
Göteborg	19,899	4.33 less PCa deaths per 1000 men invited (FU 18 ys)	231	10

RCT, randomized controlled trial; **ERSPC**, European Randomized Study of Screening for Prostate Cancer; **PLCO** Prostate, Lung, Colorectal and Ovary Cancer Screening Trial; **NNI**, Number Needed to Invite; **NND**, Number Needed to Diagnose; **FU,** Follow-up; **ys**, years.

2.1 Harms of PSA-based screening procedure

First, false positive PSA tests result in the performance of unnecessary prostate biopsy procedures. In the ERSPC trial 140,040 PSA test were performed and 23,574 (16.8%) PSA tests were considered positive. Most positive tests, namely 75.8%, were in fact false positive, i.e. no prostate cancer was found during prostate biopsy (Table 2).[28] Prostate biopsies are associated with pain and discomfort and can also cause hematuria, hematospermia and hematochezia, which are most often self-limiting. A more serious complication of prostate biopsies is infection, leading to sepsis, requiring broad-spectrum antibiotics and prolonged periods of hospitalization. The hospitalization rates after prostate biopsy range from 0% to 6.3%.[29] Mortality after a prostate biopsy is extremely rare, but if an infection does occur men require an immediate assessment and treatment.[29]

Secondly, PSA-based screening can lead to the diagnosis of PCa that will never become clinically significant. Approximately half of the PCa cases detected through PSA-based screening can be considered as being overdiagnosed. Detection and certainly treatment is of no benefit.[15, 30] Harms of prostate cancer treatment include urinary incontinence, erectile dysfunction and bowel symptoms.[31] Urinary incontinence and erectile dysfunction is more common in patients following radical prostatectomy, while bothersome bowel function is more often seen in patients following radiotherapy.[31] These harms have a significant effect on the quality of life and therefore diminish the number of quality-adjusted life years (QALYs) due to screening. PSA-based screening is predicted to adjust 73 life-years over the lifetime of 1000 men who underwent PCa screening. Due to overdiagnosis and overtreatment, this number is reduced to 56.[32]

Table 2 Test results of the ERSPC and Göteborg trials

RCT	Number of PSA tests	Screen test positive (%)	Biopsies	Positive biopsies (%)
ERSPC	140,040	23,574 (16.8)	20,188	4883 (24.2)
Göteborg	34,442	5365	4654	1272

RCT, randomized controlled trial; **ERSPC**, European Randomized Study of Screening for Prostate Cancer.

The screening interval was annually in the PLCO trial and every 2 to 4 years in the ERSPC trial study. The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) was initiated to assess the effectiveness of a less intensive screenings strategy. 415,357 men aged 50-69 were randomized into either an intervention or control group. The intervention group was offered a single PSA test. The control group received usual care that involved no screening. Finally, 64,436 men in the screening arm had a valid PSA test result. After a median follow-up of 10 years, there was no significant difference in PCa-related death between the intervention and the control groups. A higher incidence of PCa was reported in the intervention group. The CAP trial highlights that a single PSA screening leads to overdetection of PCa without reducing PCa-related mortality, although longer follow-up should become available to either confirm or change current conclusions.[33]

3 Active Surveillance

PCa can be categorized into low-risk, medium-risk and high-risk PCa (Table 3). PCa is categorized according to the PSA level, Gleason Score (or grade group) and clinical stage. Active surveillance is a treatment strategy that strives to avoid unnecessary side effects of PCa treatment. Patients with low-risk PCa are being monitored to identify if progression occurs and triggering a switch to active treatment. If progression does not occur, harms of treatment are prevented. For low-risk PCa, active surveillance has comparable survival rates to radiotherapy and radical prostatectomy. Therefore, active surveillance is the preferred treatment modality for low-risk PCa.[34, 35]

Hence, the most important goal of active surveillance is reducing overtreatment. Unfortunately, the effect of active surveillance is limited. The Prostate Cancer Research International Active Surveillance (PRIAS) study is a prospective observational study of low-risk PCa patients undertaking active surveillance.[36] Of the first 500 men included in the PRIAS study more than half switched to definite treatment within 2.3 years, although a significant part of men did not have any sign of progression. Therefore, screening should aim to selectively detect clinically significant prostate cancer (csPCa), defined as Gleason score $\geq$ 7, and avoid the detection of low-risk PCa.[37]

