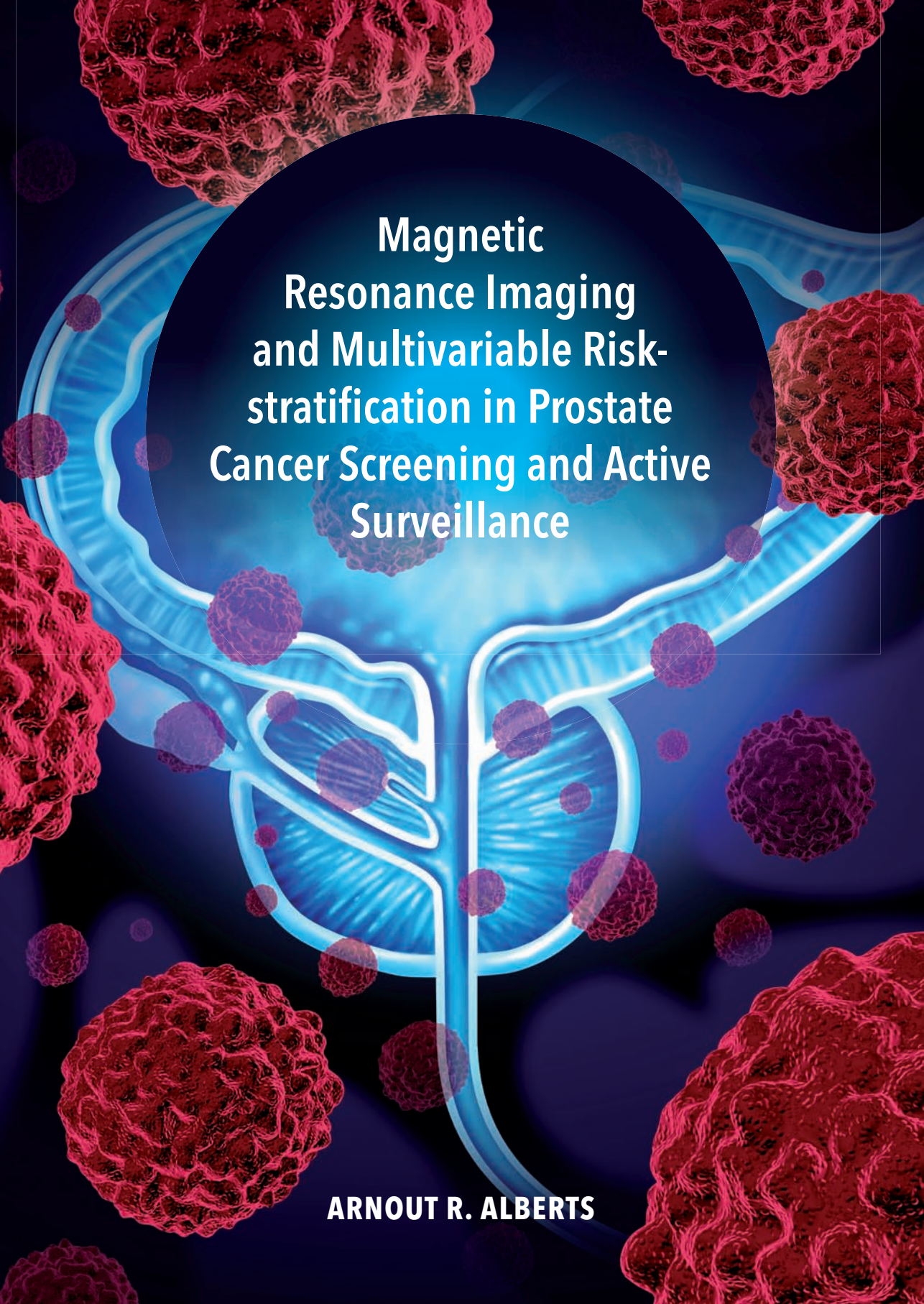

Magnetic Resonance Imaging and Multivariable Risk-stratification in Prostate Cancer Screening and Active Surveillance

ARNOUT R. ALBERTS

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Magnetic Resonance Imaging and Multivariable Risk-stratification in Prostate Cancer Screening and Active Surveillance

MRI en multivariabele risico-stratificatie bij prostaatkanker screening en een actief afwachtend beleid

Proefschrift

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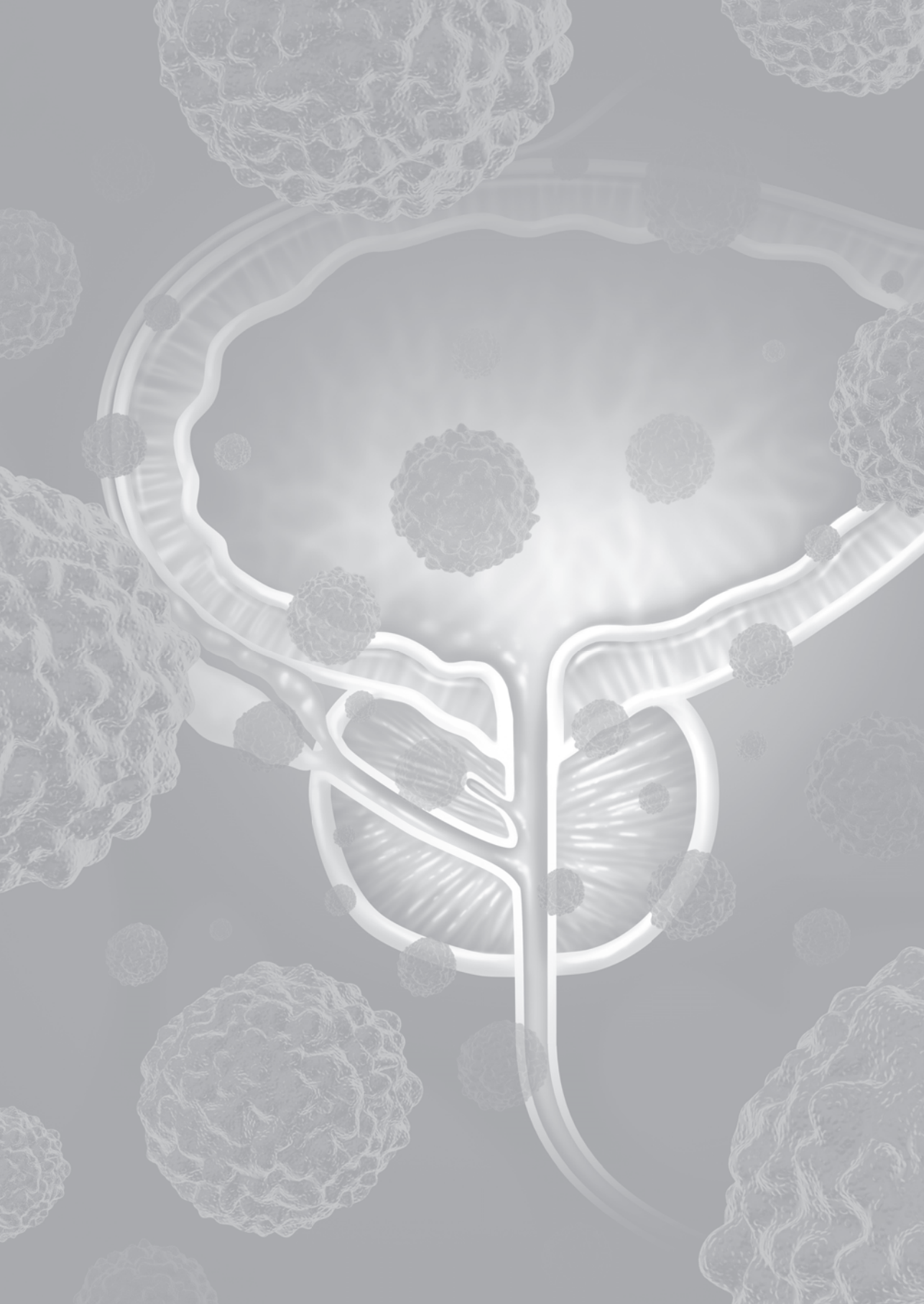


Chapter 1

General introduction

Prostate cancer

The prostate is a gland located between the male bladder and the pelvic floor, surrounding the urethra (figure 1). The Flemish anatomist Andreas Vesalius was the first to illustrate the prostate in 1538. The prostate secretes fluid that constitutes 30% of the semen volume, along with sperm cells from the testicles and fluid from the seminal vesicles located above the prostate gland. The presence of prostate cancer means that a single or multiple tumors have developed in the prostate gland due to abnormal growth and division of prostate epithelial cells, caused by the accumulation of mutations in their DNA (figure 1). The malignant cancer cells have the potential to spread to other parts of the body, usually the lymph nodes and bones at first, where they can cause metastatic tumors and eventually lead to death. Prostate cancer is the second most common cancer in men worldwide and, in general, affects men aged 50 years or older. In 2012 an estimated 1.1 million men were diagnosed with prostate cancer worldwide and 307.000 men died of their disease (1). In 2015 a total of 10.469 men were diagnosed with prostate cancer in the Netherlands and 2641 died of their disease (2).

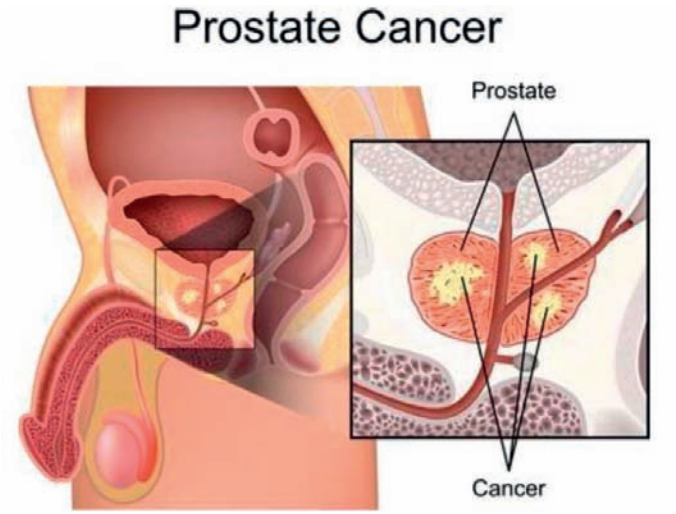


Figure 1: Male genitourinary system with cancer located in the prostate. Adapted from: http://en.israemedic.co.il/index.php/oncologia/Prostate-cancer-treatment-in-Israel

Prostate cancer detection

Prostate-specific antigen (PSA) is a protein that is produced and excreted in the bloodstream almost exclusively by prostate epithelial cells. The function of PSA is to liquefy the semen in order to improve the motility of sperm cells. In prostate cancer, the serum PSA level is often elevated due to increased PSA production by the tumor cells as well as increased leakage of PSA in the bloodstream. The elevation of the serum PSA level usually

precedes the occurrence of the first symptoms of the disease, which are often caused by metastases. Therefore, PSA can be used as a marker for early prostate cancer detection. However, PSA lacks specificity, meaning that it can also be elevated in a number of benign conditions such as benign prostatic hyperplasia (benign enlargement of the prostate) and prostatitis (inflammation of the prostate).

The digital rectal examination plays an important role in the detection of prostate cancer next to PSA. The location of the prostate just anterior of the rectum allows for palpation with the index finger through the anus. Digital rectal examination can detect nodules in the posterior and lateral parts of the prostate, suggestive of the presence of a tumor.

In case of a clinical suspicion of prostate cancer, based on an elevated PSA-level and/or an abnormal digital rectal examination, a prostate biopsy is performed. A transrectal ultrasound, which can also detect lesions suspicious for cancer, is used to guide the prostate biopsy. A total of 8 – 12 biopsy cores are taken divided over the prostate gland in a systematic fashion. These biopsy cores are then examined under the microscope by a pathologist for the presence of prostate cancer cells. Although most men experience no or only minor complaints after a prostate biopsy such as pain, temporarily hematuria (blood in the urine) and hematospermia (blood in the semen), approximately 3% of men experience a prostate infection despite antibiotic prophylaxis (3).

Prostate cancer screening

The majority of men diagnosed with prostate cancer had (locally) advanced prostate cancer before the discovery of PSA as a biomarker and half of these men died of the disease (4, 5). After PSA was approved as a biomarker in 1986, it was widely adopted in opportunistic screening (outside of an organized screening program) in the early 1990s (6, 7). This led to a dramatic increase of the prostate cancer incidence (number of new prostate cancer diagnoses per 100.000 men per year) and, together with improvements in treatment modalities, led to a decrease of the prostate cancer-related mortality (number of prostate cancer deaths per 100.000 men per year) in the United States and Europe (8, 9). The increase in prostate cancer incidence and decrease in mortality in the Netherlands since 1990 are shown in figure 2a and figure 2b, respectively.

Next to widespread opportunistic screening, the rise of PSA as a biomarker led to the initiation of several prostate cancer screening studies investigating the effect of screening on mortality (10). The most substantial evidence on the effect of screening on prostate cancer mortality comes from the European Randomized study of Screening for Prostate Cancer (ERSPC). This study, initiated in the early 1990's, randomized close to 200.000 men aged 50 – 74 years in 8 European countries (the Netherlands, Belgium, Finland, France, Italy, Spain, Sweden and Switzerland) into a screening or control arm (11). Men in the screening arm received PSA testing with an interval of 2 – 4 years, followed by transrectal ultrasound-guided systematic biopsy in case of an elevated PSA. Men in the control arm

received standard of care. At a median follow-up of 13 years, the ERSPC study showed a 21% relative reduction of the prostate cancer mortality and a 30% relative reduction of metastatic disease in the screening arm (12). For the individual, the through screening achieved mortality reduction can be up to 50% when comparing a man not screened at all with a man fully compliant to the screening protocol (13).

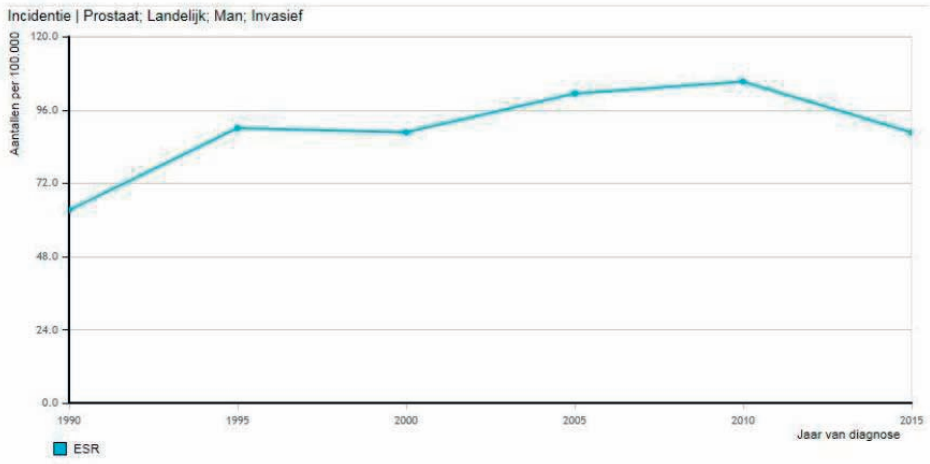


Figure 2a: Prostate cancer incidence over time in the Netherlands standardized for the age distribution in Europe (European standardized rate). Adapted from: http://www.cijfersoverkanker.nl

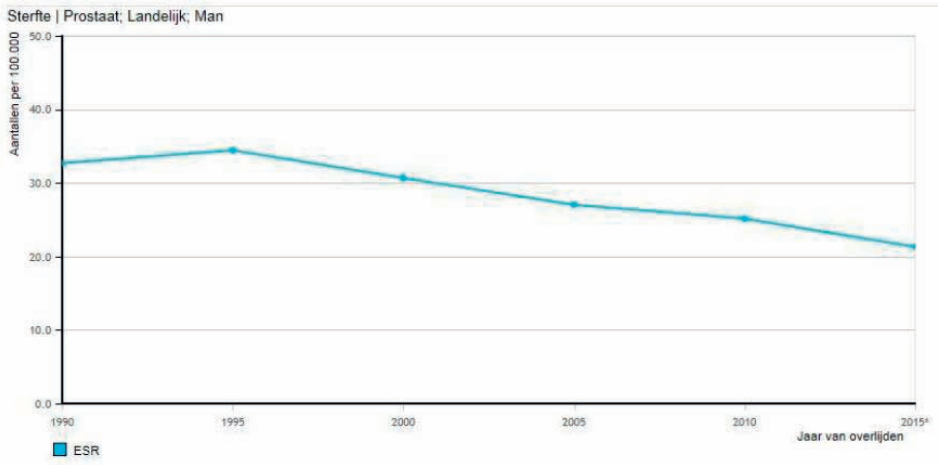


Figure 2b: Prostate cancer mortality over time in the Netherlands standardized for the age distribution in Europe (European standardized rate). Adapted from: http://www.cijfersoverkanker.nl

Unfortunately, there is also a significant downside of PSA-based prostate cancer screening. Many men receive unnecessary PSA testing and more importantly unnecessary biopsies, without experiencing benefit from screening. On top of that, the cancers detected by screening are often clinically insignificant, meaning that they have a low a potential of causing symptoms during a man's lifetime. The detection of cancers that would have never been diagnosed had it not been for screening is referred to as overdiagnosis. The fraction of screen-detected prostate cancers that are overdiagnosed is estimated to be up to 50% (14, 15). Unfortunately, these overdiagnosed cancers are often treated by surgery or radiotherapy. These invasive treatments have potential side effects, such as incontinence and impotence, which can have a significant impact on the quality of life (16, 17).