Table 3 Risk stratification for prostate cancer

Risk group	Clinical stage	PSA-value (ng/mL)	Gleason score (grade group)
Low-risk	T1-T2a	PSA<10	< 7 (1)
Intermediate-risk	T2b-T2c	PSA 10-<20	7 (2-3)
High-risk	≥T3	PSA ≥ 20	8-10 (4-5)

4 Prostate cancer screening according to the guidelines

An overview of different international guidelines and their recommendation regarding PSA-based PCa screening is presented in Table 4. The guidelines agree that PCa screening should only be offered to well-informed men with a reasonable life expectancy. The guidelines present conflicting information about the commencement of PSA screening and what the interval period should be. It is advised not to perform prostate biopsy solely based on the PSA level. Additional tests should be used to increase the specificity of PSA, in order to reduce unnecessary biopsy procedures and overdiagnosis.

Table 4 Most recent international guidelines recommendations on PCa screening

Organization	Offer prostate screening to	Starting from	Interval	Stop at
EUA	Well-informed men with a life expectancy ≥ 10 years	50 yr or 45 yr if a positive FH or AA	2-8 years depending on the initial PSA level	70 yr
AUA	Well-informed men with a life expectancy > 10-15 years	55 yr	Minimal 2 years depending on the initial PSA level	70 yr
NCCN	Well-informed men with a life expectancy ≥ 10 years	45 yr	2-4 years for men with serum PSA < 1. 1-2 years for men with serum PSA 1-3	75 yr
USPSTF	Well-informed men	55 yr		69 yr

EUA, European Association of Urology; **AUA**, American Urological Association, **NCCN**, National Comprehensive Cancer Network; **USPSTF**, U.S. Preventive Services Task Force; **AA**, African American; **FH**, family history; **yr**, years of age.

4.1 PSA level and testing interval

There is no clear cut-off value for PSA. It will always be a trade-off between sensitivity and specificity.[38] The ERSPC trial study argued that if a purely PSA based algorithm is applied, the optimal cut-off level should be 3.0 ng/ml. Increasing this cut-off level tof 4.0 ng/ml would mean a considerable increase in missed diagnoses of csPCa.[39] Lowering the cut-off would imply a

higher sensitivity but an even lower specificity, resulting in an considerable increase of potentially unnecessary biopsies.[39]

The optimal screening interval is not yet known. It has been suggested that annual screening has no advantage versus screening every other year.[19] The screening interval could also be adjusted to a baseline PSA value. Data from the Goteborg trial suggest that the interval of men with a PSA level lower than 1.5ng/ml should be no less than three years. In their cohort, 4088 men had a baseline PSA level lower than 1.5ng/ml and only three men (0.07%) would have a delayed diagnosis if the interval would have been three years instead of annual. Six men would have a delayed diagnosis if the interval would have been four years.[40]

4.2 PSA Screening Age

There is no consensus about the optimal patient age for when PSA screening should be initiated and discontinued. The randomized controlled trials outlined above mainly focus on males aged 55 to 69 years, making it hard to give an advice for males outside this age range.

PCa incidence is strongly related to age. Every 5 years, the risk of PCa increases by more than 50%.[41] Screening men below 50 years of age will most likely not be beneficial due to the very low incidence of csPCa. Men with a risk factor, such as positive family history or of African American origin, might benefit from screening at an earlier age.

The Göteborg trial initiated screening at ages 50-55, therefore provides relevant information about the effect of screening from age 50. Unfortunately, it is likely that the control arm has been exposed to PSA-screening in recent years. To overcome this problem, an age-matched cohort of men from the Swedish Malmö Preventive Medicine Project was used as the control arm. These men have similar follow up as the intervention group of the Göteborg trial and they are considered being a pre-PSA era cohort, making them suitable as a control group. In total 3479 men aged 50 to 55 were screened in the Göteborg trial. They were compared to the Malmö cohort consisting of 4060 men. At follow up of at 17 years, screening resulted in a relative reduction of 71% of PCa specific death. The incidence ratio was 2.56, meaning that patients in the screening arm were more than two-fold likely to be diagnosed with PCa. This results in a NNI of 176 and a NND of 16, which is comparable to the numbers reported in the ERSPC trial. Therefore starting screening at ages 50-54 should be considered.[42]