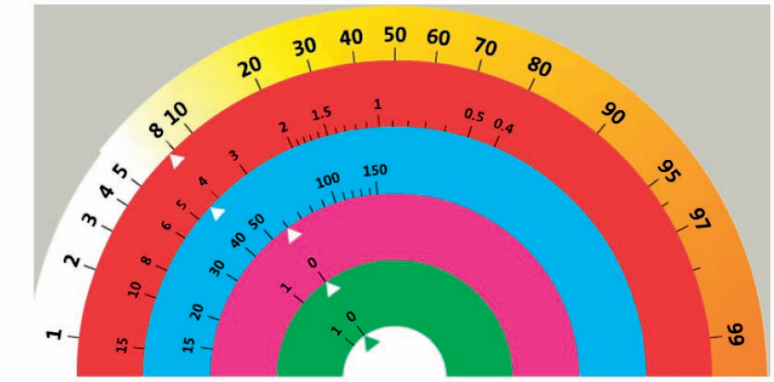
Up to now, the harms of population-based prostate cancer screening are considered to outweigh the benefits. Therefore, an organized screening program on a national level, which has already been implemented for breast cancer, cervical cancer and colon cancer in the Netherlands, has not been initiated for prostate cancer. Nevertheless, as the individual can significantly benefit from screening, the (inter)national guidelines recommend the process of shared decision making in which the patient who is asking to be screened does have the right to be screened after being well informed by his doctor on the potential harms and benefits (10). Since the beginning of opportunistic PSA-based prostate cancer screening in the early 1990's, we have been making progress on how to deal with the harms of screening. While risk-based patient selection for prostate biopsy using prediction models and/or magnetic resonance imaging is able to partly remediate the problem of unnecessary biopsies and overdiagnosis, active surveillance can counteract the problem of overtreatment.

Grading of prostate cancer

Prostate cancer is graded by the pathologist after microscopic examination of the biopsy specimens using the Gleason score (18). This prognostic grading system gives a grade of cellular differentiation ranging from 3 to 5, where grade 3 is well differentiated and grade 5 is poorly differentiated. The Gleason score is the sum of the primary (most common) Gleason grade pattern and the secondary (next most common) Gleason grade pattern in a biopsy core. Gleason score 3+3=6 prostate cancer is often classified as clinically insignificant disease, as Gleason grade 3 prostate cancer in the absence of a higher-grade tumor component (Gleason grade 4 or 5) virtually does not metastasize (19-21). Unfortunately, the absence of a higher-grade tumor component can only truly be ascertained after surgical removal of the prostate. Conversely, Gleason score ≥3+4=7 prostate cancer is often classified as significant disease due to its potential to cause metastases and prostate cancer death. Recently, it was discovered that certain growth patterns (e.g. cribriform growth) of grade 4 prostate cancer reflect more aggressive disease than others (22).

Prediction models

Prediction models are statistical formulas that on the basis of many that already have undergone the intervention can predict the outcome of one man facing the decision to undergo the intervention. Several models have been developed for the prediction of prostate cancer in a transrectal ultrasound-guided systematic biopsy, the web-based ERSPC risk calculators being the best performing models (23, 24). The ERSPC risk calculators are constructed based on data of 3624 men attending in the first screening round and 2896 men attending in the second screening round of the Rotterdam section of the ERSPC study (25). These risk calculators combine data on the PSA level, digital rectal examination, transrectal ultrasound, prostate volume and previous biopsy status of all these men to predict the risk of finding any prostate cancer and aggressive prostate cancer in the biopsy of a specific patient (figure 3). Patient-selection for prostate biopsy based on the ERSPC risk calculators has been shown to reduce the number of unnecessary biopsies by approximately 33% and to result in a more favorable significant-to-insignificant prostate cancer ratio in those men who receive a biopsy (25-30).



Uitslag
De kans op een positieve punctie **8%**

De kans op een hooggradig
of gevorderd prostaatkanker* is **1%**
**gedefinieerd als een Gleason score >= 7*
en/of een klinisch stadium > T2B

Opmerking: gebaseerd op de gegevens beschreven door Roobol et al Eur Urol 2009
stellen wij de volgende algoritme voor:

Kans op positieve biopsie	Actie
< 12.5%	Geen biopsie
12.5% - 20.0%	Overweeg biopsie, afhankelijk van comorbiditeit en indien verhoogd risico op agressieve prostaatkanker (>4%)
>= 20.0%	Prostaatbiopsie

Figure 3: Prostate cancer risk of an individual patient calculated with an ERSPC risk calculator. Adapted from: www.prostatecancer-riskcalculator.com

Multiparametric MRI

Prostate cancer is often missed by random transrectal ultrasound-guided systematic biopsy. Nowadays, multiparametric magnetic resonance imaging (MRI) is increasingly used in the early detection of prostate cancer, especially in case of a sustained suspicion of prostate cancer after a previous biopsy (31). The multiparametric MRI-scan combines the standard anatomical T2-weighted images with the functional diffusion weighted images and dynamic contrast enhanced images (32, 33). Diffusion weighted imaging reflects the diffusion of water molecules and thus the cell density in specific areas of the prostate. Naturally, a higher cell density is correlated with a higher likelihood of a tumor being present in a specific area. In dynamic contrast enhanced imaging the patterns of inflow and washout of contrast in specific prostate areas are assessed. The multiparametric MRI has a high sensitivity and negative predictive value for aggressive prostate cancer, meaning that most aggressive prostate cancers are detected by MRI and that aggressive cancer is unlikely to be present if the MRI does not show a cancer-suspicious area (34-36). Individual lesions suspicious for cancer on MRI are graded according to the standardized Prostate Imaging: Reporting and Data System (PI-RADS) score (32, 33). Suspicious lesions can be targeted during biopsy in three ways: I) with the patient positioned in the MRI-scanner (In-bore targeted biopsy), II) after fusion of the MR images with the transrectal ultrasound visually (cognitive targeted biopsy) or III) software assisted (MRI-transrectal ultrasound fusion targeted biopsy). MRI-targeted biopsy tends to detect more aggressive cancers and less non-aggressive cancers than transrectal ultrasound-guided systematic biopsy (37, 38). Besides the additional costs, the current lack of widespread expertise of radiologists is a drawback of multiparametric prostate MRI.

Active Surveillance

Traditionally, patients with localized prostate cancer (tumor confined to the prostate) were actively treated with curative intent. Radiation therapy and surgery (radical prostatectomy) can have a severe impact on urinary, bowel and sexual function and thus the patient quality of life (17). With the understanding that a considerable proportion of screen-detected prostate cancers are overdiagnosed came a strategy to monitor these so-called clinically insignificant cancers, as opposed to overtreating them. The aim of active surveillance is to delay or even completely avoid unnecessary invasive treatment. Patients on active surveillance are in general monitored according to a strict follow-up schedule including repeated PSA measurements, digital rectal examinations and prostate biopsies. If disease reclassification (signs of higher risk disease) occurs during follow-up, men should be able to switch to active treatment without losing the window of curability. Active surveillance has been shown to be safe at long-term follow-up with a 10-year and 15-year cancer-specific survival of respectively 98% and 94% in a Canadian cohort (39). A variety of protocols and guidelines on active surveillance are currently available (40). In 2006, the Prostate cancer

Research International: Active Surveillance (PRIAS) study was initiated at the Erasmus University Medical Center in Rotterdam (41). To date, PRIAS is the largest observational active surveillance study worldwide, including over 6.500 patients in over 20 countries. As in the Canadian cohort, the 10-year cancer-specific survival in the PRIAS study is excellent: >99% (42). On the other hand, approximately 50% of men in the PRIAS study have disease reclassification within 5 years of follow-up, indicating that difficulties remain up to now to determine which men are suitable for active surveillance (42).

Objectives of this thesis

The first objective is to determine how a reduction of the harms of prostate cancer screening (i.e. unnecessary biopsies and overdiagnosis of clinically insignificant cancer) can be established without affecting the benefit (i.e. reduction of metastatic disease and prostate cancer mortality). The second objective is to investigate how current protocols on active surveillance for clinically insignificant prostate cancer can be improved.

Outline of research questions addressed in this thesis

The first part of the thesis will focus on prostate cancer screening and is divided into four chapters. These four chapters will focus on the following research questions:

Can we reduce the harms of prostate cancer screening (i.e. unnecessary biopsies and overdiagnosis) without affecting the benefit of a reduction of metastatic disease and prostate cancer mortality?

- Can we select those men who may benefit from screening and refrain from screening in those who may not benefit? (Chapter 2 and 3)
- Can we select those men who need a biopsy using currently available prediction models, thereby avoiding unnecessary biopsies and overdiagnosis? (Chapter 3, 4 and 5)
- Can magnetic resonance imaging help to improve currently available prediction models? (Chapter 3 and 5)

The second part of the thesis will focus on active surveillance and is divided into three chapters addressing the following research questions:

Can we improve current protocols on active surveillance for clinically insignificant prostate cancer?

- Can we selectively identify those men who are suitable for surveillance based on magnetic resonance imaging and the prostate cancer growth pattern? (Chapter 6 and 8)
- Do men on active surveillance comply with current strict follow-up protocols, including repeated biopsies, and if not, what are the reasons for non-compliance? (Chapter 7)
- Can we selectively identify those men who need a follow-up biopsy using magnetic resonance imaging, avoiding unnecessary biopsies in men at low risk of reclassification? (Chapter 8)

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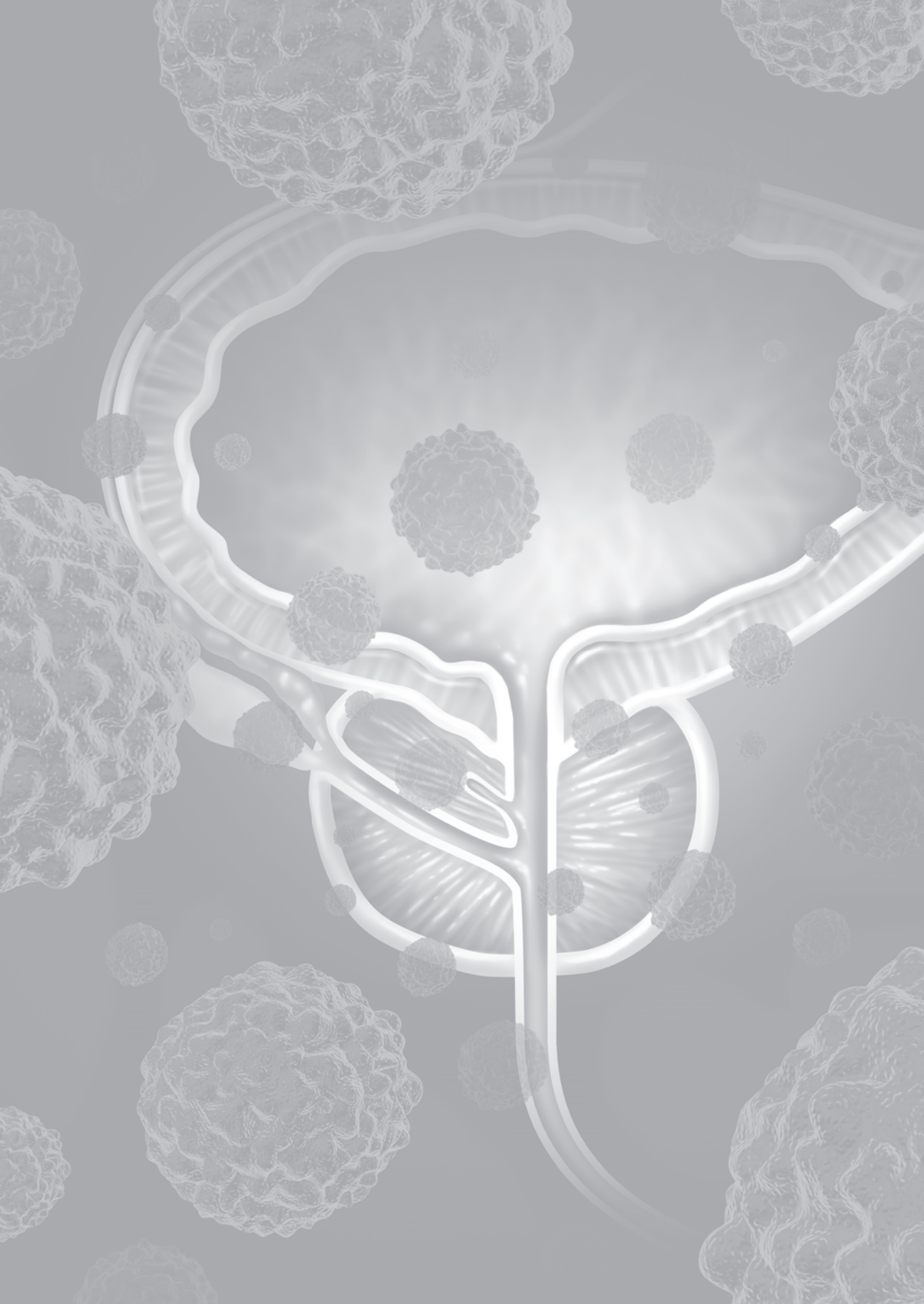
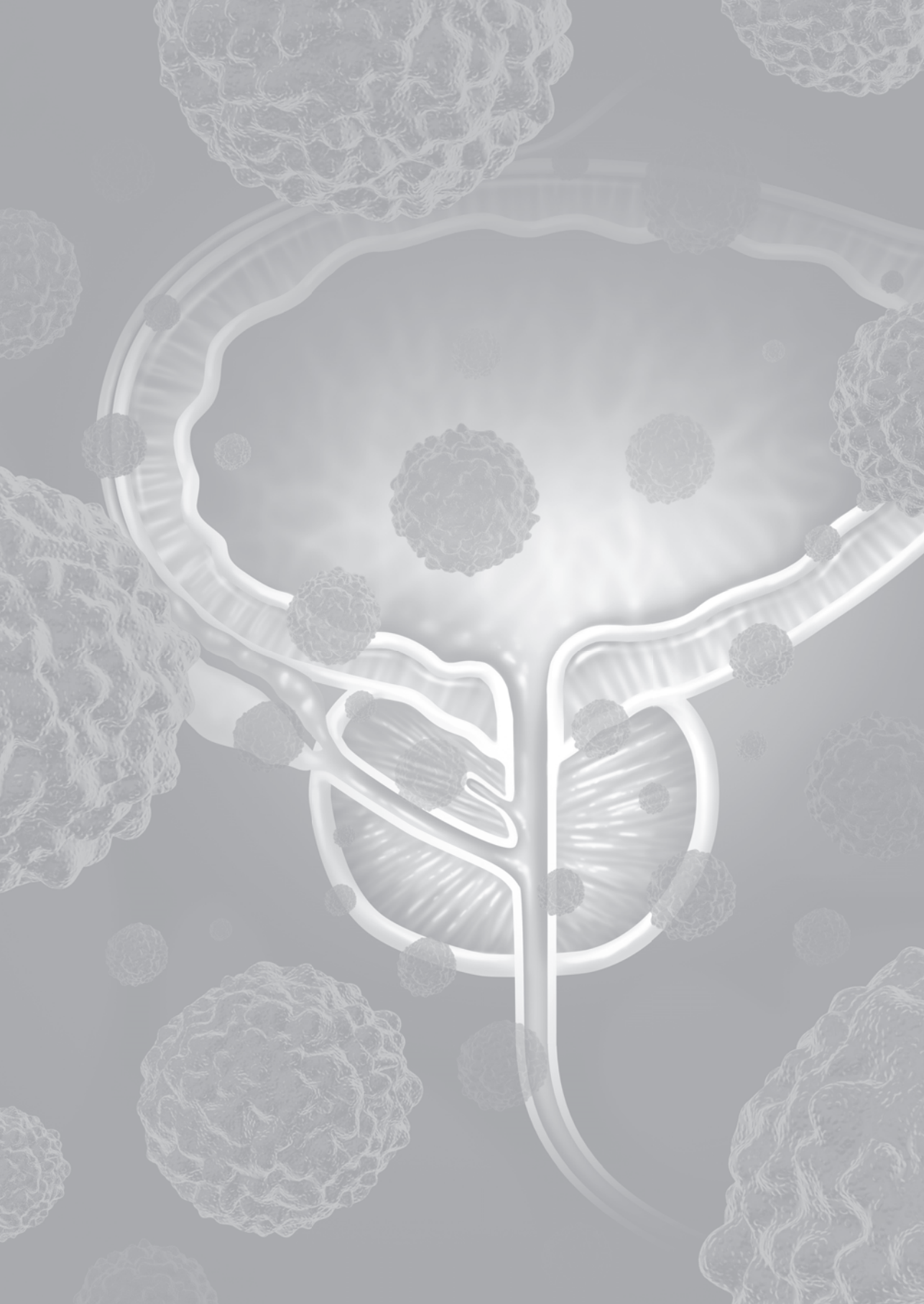


Part I

Screening



Chapter 2

Prostate-specific antigen-based prostate cancer screening: Past and future

Arnout R. Alberts, Ivo G. Schoots and Monique J. Roobol

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ABSTRACT

PSA-based prostate cancer screening remains a controversial topic. Up to now, there is worldwide consensus on the statement that the harms of population-based screening**,** mainly as a result of overdiagnosis (the detection of clinically insignificant tumors that would have never caused any symptoms)**,** outweigh the benefits. However, worldwide opportunistic screening takes place on a wide scale. The European Randomized study of Screening for Prostate Cancer (ERSPC) showed a reduction in prostate cancer mortality through PSA-based screening. These population based data need to be individualized in order to avoid screening in those who cannot benefit and start screening in those who will. For now, lacking a more optimal screening approach, screening should only be started after the process of shared decision making. The focus of future research is the reduction of unnecessary testing and overdiagnosis by further research to better biomarkers and the value of the multi-parametric MRI (mpMRI), potentially combined in already existing PSA-based multivariate risk prediction models.

Increasing incidence of prostate cancer

Prostate cancer (PCa) is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide (1). In 2008, an estimated 899.000 new prostate cancer cases and 258.000 new deaths occurred worldwide (1). About one in six men in the United States will be diagnosed with prostate cancer, while one in 36 men will die from this disease (2). In Europe during the year 2012 416.732 new PCa cases were diagnosed, and 92,247 men died from the disease (3). The prostate cancer incidence in Asian countries such as Japan is substantially lower than in Europe and the United States, mostly due to the approximately 5 fold lower exposure rate to PSA-based screening (4). As a result of the low exposure rate to screening, the rates of metastases and death from prostate cancer in Asian countries are higher than in Western countries.

Since prostate cancer is predominantly a disease of elderly men, it forms a major health problem in 'developed' countries where the life expectancy is relatively high (5). As the number of people aged over 60 years is expected to triple to 2 billion by 2050 (6), the prostate cancer incidence will inevitably increase in the future.

Prostate-specific antigen

Prostate-specific antigen (PSA) is a kallikrein-like serine protease. This enzyme is almost exclusively produced by the epithelial cells of the prostate, making it an organ-specific marker. However, PSA is not a cancer-specific marker. Benign prostate hyperplasia (BPH) and prostatitis can cause PSA elevation in the serum as well. Moreover, (clinically significant) PCa can be present in men without elevated PSA values (7, 8). In the pre PSA era, prostate cancer was mainly diagnosed by digital rectal examination (DRE). DRE has poor sensitivity, limited specificity and high inter-observer variability for the detection of prostate cancer (9-11). In 1987, PSA was introduced in the United States to evaluate treatment response after intended curative therapy. Soon after, PSA was widely used for opportunistic screening, causing a favorable stage shift at time of diagnosis and a subsequent increase of the disease incidence and a start of the decline of the mortality (12, 13). The wide adoption of PSA in opportunistic screening led to research on its potential role in reducing prostate cancer mortality, next to creating a favorable stage shift (14). Several PSA-based screening trials were conducted (table 1), often combining PSA with DRE, mainly to improve selection in men with low PSA levels (9).

Rise of the PSA-based screening trials

In 1981, a non-randomized population-based study of prostate cancer screening was started in the Gunma prefecture of Japan (15). Men aged 50-79 years were screened using DRE and prostatic acid phosphatase (PAP) as screening modalities. Between 1992 and 2000 men from Gunma were screened with PSA instead of PAP, and with additional transrectal ultrasonography (TRUS). A total of 13.021 men received a PSA test, of who 92.6%

Table 1. Overview of the PSA-based prostate cancer screening trials

Screening Trial	Country	Number of Participants	Age group (years)	Randomized	PCa mortality reduction
Gunma Study (16)	Japan	13.021	50-79	no	Unknown
Norrköping Study (18)	Sweden	9026	50-69	semi	No
Stockholm Study (19)	Sweden	1782	55-70	no	No
Quebec Study (20)	Canada	46.486	45-80	yes	Yes (*RR* = 0.38)*
Tyrol Study (22)	Austria	21.078	47-75	no	Yes (*RR* = 0.70)
PLCO study (26)	United States	76.685	55-74	yes	No
Göteborg Study (23)	Sweden	19.904	50-69	yes	Yes (*RR* = 0.56)
ERSPC (29)	8 European countries	162.243	55-69	yes	Yes (*RR* = 0.79)

**RR* = 1.09 after analysis on an intention-to-treat basis

had an initial PSA level of 4.0 ng/mL or less. Prostate cancer detection rates were 0.18%, 1.0% and 3.6% at a PSA level of < 1.0 ng/ml, 1.0-1.9 ng/ml and 2.0-4.0 ng/ml respectively (16). Two early PSA-based screening trials were conducted in Sweden. The first study was initiated in Norrköping in 1987, where every sixth man (n=1494) aged 50-69 years was invited for screening with DRE and later on PSA every 3 years (17). The 7532 uninvited men acted as the control arm of the study. After 20 years of follow-up, the rate of prostate cancer mortality did not differ significantly between men in the screening arm and those in the control arm of the Norrköping trial (18). The second Swedish study was conducted in Stockholm in 1988. A total of 1782 men aged 55-70 years were screened with PSA and TRUS, followed by prostate biopsies in the presence of a suspicious lesion or a PSA > 10 ng/ml. An unscreened group of 27.204 men served as the control arm. Again, this study did not show an effect on the prostate cancer mortality at a follow-up of 15 years (19).

In 1988, a PSA-based screening trial was conducted in Quebec, Canada. A total of 46.486 men aged 45-80 years were randomized to a screening and control arm in a 2:1 ratio. Of the 31.133 men in the screening arm, only 7348 men received actual screening. The PSA cut-off value to perform a TRUS was 3.0 ng/ml. Hypoechoic lesions were biopsied. The 11-yr follow-up results of the Quebec trial were published in 2004 (20). The study analysis was performed on a 'screening received' rather than an intention-to-treat basis, and hence reporting a present (*RR* = 0.38) instead of an absent (*RR* = 1.09) prostate cancer mortality reduction. This study was heavily criticized on its methodology.

Between October 1993 and September 1994, a non-randomized register study on PSA-based screening was conducted in the federal state of Tyrol, Austria (21). A screened population of 21.078 men aged 47-75 years was compared with the unscreened rest of Austria. Prostate biopsy criteria were based on age-specific reference PSA levels. 8% of the screened men had an elevated PSA, 48% of these men underwent biopsies. 25% of the biopsied men had prostate cancer. With follow-up until 2008, this study showed a significant reduction in prostate cancer mortality (*RR* = 0.70) in screened men from Tyrol aged > 60

years compared with the mortality rate from 1989 to 1993 (22). It was concluded that the prostate cancer mortality reduction was probably due to the combination of a favorable stage shift and active treatment.

Two largest randomized screening trials

The two largest randomized PSA-based screening trials are the prostate arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial and the ongoing European Randomized Study of Screening for Prostate Cancer (ERSPC). The Göteborg screening trial has randomized 20.000 men between biannual PSA-based screening and a control group and forms part of the ERSPC (23). Both the PLCO trial and the ERSPC reported their outcomes on prostate cancer mortality reduction after a median follow-up of 9 years (24, 25) and 12 years (26, 27), remarkably with contradictory results. The PLCO trial was conducted in 10 centers across the United States from 1993 to 2001. A total of 76.693 men aged 55-74 years were randomized to a screening or control arm in a 1:1 ratio. Screened men were offered an annual PSA test for 6 years and DRE for 4 years. At a follow-up of 7 years, the prostate cancer incidence was 116 per 10.000 person-years in the screening arm and 95 per 10.000 person-years in the control arm (25). There was no difference in prostate cancer mortality between the screening (50 deaths) and control arm (44 deaths). The outcome at a follow-up of 10 years was similar. After 13 years of follow-up, the prostate cancer incidence was 108 per 10.000 person-years in the screening arm and 97 per 10.000 person-years in the control arm (26). Again, there was no difference in prostate cancer mortality between the screening (158 deaths) and control arm (145) (*RR* = 1.09).

Due to the excessive contamination rate in the control arm (53%), confirmed by the similar incidence figures in both arms, and the poor biopsy rate (≈ 40%) of men that were positive at screening the PLCO trial lacks sufficient power to demonstrate an effect on prostate cancer mortality (28). The ERSPC was initiated in 1991 and is still ongoing. Men between 50-74 years, with a predefined core age group between 55-69 years, from eight different European countries were randomized between a screening (72.952) and control arm (89.435). Numbers reflect 7 centers since France joined too late to be part of currently reported mortality analyses. Men were screened with an interval of 2-4 years. Prostate biopsies were performed when PSA was > 3.0 ng/ml in most centers. The main outcome of the study was reported for the core age group of 55-69 years. After a median follow-up of 9 years, the cumulative prostate cancer incidence was 8.2% in the screening arm and 4.8% in the control arm (24). A significant prostate cancer mortality reduction was seen in the screening arm (214 deaths) compared with the control arm (326 deaths) yielding a *RR* of 0.80 and thus a relative risk reduction of 20% of prostate cancer death. The absolute risk reduction was 0.71 deaths per 1000 men, yielding a NNI of 1410 and NND of 48. After a median follow-up of 11 years, the relative risk reduction of prostate cancer death was 21% (p=0.001) and thus similar (27). The relative risk reduction adjusted for noncompli-

ance was 29%. The absolute risk reduction increased however and was 1.07 deaths per 1000 men, giving a NNI of 1055 and a NND of 37. The overall risk reduction of metastases, causing symptomatic disease that precedes death by 2 to 3 years, was 31% in favor of screening. After a median follow-up of 13 years, the relative prostate cancer mortality reduction remained stable at 21%, with a relative risk reduction of 27% after adjustment for noncompliance (29). The absolute prostate cancer mortality reduction increased further to 1.28 deaths per 1000 men, translating into a NNI of 781 and NND of 27. These findings support the outcome of modeling studies which all predict much lower NNI (98) and NND (5) when looking at the effect of PSA-based screening over a life time (30, 31). Sub analysis of the Rotterdam section of the ERSPC showed a relative prostate cancer mortality reduction of no less than 51% after adjustment for non-participation and PSA contamination (32). This indirectly shows that the prostate cancer mortality reduction by population-based screening could be substantially greater in Asian countries, with a low exposure rate to opportunistic screening, compared to Western countries. The two largest prostate cancer screening trials are different in design and conduct. The ERSPC shows an effect on the prostate cancer mortality of systematic, strictly protocol, PSA-based screening as compared to little opportunistic screening. The PLCO did or could not show this effect on prostate cancer mortality; the biopsy protocol was less strict and large scale opportunistic screening took place in the control arm. Therefor the outcomes of both trials on prostate cancer mortality cannot be compared (33, 34). During the running period of the two trials, the prostate cancer mortality declined by 42% (1991 and 2005) (35). Modeling studies estimate that 45-70% of the observed decline in prostate cancer mortality in the United States is attributed to the stage shift at disease diagnosis, while advances in the primary treatment (22-33%) and other interventions play a less important role (30, 35).

Meta-analyses on PSA-based screening

Despite the fundamental differences in performance of the ERSPC and PLCO trial, several meta-analyses have been conducted combining the main outcome (i.e. prostate cancer mortality) of both trials, along with the outcome of the smaller PSA-based screening trials (36-38). Djulbegovic et al. conducted a meta-analysis of six randomized controlled trials on prostate cancer screening, involving 387.286 men (36). This study showed an increase in prostate cancer detection by screening, but no significant reduction of the prostate cancer mortality ($RR = 0.88$, $p=0.25$). Both the Cochrane meta-analyses of Ilic et al., conducted in 2011 ($RR = 0.95$, $p=0.38$) and 2013 ($RR = 1.00$, $p=0.99$), were not able to show a significant reduction of the prostate cancer mortality by PSA-based screening (37, 38). However, these meta-analyses have been heavily criticized on their limitations, making the conclusions invalid (39). Methodological shortcomings of the individual trials included in the meta-analyses were bias during and after randomization, contamination of the unscreened arm and short duration of follow-up.

Harms associated with PSA-based screening

The potential benefit of prostate cancer mortality reduction by PSA-based screening must always be weighed against the potential harms for the screened individual or population. Both in the clinical setting and within a screening trial, an elevated PSA is followed by a prostate biopsy. This technical procedure normally holds a minor risk. Hematuria lasting more than 3 days (23%) and hematospermia (50%) are very common but benign (40) . Fever developed after a prostate biopsy is relatively rare (3.5%), leading to a hospitalization-requiring sepsis in 0.5% of all biopsied men (40, 41). In as many as 75% of men the result of the (unnecessary) biopsy is benign, but even a negative biopsy result can cause an elevated level of distress (42). Taking into account the nearly 1 million prostate biopsies that are performed annually in the United States alone, these physical and psychological discomforts form one of the important drawbacks of PSA-based screening. Another very important disadvantage of prostate cancer screening is overdiagnosis and subsequent overtreatment. Based on data of the Surveillance, Epidemiology and End Results (SEER) registry, it has been estimated that prostate cancer screening in the United States results in 28% of overdiagnosed cases (30). The rate of overdiagnosis within the ERSPC trial was estimated to be approximately 50% (43, 44). In a comprehensive overview of Loeb et al. the estimated overdiagnosis by PSA-based screening ranged widely, from 1.7% to 67%, depending on the method of assessment (45). Several strategies have been contemplated to reduce the rate of overdiagnosis, like higher PSA thresholds for biopsy in older men and larger screening intervals in men with low baseline PSA values (46, 47), however a solution is currently lacking. The diagnosis of a clinically insignificant tumor often leads to an unnecessary invasive treatment like radical prostatectomy or radiotherapy with the intent to 'cure' the patient. These treatments often cause side effects, like incontinence and impotence. Hence overtreatment of insignificant prostate cancer is a serious problem with a large impact on the quality of life. The nowadays increasingly used strategy of Active Surveillance (48) with regular PSA and DRE check-ups and repeated prostate biopsies could solve part of the problem by reducing the rate of overtreatment with so far minimal risks of progression and prostate cancer death (49). Invasive treatment for potentially indolent prostate tumors is delayed or even prevented. However, the regular check-ups and repeated prostate biopsies are invasive on its own and might cause anxiety and distress. Thus, the ideal solution for the problem of overtreatment would still be to prevent overdiagnosis by the exclusive detection of clinically significant prostate cancers.

Prostate cancer screening guidelines

Mainly due to the problem of overdiagnosis, prostate cancer screening remains a highly controversial topic of an ongoing debate. The various positions on screening of associations worldwide are reflected in the number of different, often contradictory guidelines for clinical practice (Table 2) (50).

Table 2. Current guidelines on PSA-based prostate cancer screening

Guideline Group	Year	Screening Age	Screening Interval
National Comprehensive Cancer Network (60)	2014	• There should be a baseline DRE and PSA at 40y. • > 50y annual screening.	• Repeat screening at 45y if PSA is <1.0 ng/mL. • >50y annual-biannual screening.
American Urological Association (56)	2013	• <55y no routine screening if at average risk. • 55-69y if at average risk • ≥70y if life expectancy > 10-15y	• At least biannual screening • Individualized interval based on baseline PSA
European Association of Urology (52)	2013	• There should be a baseline PSA ≥40-45y.	• Individualized interval based on baseline PSA • Interval of 8y if baseline PSA <1.0 ng/mL. • Once every 2-4y if baseline PSA > 1.0ng/ml • Stop screening >75y if baseline PSA <3.0 ng/mL
American College of Physicians (57)	2013	• 40 y if at highest risk* • 45 y if at high risk** • 55-69y if life expectancy > 10-15y	• Consider intervals > 1y
US Preventive Services Task Force (55)	2012	• Screening should not be offered	_
American Society of Clinical Oncology (58)	2012	• Men with life expectancy > 10y	_
Canadian Urological Society (117)	2011	• Consider a baseline PSA between 40-49y • ≥40y if at high risk • ≥ 50y if at average risk and life expectancy ≥10y	• Consider intervals up to 4y
American Cancer Society (59)	2010	• 40 y if at highest risk* • 45 y if at high risk** • > 50 y if at average risk and a life-expectancy >10 y.	• Annual screening if PSA ≥2.5 ng/ml • Biannual screening if PSA < 2.5 ng/ml
Japanese Urological Association (61)	2010	• Recommends screening • ≥50y if at average risk • ≥40y and family history	• Once every 3y if PSA <1.0 ng/mL • Annual screening if PSA > 1.0 ng/mL.
American College of Preventive Medicine (51)	2008	• No screening at any age • Potential benefit if at high risk	_

*highest risk: several first-degree relatives diagnosed with PCa < 65 years

**high risk: African American men and/or a first-degree relative with PCa

There is more or less consensus on the statement that there is currently insufficient evidence for routine population-based PSA screening (51, 52). This was again underlined in the Melbourne Consensus Statement on the early detection of prostate cancer, formed by a multidisciplinary panel of the world's leading experts on this subject (53). However, population-based estimates of overdiagnosis, causing a negative benefit-harms ratio of population-based screening, are difficult to translate to the individual (54). Unlike the US Preventive Services Task Force, that strongly recommends against any form of prostate cancer screening (55), almost all associations recommend to individualize opportunistic screening with the process of shared decision making (52, 53, 56-60). During this process, men are well informed on the currently existing pros and cons before they make a definite decision on 'to screen or not to screen'. The recommended age group and screening interval differ between the various guidelines. There is level 1 evidence on prostate cancer mortality reduction by screening provided by the ERSPC in the core age group of 55-69 years (24, 27, 29). Therefore, this is the recommended age group for men at average risk (i.e. without a first-degree relative with PCa and not of African descent) in the American Urological Association (AUA) guideline on prostate cancer screening (56). The American Cancer Society (ACS) guideline on the other hand, recommends screening motivated men from the age of 50 years on (59). This guideline also recommends screening men above 70 years with a life expectancy of more than 10 years, since these men may benefit from screening as well. The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) recommend a baseline PSA at 40 years (52, 60), same as the Melbourne Consensus Statement (53). Several guidelines recommend to screen motivated men under the age of 50 years if there is an increased risk of prostate cancer (56, 59, 61). Recommendations on the screening interval vary from annual screening in men with a PSA of 2.5 ng/ml or above (59), to an interval of 8 years in men with a baseline PSA of less than 1.0 ng/ml (52).