Most deaths from PCa are in men of higher age group.[41] The guidelines agree to restrict PSA-based screening to men with a life expectancy of 10-15 years and to stop screening at the age of 70 to 75 year. The recommendation to stop screening at the age of 70 results from the fact that screening above the age of 70 leads to unacceptable high overdiagnosis.[30] Ceasing screening at 70 years does result in missing cases of csPCa, which may become lethal. Better methods to select patients at risk of harboring csPCa are needed before screening above the age of 70 should be initiated.[41]

5 The use of additional tests

PSA tests are relatively inexpensive and easy to conduct. PSA has a high sensitivity but lacks specificity at a cut-off value of 3 ng/ml. Therefore, PSA tests can be used as a first test to select patient with an elevated risk of harboring csPCa. To improve the specificity of the PSA test, reflex tests can be used if PSA is considered to be elevated. An improved specificity reduces the number of unnecessary prostate biopsies and overdiagnosis. Risk calculators, biomarkers and magnetic resonance imaging (MRI) can be used as reflex tests.

5.1 Digital Rectal Examination

It is long known that digital rectal examination (DRE) can attribute to the specificity of a PSA test.[6] An abnormal DRE is associated with a higher risk of csPCa at all PSA levels, demonstrating its usefulness. DRE should be part of the initial risk assessment for PCa because it gives information on nodularity and prostate volume. These two outcomes can be used in risk-assessment tools.[43, 44]

5.2 Risk calculators

Many different risk calculators are developed to improve the specificity of PSA. Six risk calculators have been externally validated in more than five study populations other than the development population namely; ERSPC Rotterdam prostate cancer risk calculator (RPCRC),[45] Finne,[46] Chun,[47] Karakiewicz,[48] Prostate Cancer Prevention Trial (PCPT)[49] and ProstaClass.[50, 51] All risk calculators include PSA-level and DRE results, but differ on the other clinical information that are included. Among others, age, prostate volume, free PSA and previous negative biopsy are included in the different risk calculators. The above-mentioned risk calculators and the so-called Sunnybrook risk calculator[52] showed comparable results in a recent head-to-head comparison.[53] Four of these risk calculators have the ability to separately predict the risk of harbouring low-risk or csPCa i.e.; ERSPC RPCRC, PCPT HG, PCPT 2.0 and Sunnybrook. The ERSPC RPCRC showed to be superior in the prediction of men at risk of harbouring csPCa.[53] The ERSPC RPCRC includes PSA-level, prostate volume, DRE outcome and previous negative biopsy as input variables.[45] The ERSPC RPCRC reduces the number of biopsies and diagnosis of low-risk PCa with 32% and 25% while keeping a 95% sensitivity for detecting csPCa.[53]

5.3 The use of biomarkers

The 4Kscore combines the measurement of four kallikrein markers with clinical information to predict the outcome of prostate biopsy. Clinical information that is used includes age, DRE and history of prior biopsy.[54] The 4Kscore showed the ability to reduce 30-58% of the prostate biopsies at the cost of missing 1.3-4.7% of csPCa in men referred for prostate biopsy.[54]

The Prostate Health Index test (PHI) uses proPSA, free PSA and PSA in a mathematical formula to predict the outcome of prostate biopsy (proPSA/free PSA x √PSA). At the cost of missing 5% of the csPCa around 40% of biopsies could be avoided and there would be a reduction of 21% of low-risk PCa biopsies.[55]

In an external cohort consisting of 531 men, the 4Kscore and PHI showed similar ability

to predict detection of csPCa. Both tests could significantly reduce the number of unnecessary biopsies in comparison to PSA alone.[56]

The selectMDX is a risk model that includes two mRNA biomarkers in urine, namely HOXC6 and DLX1 next to clinical information as DRE, PSA doubling time, history of prostate biopsy, prostate volume and family history to predict the outcome of prostate biopsy. The selectMDX could reduce the number of prostate biopsies with 42% at the cost of missing 2% of the csPCa cases.[57]

PCa Antigen 3 (PCA3) is another mRNA biomarker in urine. The role of PCA3 in predicting the presence of significant PCa remains unclear. PCA3 is assumed to be most valuable after previous negative prostate biopsies or in combination with other biomarkers.[58]

The Stockholm-3 model (S3M) combines different biomarkers, genetic polymorphisms and clinical variables (among others DRE and prostate volume) to predict the outcome of prostate biopsies. In a screenings cohort consisting of 47,688 men aged 50-69 years, the S3M could reduce the number of biopsies with 32% at the same level of sensitivity of PSA alone.[59] Moreover, in people with a PSA level above 3 ng/ml, the S3M test could reduce the total number of biopsies with 32% at the cost of missing 10% of the csPCa cases.[60]

The use of biomarkers holds a promising potential to improve patients selection for prostate biopsy. However, head-to-head comparisons and external validation for the different biomarkers are scarce. Further data is needed to assess the exact role of biomarkers in clinical practice. Incorporation of biomarkers into risk calculators can further help in selecting patients for prostate biopsy. Cost-effectiveness is an important issue regarding the use of biomarkers and genomics.[61] In a recent head-to-head comparison, risk calculators incorporating prostate volume showed to be superior in identifying men at risk for csPCa.[53] Therefore, incorporation of prostate volume into risk calculators is recommended.[53, 62]

5.4 Transrectal ultrasound guided biopsies

In general, to rule out or to confirm a suspicion of PCa transrectal ultrasound guided (TRUS) biopsy is performed. Currently, a 10- to 12-core approach with emphasis on the lateral areas of the prostate is recommended by the reported clinical guidelines.[63-65] This approach diagnoses significantly more PCa than the traditional sextant biopsies.[63, 65, 66] The effect of obtaining more than 12 cores seems marginal while the complication rate increases when more biopsies are taken.[67]

csPCa can be missed during TRUS biopsies, leading to repeat biopsy sessions.[68] However, it has been shown that the chance of finding csPCa after initial negative TPUS guiding biopsies is low. Moreover, the PCa-specific mortality rate after initial negative sextant biopsies is extremely low, only a 0.5% after a 15-year follow up.[69]

5.5 MRI targeted biopsies

MRI holds a very promising potential in the

detection of csPCa. MRI can detect areas suspicious for csPCa and these areas can be targeted biopsied.[68, 70] Because MRI is relatively expensive, it is often used as a reflex test. MRI can be used in the repeat biopsy setting and in the initial biopsy setting.

MRI has a high negative predictive value in the repeat biopsy setting. Therefore, it is used to exclude PCa and prevent unnecessary biopsies.[64, 71] It is recommended to perform a prostate MRI before repeat biopsy.[71] Risk tools should be used to determine who should undergo prostate MRI.[71] The ERSPC RPCRC can avoid half of the unnecessary MRIs in the repeat biopsy setting, therefore reducing unnecessary risks and costs.[72]

The high negative predictive value of MRI in the repeat biopsy setting has led to an increased use of MRI in biopsy naïve patients. In general, the negative predictive value depends on the prevalence. The lower the prevalence the higher the negative predictive value and vice versa. In the initial biopsy setting csPCa is more prevalent than in the repeat biopsy setting, therefore the negative predictive value of MRI is less in the initial biopsy setting.[71] A systematic review reported a median MRI negative predictive value for csPCa of 80.4% and 88.2% for the initial and repeat biopsy setting respectively. So, MRI will miss 1 in 5 csPCa cases in the initial biopty setting. Therefore, MRI cannot yet replace TRUS systematic biopsies in the initial biopsy setting.[71]

Recently, 532 men aged 45-74 years of age who were referred for PCa workup underwent the S3M test, MRI, systematic biopsies and MRI-targeted biopsies if a lesion was identified. Respectively 32 and 24 of the total 194 csPCa cases would have been missed using systematic or MRI-targeted biopsy only, demonstrating that both methods miss csPCa. Performing MRI and systematic biopsies only in men with a risk of more than 10% for csPCa using the S3M test would reduce the number of MRIs and prostate biopsies with 38% at the cost of missing 16 csPCA cases.[73]