New prostate cancer markers

To date, PSA has remains the single most predictive tumor marker for identifying men at increased risk of prostate cancer. However, as stated earlier, the suboptimal performance characteristics of PSA in prostate cancer detection leads to unnecessary testing, overdiagnosis and overtreatment. Numerous studies have been conducted to identify next generation prostate cancer biomarkers (-omics) in serum and urine (62), like prostate cancer antigen 3 (PCA3) and TMPRSS2-ERG.The genetic marker hypermethylated Glutathione S-transferase P1 (GSTP1) shows promise in reducing the number of unnecessary biopsies (63) and stratifying men with aggressive prostate cancer (64, 65). So far, no biomarker has the potential to replace PSA, although some can have a complementary role, modestly improving the performance of prostate cancer detection. The success of the PSA test led to studies on the performance of other kallikrein markers in prostate cancer detection.

The percentage free PSA turned out to be lower in men with prostate cancer compared with those without (66). A correlation of lower percentage free PSA with higher probability of a positive biopsy result was shown (67-70). However, the percentage free PSA was not widely implemented as a screening tool due to inconsistent performance in later studies (71, 72). The [-2] isoform of Proenzyme PSA (proPSA) is a promising biomarker in prostate cancer screening due to its correlation with prostate cancer rather than BPH and its accuracy in the detection of cancer (73, 74). The percentage [-2] proPSA particularly is a good predictor of cancer in men with a PSA of 2-10 ng/ml (75). In a small retrospective study, the AUC of percentage [-2] proPSA (0.73) was significantly greater than of total PSA (0.52) and percentage free PSA (0.53) (75). In a larger prospective study, percentage [-2] proPSA had an improved specificity of 44.9% compared with total PSA and percentage free PSA (30.8% and 34.6%, respectively) at an 80% sensitivity (76). In addition, this study showed that the percentage [-2] proPSA increases with increasing Gleason score, and is higher in aggressive cancers (76). The Beckman Coulter Prostate Health Index (PHI®) can be considered a 'marker' as well. This index is calculated by the following formula: PHI = ([-2] proPSA/freePSA) × √PSA. Both [-2] proPSA (AUC = 0.76) and PHI (AUC = 0.77) outperform total PSA and percentage free PSA in the PSA range of 2.5-10.0 ng/ml (77). More recent studies underline the superior predictive ability of PHI and percentage [-2] proPSA (78, 79), with a significant improvement of the accuracy compared with standard PSA-based screening (+11% and +10%, respectively)(78). The performance characteristics of PSA can also be improved by combining the test in a panel of four kallikrein markers (i.e. total PSA, free PSA, intact PSA, and hK2). This kallikrein panel improves the AUC of standard PSA-based screening from 0.63 to 0.78 in men with a PSA ≥ 3.0 ng/ml (80).The kallikrein panel could potentially reduce the unnecessary biopsy rates by nearly 50% (81, 82). It seems as if we are far from done with the PSA test. Part of the future of prostate cancer screening lies in improving the performance of PSA, either by using percentage [-2] proPSA/PHI or a kallikrein marker panel with hK2.

Prediction tools to improve PSA-based screening

In addition to combining PSA with other kallikrein markers, the predictive capability can be improved by combining the PSA test with other pre-biopsy variables like the DRE, TRUS and prostate volume (83). Multivariate risk stratification in prostate cancer screening can be done by using various nomograms and prediction tools (84). Two of the most frequently used prediction tools in PSA-based screening are the risk calculators based on data from the Prostate Cancer Prevention Trial (PCPT) and the Rotterdam section of the ERSPC (85, 86). Both risk calculators are specifically of aid in reducing the number of unnecessary prostate biopsies and the rate of overdiagnosis. The Rotterdam Prostate Cancer Risk Calculator (RPCRC, www.prostatecancer-riskcalculator.com) outperforms the PCPT risk calculator in external populations (accuracy of 0.71-0.80 vs. 0.57-0.74) (84). Unfortu-

nately, despite various multicenter validation studies (87-89), the usage of the RPCRC is still insufficiently integrated in daily clinical practice. Part of the future of individualized PSA-based screening lies in the broad implementation of multivariate risk stratification with (improved) prediction tools like the RPCRC.

Multi-parametric MRI of the prostate

Prostate cancer is the only solid malignancy that is often diagnosed by blind random biopsy of the organ, without visualization of the tumor. The transrectal ultrasound-guided random prostate biopsy was originally performed using the sextant method (90). Nowadays, additional biopsies cores are usually taken since an extended scheme increases the prostate cancer detection by a factor of 1.3 (91). Random prostate biopsy is poor at sampling tumors in the anterior, midline, and apex region of the prostate (92, 93), leading to the underdiagnosis of clinically significant disease. Furthermore, up to one in three low risk tumors on random biopsy are upgraded or upstaged based on the radical prostatectomy specimen (94). In contrast with transrectal ultrasound-guided random biopsy, transperineal template saturation biopsy also samples the anterior prostate. Besides achieving higher detection rates, saturation biopsy also increases the rate of insignificant disease (95). Furthermore, saturation biopsy is more invasive, expensive, time-consuming and usually requires general anesthesia. The multi-parametric MRI (mpMRI) is increasingly used in PSA-based screening and could be the solution to the underdiagnosis of clinically significant disease by random prostate biopsy. The mpMRI has a high degree of accuracy in the detection of clinically significant prostate cancer confirmed by radical prostatectomy (96). The mpMRI detects greater than 90% of significant prostate cancers (97, 98). However, the mpMRI is less reliable at detecting small tumors (<0.5cc), low-grade disease (Gleason score 6) or tumors in the transitional zone (97). In mpMRI the anatomical T2-weighted images are combined with functional parameters: dynamic contrast enhancement (DCE), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, and sometimes spectroscopy. Higher signal-to noise ratios provided by three-Tesla magnets further improve the accuracy of the mpMRI. Different scoring systems have been developed to address suspicious lesions on mpMRI. Suspicious lesions can be classified on a 3-point scale, ranging from low, moderate, to high suspicion, or on a 5-point scale (Likert or PI-RADS), ranging from 1 (no suspicion) to 5 (high suspicion) according to the likelihood of significant prostate cancer being present (99-101). The PI-RADS (Prostate Imaging – Reporting and Data System) 5-point scale was developed by the European Society of Urogenital Radiology (ESUR) (101). Suspicious lesions on mpMRI can be used as targets for biopsy. MRI-targeted biopsy can be performed in the MRI scanner (in-bore). More commonly, target biopsy is performed under ultrasonographic guidance based on cognitive registration of the mpMRI images or after the process of MRI-Ultrasonography fusion. In a recent study, the prostate cancer detection rate of cognitive target biopsy and fusion biopsy was similar, while both techniques had performed better than random biopsy

(102). Several devices for MRI-Ultrasonography fusion have been approved by the US Food and Drug Administration (FDA) (103). Although MRI-Ultrasonography fusion biopsy is an indirect form of target biopsy, the average distance between desired and actual biopsy location is minimal (1.7-2.4mm) and thus an acceptable margin of error that may be overcome by taking 2-3 cores (104, 105). Recently, a systematic review was conducted comparing the accuracy of MRI-targeted biopsy with random biopsy for the detection of clinically significant disease (106). Both target biopsy and random biopsy detected significant cancer in an equivalent number of men (43%). Missed significant cancers occurred in an equal amount of men using target biopsy and random biopsy. Since a third fewer men were biopsied using the MRI-targeted biopsy approach, target biopsy was more efficient. A mean of 3.8 target cores were taken compared with 12 random cores. MRI-targeted biopsy avoided the diagnosis of insignificant cancer in 10% of the presenting population. Thus it seems that a MRI-targeted biopsy approach could reduce the number of men biopsied, the number of biopsies per men and the number of men diagnosed with insignificant disease, while the number of men diagnosed with significant disease remains the same. However, since 12-20% of significant cancers are missed by MRI-targeted biopsy and are detected by random biopsy (107-109), the target biopsy is currently still complementary and thus not replace the random biopsy. The variability in methodology of the studies included in the systematic review limit the strength of outcomes. More recently, a systematic review and meta-analysis was conducted comparing the accuracy of MRI-targeted biopsy with random biopsy in the same man (110). Only studies with patient data comprising individual MRI-targeted biopsy and random biopsy results for the same patient were selected for this study. In men with a suspicious lesion on mpMRI, the overall prostate cancer detection rate was equal for target biopsy and random biopsy. However, in contrast with the results of the previous systematic review, target biopsy had a higher detection rate of significant prostate cancer than random biopsy (sensitivity = 0.91 vs 0.76). Again, target biopsy had a lower detection rate of insignificant disease (sensitivity = 0.44 vs 0.83). Subgroup analysis revealed an improved detection rate of significant prostate cancer by target biopsy in men with previous negative random biopsy (relative sensitivity = 1.54), rather than in biopsy-naïve men (relative sensitivity = 1.10). There was significant heterogeneity in this meta-analysis, which limits the strengths of the conclusions. Furthermore, the authors state that the comparison of target biopsy with random biopsy needs to be regarded with caution, as a consequence of underlying methodological flaws of MRI-targeted biopsy. The EAU(111) and ESUR (112) guidelines state that the mpMRI and subsequent target biopsy may be used in men with high suspicion of prostate cancer after previous negative random biopsy. The meta-analysis of Schoots et al. underlines this recommendation (110). There is currently no indication for the usage of the mpMRI in clinical practice for screening of biopsy-naive men. The true value of the mpMRI and target biopsy and their place in prostate cancer screening has not yet been established. To allow better comparison, the reporting (of histological results) of individual studies on MRI-targeted bi-

opsy should be more standardized. Recently, the STAndards of Reporting for MRI-Targeted biopsy studies (START) consensus panel recommended comparing the detection of significant disease in random cores versus target cores in the same cohort of men (113). Studies should report histologic results of random and target cores separately using Gleason score and maximum cancer core length. A table comparing detection rates of significant and insignificant disease by target and random biopsy should also be used. Target biopsy cores tend to show longer cancer core length and higher Gleason score than random biopsy cores (107) . Thus, target biopsy tends to classify the same disease more often as significant than random biopsy. Therefore, target biopsy might need a new definition of significant disease. In the future, if preliminary data are confirmed, mpMRI and MRI-targeted biopsy may provide a partial solution to the problem of overdiagnosis by PSA-based screening. Usage of the mpMRI could lead to lower rates of diagnosed insignificant cancer (106, 110). Moreover, usage of the mpMRI could avoid 13-58% of unnecessary prostate biopsies (107-109, 114). Thus, the widely validation and implementation of the mpMRI could be the most important development in PSA-based screening in the near future. Limitations for this development are not only the fact that current mpMRI data are preliminary, but also the lack of widespread expertise on the mpMRI of radiologists. The interpretation of the mpMRI requires dedicated training and has a long learning curve (115, 116).

CONCLUSION

The ERSPC has provided level 1 evidence on prostate cancer mortality reduction by systematic, strictly protocol PSA-based screening. The wide scale introduction of PSA in an opportunistic prostate cancer screening setting has caused a staged shift at diagnosis and subsequent mortality reduction. Unfortunately, the suboptimal performance characteristics of PSA lead to unnecessary testing, overdiagnosis and overtreatment. As a result, population-based prostate cancer screening purely based on the PSA test has a negative benefit-harms ratio. However, population-based estimates of effect and overdiagnosis are hard to translate to the individual. Therefore, most guidelines recommend applying the strategy of shared-decision making when it comes to opportunistic screening. In addition, a more individual approach is advised with less screening in men with low PSA values and men with a limited life expectancy. In the near future, further efforts should be made to reduce unnecessary testing and overdiagnosis. These goals could be accomplished by the wide scale validation and implementation of (new) prediction models, the mpMRI and the combination of PSA with other kallikrein markers.

Conflicts of Interest

None declared.

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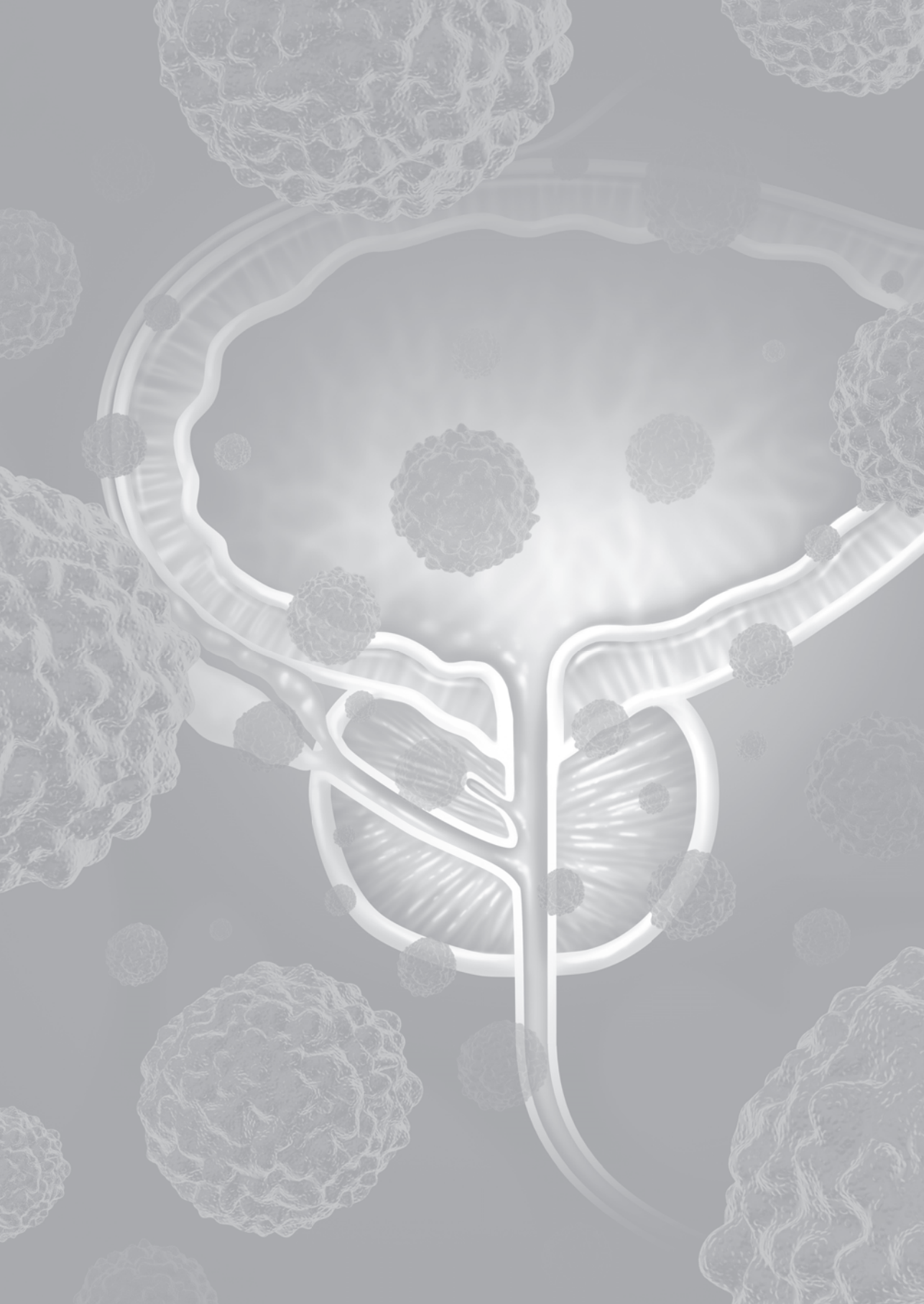

Chapter 3

Characteristics of prostate cancer found at fifth screening in the European Randomized study of Screening for Prostate Cancer Rotterdam: can we selectively detect high-grade prostate cancer with upfront multivariable risk-stratification and Magnetic Resonance Imaging?

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ABSTRACT

Background: The harm of screening (unnecessary biopsies and overdiagnosis) generally outweighs the benefit of reducing PCa mortality in men aged ≥70 years. Patient-selection for biopsy using risk-stratification and MRI may improve this benefit-to-harm ratio.

Objective: To assess the potential of a risk-based strategy including MRI to selectively identify men aged ≥70 years with high-grade PCa.

Design, setting and participants: 337 men with PSA ≥3.0 ng/ml at 5th screening (71–75 years) in the ERSPC Rotterdam were biopsied. 179 men received 6-core TRUS-Bx, while 158 men received MRI, 12-core TRUS-Bx and fusion TBx in case of PI-RADS ≥3 lesions.

Outcome measurements and statistical analysis: Primary outcome was the overall, low-grade (Gleason score 3+3) and high-grade (Gleason score ≥3+4) PCa rate. Secondary outcome was the low- and high-grade PCa rate detected by 6-core TRUS-Bx, 12-core TRUS-Bx and MRI ± TBx. Tertiary outcome was the reduction of biopsies and low-grade PCa detection by upfront risk-stratification with the Rotterdam Prostate Cancer Risk Calculator 4 (RPCRC4).

Results and limitations: 55% men were previously biopsied. The overall, low-grade and high-grade PCa rates in biopsy naïve men were 48%, 27% and 22%. In previously biopsied men these PCa rates were 25%, 20% and 5%. Sextant TRUS-Bx, 12-core TRUS-Bx and MRI ± TBx had a similar high-grade PCa rate (11%, 12% and 11%) but a significantly different low-grade PCa rate (17%, 28% and 7%). RPCRC4-based stratification combined with 12-core TRUS-Bx ± MRI-TBx would have avoided 65% of biopsies and 68% of low-grade PCa while detecting an equal percentage of high-grade PCa (83%) compared with a TRUS-Bx all men approach (79%).

Conclusions: After 4 repeated screens and ≥1 previous biopsies in half of men, still a significant proportion of men aged ≥70 years harbor high-grade PCa. Upfront risk-stratification and the combination of MRI and TRUS-Bx would have avoided two-thirds of biopsies and low-grade PCa diagnoses in our cohort, while maintaining the high-grade PCa detection of a TRUS-Bx all men approach. Further studies are needed to verify these results.

Patient summary: Prostate cancer screening reduces mortality but is accompanied by unnecessary biopsies and overdiagnosis of non-aggressive tumors, especially in repeatedly screened elderly men. To tackle these drawbacks screening should consist of an upfront risk-assessment followed by MRI and transrectal ultrasound-guided biopsy.

INTRODUCTION

The European Randomized study of Screening for Prostate Cancer (ERSPC) showed a 21% prostate cancer (PCa) mortality reduction at 13 years follow-up (1). Correction for nonattendance and contamination showed that the mortality reduction could be up to 51% for the individual (2). Unfortunately, screening using an algorithm with PSA and transrectal ultrasound-guided systematic biopsy (TRUS-Bx) is associated with unnecessary biopsies and overdiagnosis. Only ≈25% of men with PSA ≥3.0 ng/ml are diagnosed with PCa based on TRUS-Bx (3). The fraction of screen-detected PCa that are insignificant is estimated to be up to 50% (4). On the other hand, (high-grade) PCa are missed due to the use of a specific PSA cut-off for biopsy as well as undersampling by TRUS-Bx (5, 6). Finding an optimal harm-to-benefit ratio is challenging, especially men aged ≥70 years in whom the achieved mortality reduction generally does not outweigh the loss in quality-adjusted life years (7, 8). However, as the median life expectancy still increases and the incidence of poorly-differentiated PCa increases with age, some of these men may benefit from early detection (9-11). The drawbacks of screening at higher age could be tackled by improved patient-selection for biopsy using risk-stratification and MRI. Risk-stratification with the Rotterdam Prostate Cancer Risk Calculator (RPCRC) reduces the percentage of unnecessary TRUS-Bx by ≈33% (12-17). In a clinical setting, MRI and targeted biopsy (TBx) instead of TRUS-Bx detects significantly less low-grade PCa while detecting an at least equal percentage of high-grade PCa (18, 19). In the present study we investigate which men in the ERSPC Rotterdam 5th screening round (71 - 75 yrs) still harbor high-grade PCa. The low- and high-grade PCa detection rates of different biopsy strategies (6-core TRUS-Bx, 12-core TRUS-Bx and MRI ± TBx) are compared and the reduction of biopsies and overdiagnosis by upfront risk-stratification is assessed.

MATERIAL AND METHODS

Study population

All participants of the ERSPC Rotterdam 5th screening round (October 2010 – April 2016) were included. The study population and protocol of the ERSPC Rotterdam have been described previously (20). Starting in 1993, a total of 42.376 men aged 54 – 74 years were randomized to a screening or control arm. In the screening arm men were offered PSA testing with a 4-year interval until the age of 75 years. At each screening visit sextant TRUS-Bx was offered in case of PSA ≥3.0 ng/ml. Within the 5th (last) screening round an MRI side study (MEC approval number: 138.741/1994/152) was initiated in January 2013. A side study information brochure with informed consent form was sent attached to the blood draw invitation. At the blood sampling visit additional information on the side study was

provided by a research nurse, if needed, before men decided on participation. Men with PSA ≥3.0 ng/ml who had a contraindication or were not willing to undergo MRI received sextant TRUS-Bx (group 1). Side study participants with PSA ≥3.0 ng/ml received an MRI and 12-core (instead of 6-core) TRUS-Bx ± TBx (Group 2).

Multi-parametric MRI

According to the Prostate Imaging Reporting and Data System (PI-RADS) guidelines (21) the protocol consisted of T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) reconstructions, and dynamic contrast enhanced (DCE) imaging, as described previously (22). Imaging was performed on a 3-Tesla MRI-scanner (Discovery MR750, General Electric Healthcare) using a 32-channel pelvic phased-array coil. The images were independently analyzed by 3 urogenital radiologists (IS, RD, JB), each experienced in reading prostate MRI. The PI-RADS score was used to grade all individual lesions. After independent review of the images, consensus on the PI-RADS score of each identified lesion was reached after open discussion lead by one radiologist (IS). MRI's were classified as positive in the presence of ≥1 PI-RADS ≥3 lesions.

TRUS-Bx (fusion)

Men in group 1 with PSA ≥3.0 ng/ml received sextant TRUS-Bx. One additional core was taken from each hypoechoic lesion. Men in group 2 with PSA ≥3.0 ng/ml received 12-core TRUS-Bx blinded for MRI findings. One additional core was taken from each hypoechoic lesion. Subsequently, all PI-RADS ≥3 lesions were targeted with 2 cores per lesion using the UroStation™ (Koelis) for MRI-TRUS fusion. All biopsy procedures were performed by 3 experienced operators (AA, LB, F-JD). The biopsy specimens were graded by one expert uro-pathologist (GL) according to the ISUP 2014 Gleason score (GS) (23). GS 3+3, regardless of the maximum cancer core length, was classified as low-grade PCa, while GS ≥3+4 was classified as high-grade PCa.

Outcome measurements

Primary outcome was the overall, low-grade and high-grade PCa rate in biopsy naïve and previously biopsied men. Secondary outcome was the low- and high-grade PCa rate as detected by 6-core TRUS-Bx (group 1) and 12-core TRUS-Bx ± MRI-TBx (group 2). For in-depth analysis group 2 was divided into 12-core TRUS-Bx (group 2a) and MRI ± TBx (group 2b). Tertiary outcome was the reduction of biopsies and low-grade PCa diagnoses by upfront risk-stratification with the RPCRC4 (12).

Statistical analysis

The Mann-Whitney U test was used to test for significant differences in continuous patient characteristics between men who received sextant TRUS-Bx (group 1) and men in the MRI side study (group 2). The χ^2 test was used to test for significant differences in categorical patient characteristics and PCa detection rates between men in group 1 and 2. Cross tabulation was performed of 12-core TRUS-Bx (group 2a) *vs* MRI ± TBx (group 2b) outcomes in men in group 2 (supplementary tables 1 – 3).The McNemar's test was used to test for differences in PCa rates between group 2a and 2b. Targeted biopsy cores of hypoechoic lesions were analyzed as part of the TRUS-Bx. The risk of a biopsy positive for (high-grade) PCa was retrospectively assessed in all men using the RPCRC4, a prediction model based on data of 2896 men who were screened for the 2nd time 4 years after initial screening in the ERSPC Rotterdam (12). Men were stratified based on the RPCRC4 risk cut-off values to perform a biopsy: a risk of any PCa ≥20% and/or a risk of high-grade (GS ≥3+4) and/or locally advanced (T-stage ≥2C) PCa >3% (12). The potential reduction of MRI's, biopsies and overdiagnosis of low-grade PCa by upfront risk-stratification was assessed. Statistical tests were two sided with the criterion of significance set at p <0.05. Statistical analyses were performed with SPSS for Windows (Version 21.0. Armonk, NY:IBM Corp.).

RESULTS

Patient characteristics

A total of 1734 invited men attended for PSA testing (figure 1). A total of 23% (406/1734) attendees were eligible for biopsy based on PSA ≥3.0 ng/ml and 83% (337/406) of these men were biopsied, all of whom were MRI naïve. A total of 16% (65/406) men refused a biopsy based on anticipated burden or presence of comorbidities, while the biopsy failed in 2 men due to anal sphincter tension and was omitted in 2 men in whom MRI revealed a bladder tumor. A 6-core TRUS-Bx was performed in 179 men (group 1), of whom 62 men received TRUS-Bx after initiation of the side study: 5% (10/220) men biopsied after side study initiation had a contraindication for MRI (8 with magnetic prosthetic material, 1 with a pacemaker and 1 with GFR <30 mL/min) while 24% (52/220) men were not willing to undergo MRI, most frequently due to the extra (MRI-)visit additional to the biopsy visit and claustrophobia. A total of 158 men received MRI and 12-core TRUS-Bx ± TBx (group 2). The median age and PSA were 73 years (IQR 72 – 74) and 4.3 ng/ml (IQR 3.4 – 5.7) respectively (table 1). A total of 55% (184/337) men had received ≥1 TRUS-Bx at previous screening rounds. There were no significant differences in patient characteristics between men in group 1 and 2.

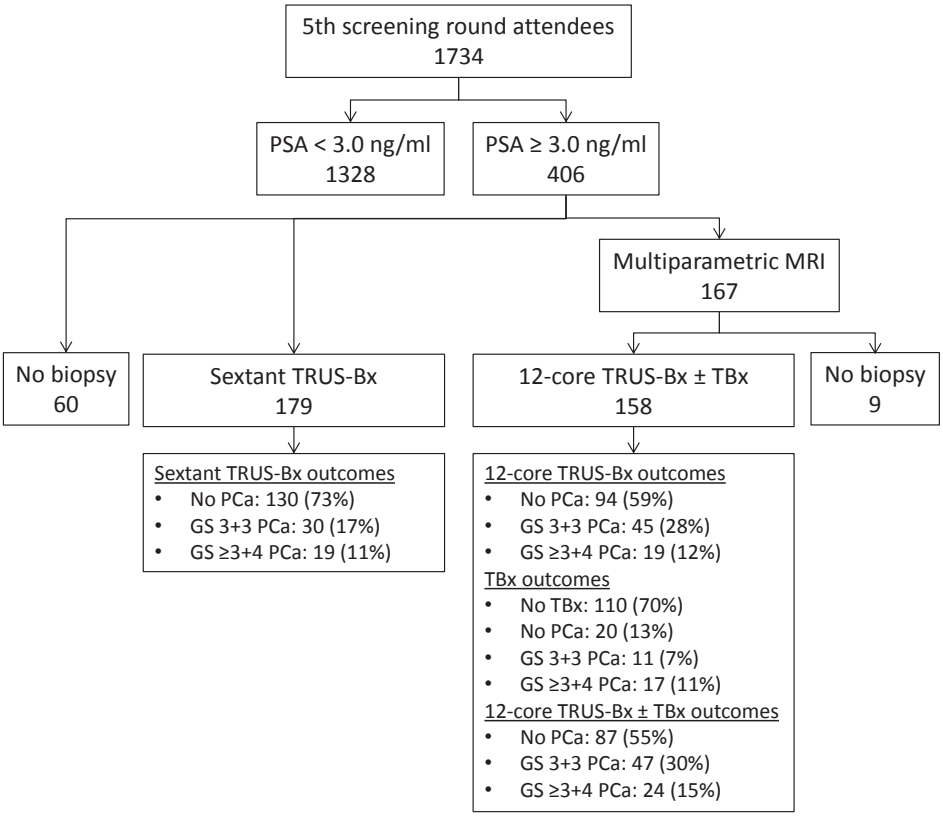

Figure 1. Flowchart of all attendees in the 5th screening round of the ERSPC Rotterdam *PSA = prostate-specific antigen, MRI = Magnetic Resonance Imaging, TRUS-Bx = transrectal ultrasound-guided systematic biopsy, TBx = targeted biopsy, PCa = prostate cancer, GS = Gleason score*

Prostate cancer detection at fifth screening (primary outcome)

A total of 36% (120/337) biopsied men were diagnosed with PCa. The low-grade PCa rate was 23% (77/337) and the high-grade PCa rate was 13% (43/337) (table 2). In biopsy naïve men the overall, low-grade and high-grade PCa rates were 48% (74/153), 27% (41/153) and 22% (33/153), respectively. The overall, low-grade and high-grade PCa rates in previously biopsied men were 25% (46/184), 20% (36/184) and 5% (10/184), respectively.

Prostate cancer detection of different biopsy strategies (secondary outcome)

The median number of biopsy cores in group 1, 2, 2a and 2b was respectively 6 (IQR 6 – 6), 12 (IQR 12 – 14), 12 (IQR 12 – 12) and 2 (IQR 2 – 3). A total of 30% (48/158) men in group 2 had a positive MRI and received MRI-TBx (table 3). The high-grade PCa rate was not significantly different between group 1 and 2 (11% *vs* 15%, $p = 0.21$). Sextant TRUS-Bx (group 1), 12-core TRUS-Bx (group 2a) and MRI ± TBx (group 2b) had a similar high-grade PCa rate of respectively 11%, 12% and 11% (table 3). The low-grade PCa rate was significantly

Table 1. Patient characteristics of all men who received a biopsy in the 5th screening round of the ERSPC Rotterdam

Patient characteristics of all biopsied men in the 5th screening round								
		Sextant TRUS-Bx (Group 1)		12-core TRUS-Bx ± MRI-TBx (Group 2)			All men	
		Median	*IQR*	*Median*	*IQR*	*p-value*	*Median*	*IQR*
Age (years)		73.2	72.2 – 74.1	73.1	72.4 – 73.8	0.82	73.1	72.3 – 74.0
PSA (ng/ml)		4.4	3.5 – 5.6	4.2	3.4 – 5.8	0.96	4.3	3.4 – 5.7
Prostate volume (ml)		48.3	35.3 – 68.4	52.9	36.8 – 70.9	0.53	50.2	35.9 – 70.1
Number of previous TRUS-Bx		1	0 – 2	1	0 – 2	0.48	1	0 – 2
		Number	*%*	*Number*	*%*	*p-value*	*Number*	*%*
T-stage DRE	T0	158	88	134	85	0.35	292	87
	T2a	15	8	9	6	0.34	24	7
	≥T2b	6	3	15	9	0.02	21	6
T-stage TRUS	T0	151	84	135	85	0.78	286	85
	T2a	25	14	20	13	0.73	45	13
	≥T2b	3	2	3	2	0.88	6	2
Previous TRUS-Bx	0	79	44	74	47	0.62	153	45
	1	48	27	35	22	0.32	83	25
	2	29	16	34	22	0.21	63	19
	3	15	8	12	8	0.79	27	8
	4	8	4	3	2	0.19	11	3
Total		179	100	158	100		337	100

TRUS = transrectal ultrasound, TRUS-Bx = transrectal ultrasound-guided systematic biopsy, MRI-TBx = MRI-targeted biopsy, IQR = Interquartile range, PSA = prostate-specific antigen, DRE = digital rectal examination

Table 2. Prostate cancer detection rates at 5th screening stratified for previous biopsy status

Prostate cancer detection rates at 5th screening in the ERSPC Rotterdam							
	Sextant TRUS-Bx (Group 1)		12-core TRUS-Bx with MRI ± TBx (Group 2)			All men (Group 1 + 2)	
	Number	*%*	*Number*	*%*	*p-value*	*Number*	*%*
Biopsy naïve men							
GS 3+3 PCa	18	23	23	31	0.25	41	27
GS ≥3+4 PCa	14	18	19	26	0.23	33	22
All	79	100	74	100		153	100
Previously biopsied men							
GS 3+3 PCa	12	12	24	29	<0.01	36	20
GS ≥3+4 PCa	5	5	5	6	0.78	10	5
All	100	100	84	100		184	100
Biopsy naïve + previously biopsied men							
GS 3+3 PCa	30	17	47	30	<0.01	77	23
GS ≥3+4 PCa	19	11	24	15	0.21	43	13
All	179	100	158	100		337	100

ERSPC = European Randomized study of Screening for Prostate Cancer, TRUS-Bx = transrectal ultrasound-guided systematic biopsy, MRI-TBx = MRI-targeted biopsy, GS = Gleason score, PCa = prostate cancer

higher in group 2 compared with group 1 (30% *vs* 17%, p <0.01). The low-grade PCa rate of 12-core TRUS-Bx was significantly higher compared with sextant TRUS-Bx (28% *vs* 17%, p = 0.01), whereas the low-grade PCa rate of MRI ± TBx was significantly lower (7%, p <0.01).

Table 3. Prostate cancer detection rates using different biopsy strategies without upfront risk-stratification

PCa detection rates using different biopsy strategies without upfront multivariable risk-stratification								
	Sextant TRUS-Bx (Group 1; *n*=179)		12-core TRUS-Bx with MRI ± TBx (Group 2; *n*=158)		12-core TRUS-Bx (Group 2a; *n*=158)		MRI ± TBx (Group 2b; *n*=158)	
	number	%	number	%	number	%	number	%
No biopsy	-	-	-	-	-	-	110	70
No PCa	130	73	87	55	94	59	20	13
GS 3+3 PCa	30	17	47	30	45	28	11	7
GS ≥ 3+4 PCa	19	11	24	15	19	12	17	11
Total	179	100	158	100	158	100	158	100

TRUS-Bx = transrectal ultrasound-guided systematic biopsy, MRI = Magnetic Resonance Imaging, TBx = targeted biopsy, PCa = prostate cancer, GS = Gleason score

TRUS-Bx versus MRI ± TBx outcomes in group 2

A total of 15% (24/158) men in group 2 were diagnosed with high-grade PCa. High-grade PCa was detected by TRUS-Bx only, MRI ± TBx only, or both in respectively 29% (7/24), 21% (5/24) and 50% (12/24) (supplementary table 1). An MRI ± TBx only and TRUS-Bx only strategy would have missed high-grade PCa in respectively 4% (7/158) and 3% (5/158) men. A total of 30% (47/158) men in group 2 were diagnosed with low-grade PCa. Low-grade PCa was detected by TRUS-Bx only, MRI ± TBx only, or both in respectively 77% (36/47), 11% (5/47) and 13% (6/47).