Recently, the MRI-ERSPC-RC was constructed, a risk calculator which includes MRI outcome into the ERSPC RPCRC. The MRI-ERSPC-RC showed an improved ability to predict finding csPCa during the prostate biopsy in comparison to the ERSPC RPCRC. In the validation cohort, the MRI-ERSPC-RC could avoid 25% of biopsy procedures, at the cost of missing 6% of patients with csPCa. Further external validation of the MRI-ERSPC-RC is needed.[74]

In summary, MRI is able to detect csPCa and allows for MRI-guided biopsies. MRI-guided biopsies reduce the number of low-risk PCa diagnoses in comparison to TRUS biopsies. It is recommended to perform a prostate MRI before repeat biopsy.[71] MRI-guided biopsies cannot yet replace systematic biopsies in the initial biopsy setting. Because MRI is an expensive technique, risk stratification to select patients to undergo MRI is advised.[72, 73]

The PSMA-PET scan is a relatively new imaging technique which is increasingly used in the management of PCa. The PSMA-PET scan is important in choosing

the best treatment for patients with a biochemical recurrence after curative treatment.[75] The role of the PSMA-PET scan in primary staging in patients before treatment is promising but not completely clear.[75] A recent prospective study investigated the use of the PSMA scan in the detection of PCa in the repeat biopsy setting. 45 patients suspected to harbor csPCa due to an elevated PSA and/or PHI with a negative MRI underwent a PSMA-PET scan. 25 patients had a positive lesion in their prostate and underwent software assisted fusion biopsy. Four indolent forms and seven clinically significant forms of PCa were found. Higher uptake values on PSMA-PET scan were reported in the patients with csPCa.[76] Although promising, further research is needed to determine the role of PSMA scan in the diagnosis of PCa.

6 Discussion

The ERSPC trial study provides evidence that PSA-based screening reduces PCa-specific mortality. In PCa screening solely based on PSA-level, harms tend to outweigh the benefits. Unnecessary prostate biopsies, overdiagnosis and overtreatment of low-risk PCa have to be reduced. Biomarkers, risk prediction models and prostate MRI will further improve the harm-benefit trade-off.

The knowledge of the clinical behaviour of PCa is increasing. PCa with a Gleason score 3+4 is often seen as csPCa. Gleason Score 4 is assigned to four different growth pattern in PCa. One of these growth patterns is called cribriform growth. Cribriform growth is associated with metastasis and adverse clinical outcome. In contrast, Gleason Score 3+4 without cribriform growth has the comparable clinical behaviour as Gleason Score 3+3.[77] Patients harboring PCa with Gleason Score 3+4 without cribriform growth pattern potential candidates for active surveillance.[77] Screening should aim to prevent the diagnosis of low-risk PCa. The definition of csPCa will potentially change, therefore changing the sensitivity and specificity of the described screening methods.

Opportunistic screening is current practice in the developed world. Opportunistic screening is abundantly performed in men of older age groups, resulting in unnecessary biopsies, overdiagnosis and overtreatment with no proven effect on PCa-specific mortality.[78] PSA-based screening in an organized program can be cost-effective if it is provided to a limited relatively young age group. PSA testing above the age of 63 is shown to be less cost-effective due to a high risk of overdiagnosis.[79] However, currently available cost-effectiveness data, based on a purely PSA based screening algorithm will change when the use of e.g. reflex tests are taken into account.

During a consensus meeting in 2016, over 30 PCa screening experts from Europe concluded that there is enough evidence to start pilot studies for the implementation of organized PCa screening. Biomarkers, risk calculators and MRI were acknowledged to potentially improve the harm-benefit trade-off of prostate screening. The screening program should aim to detect csPCa and screening-detected low-risk PCa should be considered to be recruited for active surveillance. A well-organized program is

preferred above the currently abundantly used opportunistic screening.[80]

6 Conclusion

The ERSPC trial study provides level 1 evidence that prostate screening reduces prostate specific-mortality. Screening solely based on PSA-level results in unnecessary prostate biopsies, overdiagnosis and overtreatment. Risk calculators, biomarkers and MRI including targeted biopsy show great potential in reducing these harms. Further implementation and development of these modalities is needed and will undoubtedly lead to a more favorable harm-benefit trade-off. A well-organized program is preferred above the currently abundantly applied opportunistic screening practices.

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