Avoidance of MRI's, biopsies and overdiagnosis by upfront risk-stratification (tertiary outcome)

Upfront RPCRC4-based stratification in group 1 would have avoided 67% (120/179) biopsies, while missing 33% (10/30) low-grade PCa and 26% (5/19) of high-grade PCa (table 4). RPCRC4-based stratification in group 2 would have avoided 65% (102/158) MRI's and biopsies, missing 68% (32/47) low-grade PCa and 17% (4/24) high-grade PCa. RPCRC4-based stratification in group 2a would have avoided an equal percentage of biopsies (65%) and low-grade PCa (66%), missing 29% (7/24) high-grade PCa. Although RPCRC4-based stratification in group 2b would have missed 42% (10/24) high-grade PCa, almost all low-grade PCa diagnoses (94%; 44/47) would have been avoided.

Table 4. Percentages of avoided MRI's, biopsies and low-grade PCa by multivariable risk-stratification with the Rotterdam Prostate Cancer Risk Calculator 4.

Avoided MRI's, biopsy procedures and overdiagnosis of low-grade PCa by multivariable risk-stratification								
	RPCRC4 + Sextant TRUS-Bx (Group 1; *n*=179)		RPCRC4 + 12-core TRUS-Bx with MRI ± TBx (Group 2; *n*=158)		RPCRC4 + 12-core TRUS-Bx (Group 2a; *n*=158)		RPCRC4 + MRI ± TBx (Group 2b; *n*=158)	
	number	number	number	%	number	%	number	%
MRI avoided	-	-	102/158	65	-	-	102/158	65
Biopsy procedure avoided	120/179	67	102/158	65	102/158	65	130/158	82
GS 3+3 PCa diagnosis avoided								
Biopsy strategy = ref.	10/30	33	32/47	68	29/45	64	8/11	73
12-core TRUS-Bx ± TBx = ref.	-	-	32/47	68	31/47	66	44/47	94
GS ≥3+4 PCa diagnosis missed								
Biopsy strategy = ref.	5/19	26	4/24	17	2/19	11	3/17	18
12-core TRUS-Bx ± TBx = ref.	-	-	4/24	17	7/24	29	10/24	42

RPCRC4 = Rotterdam Prostate Cancer Risk Calculator 4, TRUS-Bx = transrectal ultrasound-guided systematic biopsy, MRI = Magnetic Resonance Imaging, TBx = targeted biopsy, PCa = prostate cancer, GS = Gleason score, ref. = reference.

Biopsy complications

A total of 5.6% (19/337) men had post-biopsy fever, of whom 3.3% (11/337) were admitted. The urosepsis admission rate was 3.4% (6/179) in group 1 and 3.2% (5/158) in group 2. One man was admitted for urinary retention (group 1) and another for a transient ischemic attack one day post-biopsy (group 2). No deaths occurred.

DISCUSSION

The benefit of a mortality reduction achieved by screening must be balanced against the harms of unnecessary biopsies and overdiagnosis, particularly in elderly men (7, 8). Although the American Urological Association recommends against routine screening in men aged ≥70 years (24), older men are frequently screened in daily practice (25, 26). The European Association of Urology recommends an individualized risk-adapted strategy for early detection in men with a good performance status and life expectancy ≥10 – 15 years (27). As the median life expectancy still increases and the incidence of poorly-differentiated PCa increases with age, some men aged ≥70 years may still benefit from screening (9-11). Hence, patient-selection before biopsy is mandatory in this age group and could be achieved by the use of risk-stratification and MRI. In the present study we explored the potential such a strategy in repeatedly screened men aged 71 – 75 years in the ERSPC Rotterdam 5th screening round.

The overall PPV in the 5th screening round was 36% (120/337) and thus considerably higher than the PPV in the first (25.5%) and consecutive (≈20%) screening rounds of the ERSPC Rotterdam (3). The high PPV at 5th screening could be explained by the fact that half of men received 12-core TRUS-Bx ± MRI-TBx (PPV = 45%; 71/158) instead of 6-core TRUS-Bx (PPV = 27%; 49/179). The 27% overall PPV of 6-core TRUS-Bx is still higher than expected based on previous screening rounds, probably due to the higher age at 5th screening (9-11). The overall PPV in biopsy naïve men was ≈50% and approximately half of PCa detected in these men were high-grade. In line with findings at previous screening rounds, it is evident that biopsy naïve men after attending 4 rounds of screening with a 4-year interval (i.e. predominantly men with PSA <3.0 ng/ml for a long period) still can be diagnosed with high-grade disease (3). In addition, the PPV in previously biopsied men was still considerable (25%), most likely reflecting the known undersampling with 6-core TRUS-Bx (6). In line with previous screening rounds, 20% of PCa detected in previously biopsied men were high-grade (3). However, the fact that only 5% of previously biopsied men were actually diagnosed with high-grade PCa questions whether these men should be repeatedly screened using the PSA-based random TRUS-Bx algorithm.

Half of men in the 5th screening round received sextant TRUS-Bx and half received 12-core TRUS-Bx and MRI ± TBx, allowing a comparison of different biopsy strategies. In a clinical setting, it was shown that 6-core TRUS-Bx undersamples (high-grade) PCa as compared with 12-core TRUS-Bx (6). Furthermore, MRI ± TBx detects significantly less low-grade PCa than TRUS-Bx (18, 19). The high-grade PCa detection of MRI ± TBx is at least equal compared with TRUS-Bx in a clinical setting (18, 19). Recently, a small pilot study in the 10th screening round of the Göteborg trial investigated the value of MRI in a population-based screening setting (28). In men with PSA ≥3.0 ng/ml the low-grade PCa rates of 10-core TRUS-Bx and MRI ± TBx (cognitive) were respectively 13% (9/70) and 8% (5/65), while the high-grade PCa rates were respectively 13% (9/70) and 11% (7/65) (28). Accordingly, a similar high-grade PCa rate of sextant TRUS-Bx, 12-core TRUS-Bx and MRI ± TBx(fusion) was found in the present study (11%, 12% and 11%). Surprisingly, only the low-grade PCa rate of 12-core TRUS-Bx was higher compared with 6-core TRUS-Bx (28% *vs* 17%, p =0.01), suggesting that the use of an extended TRUS-Bx scheme would only increase the detection of low-grade disease in previously screened (and often biopsied) men. Less surprisingly, the low-grade PCa rate of MRI ± TBx was significantly lower (7%) as compared with 6-core TRUS-Bx (17%) and 12-core TRUS-Bx (28%), indicating that a screening strategy with only MRI ± TBx could significantly reduce overdiagnosis of low-grade disease. Furthermore, an MRI ± TBx strategy would cause a significant reduction of biopsies as more than two-thirds of population-based screened men with PSA ≥3.0 ng/ml have a negative MRI (28).

Another strategy to reduce unnecessary biopsies and overdiagnosis is risk-stratification before biopsy. Risk-stratification with the RPCRC is known to reduce the percentage of unnecessary TRUS-Bx by ≈33% (12-17). Furthermore, RPCRC4-based stratification could have the potential to reduce unnecessary MRI's after a previous biopsy (22). In the present study, a screening strategy with RPCRC4-based stratification and the performance of only 12-core TRUS-Bx would have avoided two-thirds of biopsies and low-grade PCa diagnoses, missing 29% (7/24) of high-grade PCa detected by the reference standard of MRI and 12-core TRUS-Bx ± TBx performed in all men. A strategy with RPCRC4-based stratification and only MRI ± TBx reduces overdiagnosis to a minimum with a low-grade PCa rate of only 2% (3/158), but misses 42% (10/24) of high-grade PCa. The optimal screening strategy seems to be the combination of RPCRC4-based stratification and the performance of both 12-core TRUS-Bx and MRI ± TBx as it avoids two-thirds of biopsies and low-grade PCa diagnoses, and misses only 17% (4/24) of high-grade PCa compared with 21% (5/24) of high-grade PCa missed by a TRUS-Bx all men approach. As the implementation of MRI in early PCa detection may be cost-effective (29, 30), this reduction in costs could certainly be achieved by the performance of additional MRI in only one-third of men (being at high-risk according to risk-assessment) while omitting a biopsy in two-thirds of men. Thus, an approach with upfront risk-stratification and the combination of MRI and TRUS-Bx has the potential to substantially reduce the drawbacks of early PCa detection in elderly men.

The MRI's in the present study were reviewed by 3 expert radiologists with years of experience with additional consensus reading. Therefore, our results may not directly translate to a setting with a single radiologist with less experience. Furthermore, MRI-TBx was performed with the MRI-TRUS fusion technique and fusion equipment is not yet widely available. However, the (high-grade) PCa detection of cognitive MRI-TBx appears to be comparable with fusion MRI-TBx and in-bore MRI-TBx (18, 19).

The present study is mainly limited by the relatively small sample size as well as the composition of our cohort. Men in the ERSPC Rotterdam 5th screening round were relatively old, were repeatedly screened and more than half of men were previously biopsied. Therefore, our results do not directly translate to a younger, screening naïve cohort. However, the nature of this cohort may help addressing how long to screen and find the so needed balance between harms and benefits in elderly men. Naturally, the presence of comorbidities (not taken into account in our study) plays a crucial role in the harm-to-benefit ratio of early detection in elderly men and thus the decision to screen the individual. However, personalized life expectancy estimation is proven to be very difficult. Currently, the median life expectancy of Dutch men aged 73 is 12.7 years according to the Dutch Central Bureau of Statistics. In our cohort, the median life expectancy might actually be higher due to selection of men with relatively few comorbidities for PSA screening and subsequent biopsy (31).

Finally, a potential limitation of the present study is the method of allocation to group 1 or 2. The decision of men on participation in the side study could potentially be influenced by others (i.e. research nurse) and introduce a selection bias. However, this decision was made before the outcome of the PSA measurement was known and patient characteristics in both groups were equal. The currently ongoing Göteborg-2 trial randomizes 40.000 men between a PCa screening and control arm, implementing (consecutive) MRI at different PSA cut-off values (28). In time, this trial will further elucidate the role of MRI in population-based screening.

CONCLUSIONS

A significant proportion of our cohort of repeatedly screened men aged ≥70 years, with often ≥1 previous biopsies, still harbored high-grade PCa. Our study results point towards a significant improvement of the harm-to-benefit ratio of early PCa detection in elderly men by multivariable risk-stratification and MRI. A screening strategy with upfront risk-stratification and the combined performance of MRI and TRUS-Bx would have avoided two-thirds of biopsies and low-grade PCa diagnoses in our cohort, while maintaining the high-grade PCa detection of a TRUS-Bx all men approach. Further studies are needed to verify these result.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Crosstab of the MRI ± TBx *vs.* 12-core TRUS-Bx outcomes in men in the ERSPC Rotterdam 5th screening round (group 2)

MRI ± TBx *vs.* 12-core TRUS-Bx outcomes in all men (group 2)							
		No MRI lesion	MRI-TBx				
			No PCa	GS 3+3 PCa	GS 3+4 PCa	GS ≥4+3 PCa	Total
TRUS-Bx	No PCa	71	16	5	**1**	**1**	94
	GS 3+3 PCa	34	2	6	**2**	**1**	45
	GS 3+4 PCa	**4**	**0**	**0**	10	0	14
	GS ≥4+3 PCa	**1**	**2**	**0**	0	2	5
	Total	110	20	11	13	4	158

Supplementary table 2. Crosstab of the MRI ± TBx *vs.* 12-core TRUS-Bx outcomes in biopsy naïve men in group 2

MRI ± TBx *vs.* 12-core TRUS-Bx outcomes in biopsy naïve men (group 2)							
		No MRI lesion	MRI-TBx				
			No PCa	GS 3+3 PCa	GS 3+4 PCa	GS ≥4+3 PCa	Total
TRUS-Bx	No PCa	25	7	1	**1**	**0**	34
	GS 3+3 PCa	17	1	4	**2**	**1**	25
	GS 3+4 PCa	**4**	**0**	**0**	8	0	12
	GS ≥4+3 PCa	**0**	**1**	**0**	0	2	3
	Total	46	9	5	11	3	74

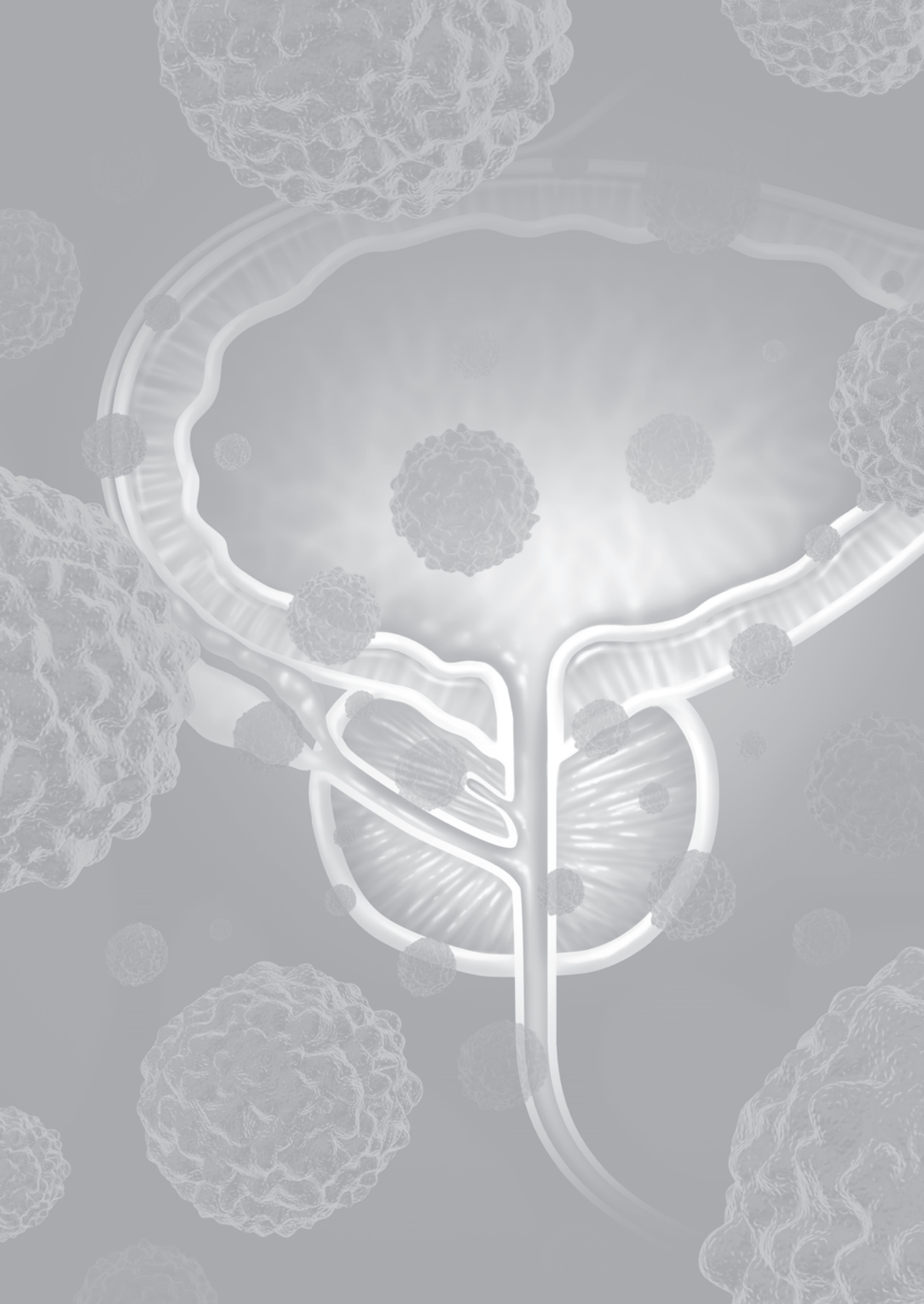
Supplementary table 3. Crosstab of the MRI ± TBx *vs.* 12-core TRUS-Bx outcomes in previously biopsied men in group 2

MRI ± TBx *vs.* 12-core TRUS-Bx outcomes in previously biopsied men (group 2)							
		No MRI lesion	MRI-TBx				
			No PCa	GS 3+3 PCa	GS 3+4 PCa	GS ≥4+3 PCa	Total
TRUS-Bx	No PCa	46	9	4	**0**	**1**	60
	GS 3+3 PCa	17	1	2	**0**	**0**	20
	GS 3+4 PCa	**0**	**0**	**0**	2	0	2
	GS ≥4+3 PCa	**1**	**1**	**0**	0	0	2
	Total	64	11	6	2	1	84

Supplementary table 4. MRI-targeted biopsy outcomes in men in Group 2 with a suspicious lesion on MRI stratified for the whole prostate PI-RADS score

MRI-TBx outcomes stratified for the PI-RADS score (Men in Group 2 with a positive MRI)								
	PI-RADS 3		PI-RADS 4		PI-RADS 5		Total	
	Number	%	Number	%	Number	%	Number	%
No PCa	13	65	6	40	1	8	20	42
GS 3+3 PCa	5	25	4	27	2	15	11	23
GS 3+4 PCa	2	10	4	27	7	54	13	27
GS ≥4+3 PCa	0	0	1	7	3	23	4	8
Total	20	100	15	100	13	100	48	100

MRI-TBx = MRI-targeted biopsy, PI-RADS = prostate imaging reporting and data system, PCa = prostate cancer, GS = Gleason score



Chapter 4

Risk-based Patient Selection for Magnetic Resonance Imaging-targeted Prostate Biopsy after Negative Transrectal Ultrasound-guided Random Biopsy Avoids Unnecessary Magnetic Resonance Imaging Scans

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ABSTRACT

***Background*:** Multiparametric MRI (mpMRI) is increasingly used in men with suspicion of prostate cancer (PCa) after negative transrectal ultrasound (TRUS)-guided random biopsy. Risk-based patient selection for mpMRI could help to avoid unnecessary mpMRIs.

Objective: To study the rate of potentially avoided mpMRIs after negative TRUS-guided random biopsy by risk-based patient selection using the Rotterdam Prostate Cancer Risk Calculator (RPCRC).

***Design, Setting and Participants*:** 122 consecutive men received a mpMRI and subsequent MRI-TRUS fusion targeted biopsy in case of suspicious lesion(s) (Prostate Imaging Reporting and Data System ≥3) after negative TRUS-guided random biopsy. Men were retrospectively stratified according to the RPCRC biopsy advice to compare targeted biopsy outcomes after risk-based patient selection with standard (Prostate-specific antigen and/or digital rectal examination-driven) patient selection.

Outcome measurements and Statistical Analysis: The rate of potentially avoided mpMRIs by RPCRC-based patient selection in relation to the rate of missed high-grade (Gleason ≥3+4) PCa. Receiver operating characteristic curve analysis was performed to determine the area under the curve of the RPCRC for (high-grade) PCa.

Results and limitations: Of the 60 men with a positive biopsy advice, 6 (10%) had low-grade PCa and 28 (47%) had high-grade PCa in targeted biopsy. Of the 62 men with a negative advice, 2 (3%) had low-grade PCa and 3 (5%) had high-grade PCa. Upfront RPCRC-based patient selection would have avoided 62 (51%) of 122 mpMRIs and 2 (25%) of 8 low-grade PCa diagnoses, missing 3 (10%) of 31 high-grade PCa. The area under the curve of the RPCRC for PCa and high-grade PCa was respectively 0.76 (95% CI 0.67 - 0.85) and 0.84 (95% CI 0.76 - 0.93).

Conclusions: Risk-based patient selection with the RPCRC can avoid half of mpMRIs after a negative prostate-specific antigen and/or digital rectal examination-driven TRUS-guided random biopsy. Further improvement in risk-based patient selection for mpMRI could be made by adjusting the RPCRC for MRI-targeted biopsy outcome prediction.

Patient summary: The suspicion of prostate cancer remains in many men after a negative ultrasound-guided prostate biopsy. These men increasingly receive an often unnecessary MRI-scan. We found that patient selection for MRI based on the Rotterdam Prostate Cancer Risk Calculator biopsy advice could avoid half of the MRIs.

INTRODUCTION

To date, following an abnormal prostate specific antigen (PSA) level and/or digital rectal examination (DRE), the next step in assessing the presence of prostate cancer (PCa) is a transrectal ultrasound(TRUS)-guided random biopsy. This combination of tests is known to result in approximately 60 – 75% benign biopsy results, questioning (1) the actual need of the biopsy, and (2) the specificity of the biopsy (1, 2). Random TRUS-guided biopsy is especially poor at sampling the anterior, midline and apex region of the prostate, leading to an underdiagnosis of PCa (3, 4). Although relatively expensive, multiparametric MRI (mpMRI) is suggested and increasingly used instead of repeated TRUS-guided biopsy in men with a sustained suspicion of PCa after negative random biopsy (5). Currently available data show that targeted biopsies of suspicious mpMRI lesions improve the detection of significant PCa, especially after previous negative random biopsy (6-8). It has already been shown that applying an upfront multivariable risk-based approach can reduce the rate of unnecessary TRUS-guided random biopsies with approximately 30% (9-12). Therefore, we question whether upfront multivariable risk stratification could also be used before the decision to perform mpMRI in the many men confronted with a negative random biopsy while clinical suspicion of PCa remains. The objective of this study is to assess the rate of potentially avoidable mpMRIs by comparing risk-based patient selection using the Rotterdam Prostate Cancer Risk calculator (RPCRC), with PSA/DRE-driven patient selection.

MATERIAL AND METHODS

Study population

From September 2013 until May 2015 a total of 122 men were referred from 12 different peripheral institutions to our tertiary referral center for a mpMRI after one or more previous negative random TRUS-guided biopsies. These men had a sustained suspicion of PCa according to the referring urologist, based on PSA (kinetics). The indication for the primary TRUS-guided biopsy in all referring centers was a PSA ≥3.0 ng/ml and/or an abnormal DRE, in accordance with the European Association of Urology guidelines (5). The biopsy scheme for the primary TRUS-guided biopsy consisted of sextant lateral biopsies with a minimum of 2 additional medial cores in all referring centers. The referring urologist ordered the performance of the mpMRI and targeted biopsy with or without additional random biopsy in our expert center. Treatment and follow-up after the mpMRI and targeted biopsy took place in the referring institutions. Data of the mpMRI and targeted biopsy were included in our prospective, institutional review board approved database. Men analyzed in this study have not been included in previous reports.

mpMRI protocol

The mpMRI protocol consisted of T2-weighted imaging, diffusion-weighted imaging with apparent diffusion coefficient reconstructions, and dynamic contrast enhanced imaging according to the European Society of Urogenital Radiology guidelines (13). MRIs were performed on a 3-T system (Discovery MR750, General Electric Healthcare) using a 32-channel pelvic phased-array coil. The images were analyzed by a single expert radiologist with more than 4 years of experience in prostate mpMRI at the start of this study. Individual lesions, as well as the whole prostate, were scored on the Prostate Imaging Reporting and Data System (PI-RADS) 5-point likelihood scale for significant PCa (13). Individual lesions with a PI-RADS score ≥3 were classified as suspicious. Suspicious lesions were delineated on the T2-weighted imaging, based on the areas with the lowest b-values on the apparent diffusion coefficient-maps.

Targeted biopsy with the MRI-US fusion technique

MRI-targeted biopsy was performed using the MRI-US fusion technique. The MRI-US fusion was performed with the UroStation (Koelis). The UroStation implements elastic registration to fuse the MRI and three-dimensional TRUS images and allows guiding and the recording of biopsy core locations on the images (14). All suspicious MRI lesions (PI-RADS ≥3) were targeted with 2 – 4 cores, depending on the lesion size. All biopsy procedures were performed by two experienced operators (urologists in training) who had managed appoximately 50 cases at the beginning of this study. In a subset of men additional random biopsies were taken on the order of the referring urologist. The random biopsy outcomes of these men are not analyzed within this study.

Pathological examination of the targeted biopsy cores

All targeted biopsy cores were examined by one expert uro-pathologist. Gleason score (GS) 3+3 PCa was defined as low-grade, while GS ≥3+4 PCa was classified as high-grade. The primary negative TRUS-guided biopsy specimens performed in the referring institutions were not centrally reviewed.

Retrospective assessment of the RPCRC biopsy advice

The RPCRC is a prediction model based on data of 3624 initially screened and 2896 repeatedly screened men in the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam (9). In the screening arm of the ERSPC Rotterdam a sextant TRUS-guided biopsy was performed in men with a PSA ≥4.0 ng/ml and/or abnormal DRE, later on in men with a PSA ≥3.0 ng/ml (15). The RPCRC uses PSA, DRE, TRUS (hypoechoic lesions) and TRUS-measured prostate volume as prebiopsy variables and takes a previously performed negative biopsy into account. The RPCRC calculates the risk of finding PCa and the risk of finding high-grade (GS ≥3+4) and/or locally advanced (T-stage ≥T2C) PCa in

random biopsy. The RPCRC is available on internet (www.prostatecancer-riskcalculator.com) and as an app for iOS/Android. The established PCa risk cut-off values to advise a TRUS-guided random biopsy are a risk of any PCa ≥20% and/or a risk of high-grade and/or locally advanced PCa >3% (9). To assess whether these established PCa risk thresholds could also be used to select men for mpMRI, the RPCRC PCa risks and biopsy advice were retrospectively determined in all men using the preMRI clinical variables.

Statistical analysis

Statistically significant differences in patient characteristics after risk-stratification were assessed using the Mann-Whitney U test for continuous data and chi-square test for categorical data. The rate of (high-grade) PCa in targeted biopsy was compared between the RPCRC-positive and RPCRC-negative group. The diagnostic accuracy of the RPCRC for any-grade and high-grade PCa in targeted biopsy was quantified using receiver operating characteristic curve analysis. Calibration of the RPCRC for any-grade and high-grade PCa in targeted biopsy was explored graphically by the construction of validation plots. Statistical tests were 2-sided with the criterion of significance set at $p < 0.05$. SPSS for Windows (Version 21.0. IBM Corp Armonk, NY, USA) was used for the statistical analysis.

RESULTS

Patient characteristics

A total of 122 men with a median age of 63 years (IQR 59 – 66) received a primary negative TRUS-guided biopsy in one of the 12 referring institutions at a median PSA level of 8.0 ng/ml (IQR 6.0 – 11.1). The median total number of negative TRUS-guided biopsies was 1 (IQR 1 – 2) using a median number of 8 cores (IQR 8 – 10). After a median time since the last biopsy of 1 year (IQR 0 – 2), the 122 men with a median age of 66 years (IQR 61 – 69) received mpMRI in our center. The sustained suspicion of PCa was mainly based on a high PSA-level: the median PSA was 13.0 ng/ml (IQR 8.8 – 18.1), as depicted in table 1. Only 27 (22%) men had a suspicious DRE and only 19 (16%) men had a suspicious TRUS. After stratification according to the RPCRC biopsy advice, men with a positive advice had significantly more often a suspicious DRE (37% *vs* 8%) and suspicious TRUS (32% *vs* 0%). Although the men with a positive advice had significantly higher median PSA-levels (14.7 *vs* 11.5 ng/ml), the most obvious difference was found in the TRUS-measured median prostate volume: men with a positive advice had significantly lower prostate volumes (39 *vs* 65 ml) resulting in a higher PSA-density (0.37 *vs* 0.19).

Table 1. Variables used for prostate cancer risk-stratification according to the Rotterdam Prostate Cancer Risk Calculator biopsy advice

Patient characteristics Characteristics							
	All men (median)	**IQR/%**	**Negative RPCRC advice (median)**	**IQR/%**	**Positive RPCRC advice (median)**	**IQR/%**	***p*-value**
PSA (ng/ml)	**13.0**	8.8 – 18.1	**11.5**	8.3 – 17.6	**14.7**	10.0 – 20.4	0.047
TRUS volume (ml)	**49**	36 – 74	**65**	50 – 90	**39**	29 – 47	<0.001
Suspicious DRE	**27**	22%	**5**	8%	**22**	37%	<0.001
Suspicious TRUS	**19**	16%	**0**	0%	**19**	32%	<0.001
Number of men	**122**		**62**		**60**		

DRE = digital rectal examination; IQR = interquartile range; PSA = prostate specific antigen; RPCRC = Rotterdam Prostate Cancer Risk Calculator; TRUS = transrectal ultrasound.

mpMRI and targeted biopsy outcomes after RPCRC-based stratification

Out of the 122 men, 54 (44%) had one or more suspicious lesions on mpMRI and 68 (56%) had a negative mpMRI. The 54 men with a suspicious mpMRI received targeted biopsy with a median number of 4 (IQR 3 – 5) cores. The targeted biopsy yielded no PCa in 15 (28%) men and low-grade and high-grade PCa in respectively 8 (15%) and 31 (57%) men. Supplementary table 1 depicts the overall PI-RADS scores of the 54 suspicious mpMRIs with the corresponding targeted biopsy GS. The corresponding GS, location and diameter of the individual mpMRI lesions are depicted in Supplementary tables 3 – 5, respectively. After RPCRC-based stratification as depicted in Figure 1 and 2, only 3 (5%) out of 62 men with a negative advice were diagnosed with high-grade PCa (2 GS 3+4 and 1 GS 4+3) while 2 (3%) had low-grade PCa. Out of the 60 men with a positive advice, 28 (47%) men had high-grade PCa (15 GS 3+4 and 13 GS ≥4+3) and 6 (10%) had low-grade PCa in targeted biopsy. Upfront RPCRC-based patient selection for mpMRI would have avoided 62 (51%) out of 122 mpMRIs, 11 (73%) out of 15 false positive mpMRIs, and 2 (25%) out of 8 low-grade PCa diagnoses, missing 3 (10%) out of 31 high-grade PCa.

Diagnostic accuracy of the RPCRC for high-grade PCa in targeted biopsy

With the established PCa risk cut-off values for a positive biopsy advice, the RPCRC had a sensitivity and specificity for high-grade PCa in targeted biopsy of 90% and 65%, respectively. The area under the curve of the continuous scores of the RPCRC for any-grade and high-grade PCa in targeted biopsy was 0.76 (95% CI 0.67 – 0.85) and 0.84 (95% CI 0.76 – 0.93), respectively.

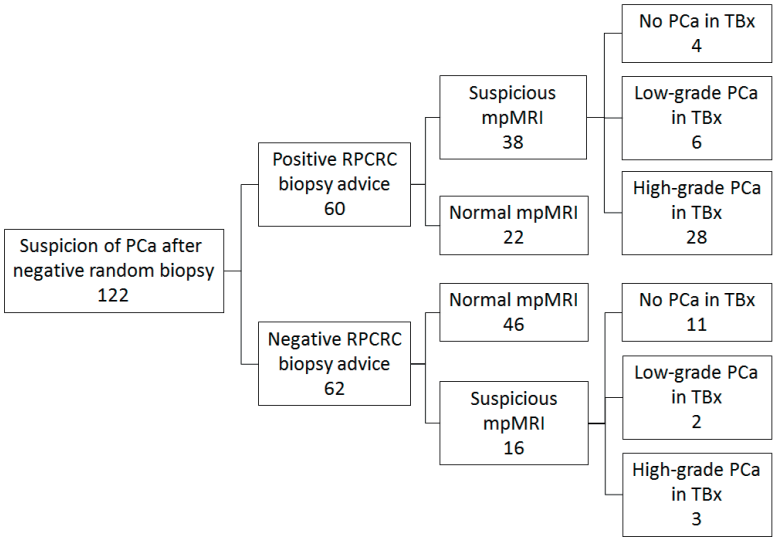

Figure 1. Multiparametric Magnetic Resonance Imaging and targeted biopsy outcomes according to the Rotterdam Prostate Cancer Risk Calculator biopsy advice. *mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer, RPCRC = Rotterdam Prostate Cancer Risk Calculator, TBx = targeted biopsy.*

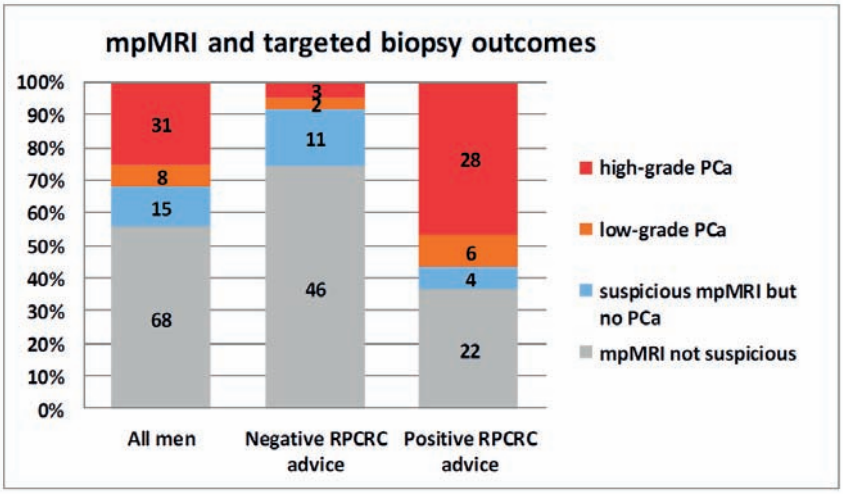

Figure 2. Multiparametric magnetic resonance imaging and targeted biopsy outcomes according to the Rotterdam Prostate Cancer Risk Calculator biopsy advice. *mpMRI = multiparametric magnetic resonance imaging, PCa = prostate cancer, RPCRC = Rotterdam Prostate Cancer Risk Calculator.*

DISCUSSION

Current clinical practice mainly entails biopsy referrals based on elevated PSA-levels and/or abnormal DRE. This approach results in many men who receive unnecessary random biopsies. Moreover, although the primary biopsy indication is often unfounded, the suspicion of PCa often remains after negative random biopsy. This results in the performance of many unnecessary expensive and burdening mpMRIs. Risk-based patient selection instead of PSA/DRE-driven selection for random biopsy reduces unnecessary biopsies and overdiagnosis (16, 17). Despite their added value, the use of prediction models before random biopsy is not well integrated in clinical practice. This could be due to lacking prebiopsy variables for risk-assessment at the time of the decision to biopsy. The decision to biopsy is often already made by the urologist based on PSA/DRE before a TRUS (including prostate volume measurement) is performed. Secondary risk-assessment before mpMRI could be more convenient than primary risk-assessment before TRUS-guided biopsy, since the prebiopsy variables are already known after the performance of the initial negative biopsy.

The RPCRC has the highest diagnostic accuracy of all available prediction models for PCa in random biopsy, with an area under the curve of 0.79 (12). RPCRC-based patient selection reduces the number of unnecessary random biopsies with approximately 30% (9, 18-20). Although the RPCRC was designed on the basis of TRUS-guided sextant biopsy data in a screening cohort, it has been validated in numerous clinical cohorts of men receiving an extended random biopsy scheme (8 – 18 cores) (10, 19, 21, 22). As expected, assessment of the calibration showed a systematic underestimation of the (high-grade) PCa risk by the RPCRC. Most likely this is due to the higher detection rate of PCa by MRI-targeted biopsy compared with TRUS-guided random biopsy after previous negative biopsy (6-8). Despite this systematic underestimation the RPCRC biopsy advice performed well in our MRI-targeted biopsy cohort. Upfront patient selection according to the RPCRC would have avoided the performance of approximately 50% of mpMRIs in our cohort, while remaining a 90% sensitivity for high-grade PCa. The number of risk-stratified men with missed high-grade PCa (3 (2%) out of 122) is acceptable. Naturally, these results should be confirmed with larger validation studies. In addition, the next logical step in order to improve the performance of the RPCRC in a targeted biopsy setting will be the addition of a calibration factor to the prediction model using mpMRI and targeted biopsy data. By enabling such an adjustment to the prediction model the number of risk-stratified men with missed high-grade PCa could possibly be reduced.

Currently available data show the improved detection of significant PCa and decreased detection of insignificant PCa by MRI-targeted biopsy compared with TRUS-guided random biopsy, especially after a previous negative biopsy (6-8). The mpMRI is increasingly used in case of (persistent) suspicion of PCa and it is imaginable that the MRI-targeted

biopsy will fully replace the TRUS-guided biopsy in the future. The increasing implementation of the mpMRI could be constrained in the future by a limited capacity, both logistically, financially, and in terms of shortage of expert radiologists. Hence risk-based patient selection for mpMRI is vital and the avoidance of approximately half of mpMRIs after previous negative biopsy could have a major clinical impact. In addition, the 73% reduction of false-positive mpMRIs and subsequent MRI-targeted biopsies by risk-stratification could have a considerable impact on patient well-being by the reduction of the (multiresistant) infection rate and patient distress.

The primary endpoint of this study was the rate of avoidable mpMRIs in relation to the rate of missed high-grade PCa by risk-stratification. To date, there is no consensus on the definition of "clinically significant" PCa in MRI-targeted biopsy (23). All GS 3+3 PCas in this study, regardless of the maximum cancer-core length, were considered "potentially indolent" since solitary GS 3+3 PCa on resection specimen is very unlikely to metastasize (24, 25) and tumor sampling by targeted biopsy is superior to random biopsy. Since upfront RPCRC-based patient selection would have avoided the diagnosis of 2 (25%) out of 8 potentially indolent tumors in our cohort, risk-based patient selection for mpMRI might have the potential to reduce overdiagnosis, besides avoiding unnecessary mpMRIs. All GS ≥3+4 PCas were classified as high-grade, in accordance with the RPCRC definition, since the presence of biopsy Gleason pattern 4 or 5 is still the main determining factor for treatment decisions. Although not all GS 3+4 PCas are aggressive and limited Gleason pattern 4 in MRI-targeted biopsy might even be considered suitable for active surveillance by some, the oncological safety is not proven and this cannot be considered standard of care yet (26).

The strength of this study lies in the fact that it represents a true clinical situation. Patients were referred from 12 different peripheral institutions to our expert center for mpMRI based on PSA and/or DRE. Since MRI-US fusion biopsy has a similar PCa detection rate as MRI-in-bore and cognitive targeted biopsy (6), our study results could be translated to all institutions with an expert radiologist performing any kind of targeted biopsies. Our study results are not limited by the learning curve phenomenon since the biopsy operators had managed a sufficient number of cases prior to the study.

A limitation of this study is the fact that the analysis was restricted to targeted biopsy outcomes. The subgroup of men who received an additional random biopsy on request of the referring urologist was small (35 of 122) and the operator was not blinded for MRI-lesions during the performance of the random biopsy. Random biopsy did not yield a single additional high-grade tumor on top of the targeted biopsy findings, underlining the limited additional value of blind sampling after previous negative biopsy (27).

Another limitation, as with the majority of studies on MRI-targeted biopsy, is the lack of a reference test. Random biopsy is not a sufficient reference test, especially after a previous negative biopsy. Transperineal template-guided biopsy as a gold standard would

have been a good reference test (28); however, this procedure would have been more appropriate in a study rather than a clinical setting. The fact that the mpMRI has a negative predictive value of 89 – 96% for high grade PCa in other expert centers reduces the importance of the lack of a reference test (28-31).

CONCLUSIONS

Multivariable risk-based patient selection with the RPCRC can avoid half of the mpMRI scans after a previous negative TRUS-guided random biopsy performed solely on the basis of an elevated PSA level and/or abnormal DRE. Further improvement in risk-based patient selection for mpMRIs could be made by enabling an adjustment to the prediction model when predicting MRI-targeted biopsy outcome.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Targeted biopsy outcomes stratified according to the overall (whole prostate) PI-RADS score.

	Men with PI-RADS 3		Men with PI-RADS 4		Men with PI-RADS 5		Total	
	Number	%	Number	%	Number	%	Number	%
No PCa	5	50	9	47	1	4	15	28
GS 3+3 PCa	0	0	4	21	4	16	8	15
GS 3+4 PCa	2	20	2	11	13	52	17	31
GS 4+3 PCa	2	20	0	0	3	12	5	9
GS ≥4+4 PCa	1	10	4	21	4	16	9	17
Total	10	100	19	100	25	100	54	100

PI-RADS = Prostate Imaging Reporting and Data System, PCa = prostate cancer, GS = Gleason Score.

Supplementary table 2. Targeted biopsy outcomes stratified according to the PI-RADS score of the individual mpMRI lesions

	PI-RADS 3 lesions		PI-RADS 4 lesions		PI-RADS 5 lesions		Total	
	Number	%	Number	%	Number	%	Number	%
No PCa	10	59	11	52	2	7	23	35
GS 3+3 PCa	1	6	4	19	4	14	9	14
GS 3+4 PCa	2	12	3	14	13	46	18	27
GS 4+3 PCa	2	12	0	0	3	11	5	8
GS ≥4+4 PCa	2	12	3	14	6	21	11	17
Total	17	100	21	100	28	100	66	100

PI-RADS = Prostate Imaging Reporting and Data System, PCa = prostate cancer, GS = Gleason Score

Supplementary table 3. Targeted biopsy outcomes stratified according to the location of the individual mpMRI lesions in the prostate

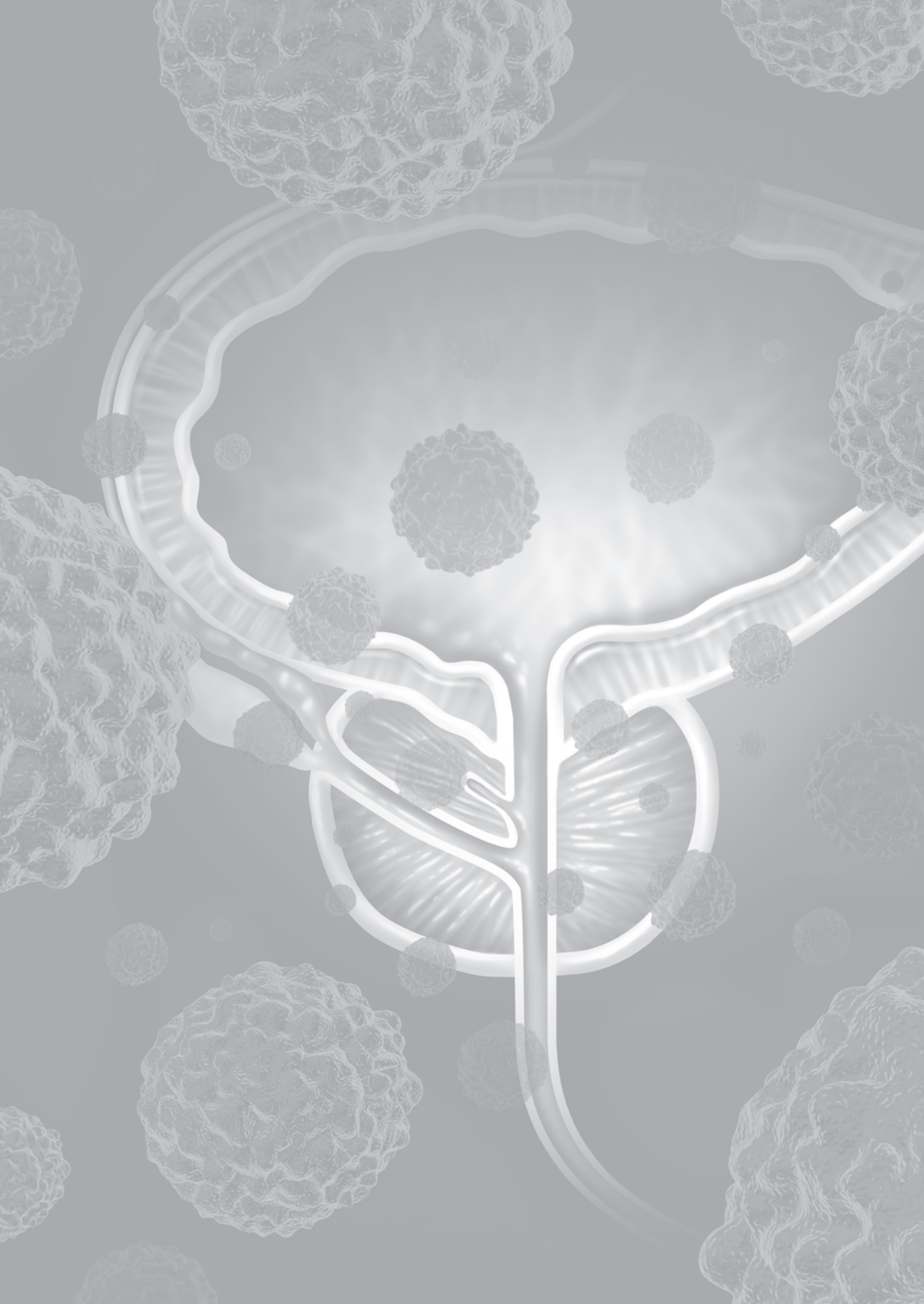
Targeted biopsy outcomes according to location of mpMRI lesions			
Number lesions		**GS 3+3 PCa**	**GS ≥ 3+4 PCa**
Right or Left			
Right	**30**	**5 (17%)**	**13 (43%)**
left	**26**	**4 (15%)**	**12 (46%)**
Both	**10**	**0 (0%)**	**9 (90%)**
Posterior or Anterior*			
Posterior	**33**	**2 (6%)**	**13 (39%)**
Anterior	**26**	**5 (19%)**	**18 (69%)**
Both	**7**	**2 (29%)**	**3 (43%)**
Peripheral or Transition zone			
Peripheral zone	**40**	**4 (10%)**	**16 (40%)**
Transition zone	**21**	**3 (14%)**	**15 (71%)**
Both	**5**	**2 (40%)**	**3 (60%)**
Base, Mid or Apex			
Base	**11**	**2 (18%)**	**4 (36%)**
Base & Mid	**8**	**1 (13%)**	**6 (75%)**
Mid	**20**	**3 (15%)**	**5 (25%)**
Mid & Apex	**7**	**0 (0%)**	**6 (86%)**
Apex	**8**	**1 (13%)**	**4 (50%)**
Base & Mid & Apex	**12**	**2 (17%)**	**9 (75%)**

**Location posterior or anterior of the prostatic urethra according to the 27 regions of interest scheme as published by Dickinson et al. Eur Urol. 2011;59:477-94.*

Supplementary table 4. Size of the individual mpMRI lesions

Size of individual mpMRI lesions		
	Median	**IQR**
Posterior* lesions (mm)	**11**	**7 – 16.5**
Anterior* lesions (mm)	**22.5**	**14.5 – 31.5**
All lesions (mm)	**16**	**10 – 26**

*mm = millimeter, *Location posterior or anterior of the prostatic urethra according to the 27 regions of interest scheme as published by Dickinson et al. Eur Urol. 2011;59:477-94.*



Chapter 5

Multivariable risk-based patient selection for prostate biopsy after magnetic resonance imaging: improving the European Randomized study of Screening for Prostate Cancer Risk Calculators by combining clinical parameters with the Prostate Imaging Reporting and Data System (PI-RADS) score.

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ABSTRACT

Background: The European Randomized study of Screening for Prostate Cancer Risk Calculators (ERSPC-RCs) help to avoid approximately 33% of unnecessary transrectal ultrasound-guided systematic biopsies (TRUS-Bx). Multivariable risk-stratification could also avoid unnecessary biopsy procedures after the performance of MRI.

Objective: To adjust the ERSPC-RC3+DRE and ERSPC-RC4+DRE for the prediction of any grade and high-grade (Gleason score ≥3+4) prostate cancer (PCa) in 12-core TRUS-Bx ± MRI-targeted biopsy (MRI-TBx).

Design, setting and participants: A total of 961 consecutive men with a clinical suspicion of PCa received mpMRI and subsequent 12-core TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3) in 5 different institutions between 2012 – 2016. Data of 504 biopsy naïve and 457 previously biopsied men were used to adjust the ERSPC-RC3+DRE and ERSPC-RC4+DRE, respectively.

Outcome measurements and statistical analysis: Logistic regression models were constructed including the linear predictor of the original ERSPC-RCs as a covariate after recalibration, as well as the overall PI-RADS score and age. The area under the curve (AUC) of the original ERSPC-RCs and the adjusted MRI-ERSPC-RCs for any and high-grade PCa was compared. Decision curve analysis was performed to assess the clinical utility of the MRI-ERSPC-RCs.

Results: The MRI-ERSPC-RC3 had a significantly higher AUC for high-grade PCa compared to the ERSPC-RC3+DRE: 0.84 (95%CI 0.81 – 0.88) *vs* 0.76 (95%CI 0.71 – 0.80), p <0.01. Similarly, the MRI-ERSPC-RC4 had a higher AUC for high-grade PCa compared to the ERSPC-RC4+DRE: 0.85 (95%CI 0.81 – 0.89) *vs* 0.74 (95%CI 0.69 – 0.79), p <0.01. Decision curve analysis showed net benefit for the MRI-ERSPC-RCs compared to the original ERSPC-RCs and a biopsy-all strategy at a high-grade PCa risk threshold of ≥5%. Using a ≥10% high-grade PCa risk threshold to biopsy for both MRI-ERSPC-RCs in our total cohort of 961 men, 25% (237/961) biopsies and 23% (34/146) low-grade PCa diagnoses are saved, missing 4% (14/345) high-grade PCa.

Conclusions: In the present study the multiple externally validated ERSPC-RCs are adjusted for the prediction of any grade and high-grade PCa in 12-core TRUS-Bx ± MRI-TBx. The MRI-ERSPC-RC3 and MRI-ERSPC-RC4 have improved discriminative ability and application of these models in our cohort of men with a high clinical suspicion of PCa would have avoided 25% of biopsy procedures, missing 4% of high-grade PCa.

Patient summary: The ERSPC risk calculators are known to help avoiding approximately one-third of unnecessary transrectal ultrasound-guided biopsies. In the present study, the original ERSPC risk calculators are updated, incorporating age and MRI data. Application of the updated MRI-ERSPC risk calculators could avoid unnecessary biopsy procedures after the performance of an MRI.

INTRODUCTION

In general, a transrectal ultrasound-guided systematic biopsy (TRUS-Bx) is performed as a first step in men with a suspicion of prostate cancer (PCa) based on an elevated prostate-specific antigen (PSA) and/or an abnormal digital rectal examination (DRE). However, in 60 – 75% of men the outcome of this TRUS-Bx is benign (1, 2). Moreover, up to 50% of those PCa detected by TRUS-Bx can be considered clinically insignificant (3). This indicates the need for a more specific, individually tailored selection for biopsy in order to reduce unnecessary biopsy procedures and the overdiagnosis of insignificant PCa. Several multivariable prediction models for PCa in TRUS-Bx are currently used in daily practice, with the European Randomized study of Screening for Prostate Cancer Risk Calculators (ERSPC-RCs) having high discriminative accuracy and being externally validated (4, 5). The ERSPC-RCs are based on data of men aged 55 – 74 years biopsied in the first screening round (n = 3624) and second screening round (n = 2896) of the Rotterdam section of the ERSPC (6). It has been shown that using the ERSPC-RCs and applying cut-off values for the individually calculated probabilities of having biopsy detectable (high-risk) PCa reduces the percentage of unnecessary TRUS-Bx by 20 – 33% (6-12). Nowadays, multi-parametric magnetic resonance imaging (mpMRI) is increasingly used due to the high negative predictive value for clinically significant PCa of approximately 90% (13-15). The European Association of Urology (EAU) PCa guideline panel recommends the performance of a pre-biopsy mpMRI in men with a sustained suspicion of PCa after previous negative TRUS-Bx (15, 16). In addition, the panel recommends to risk-stratify as an initial step before the pre-biopsy MRI to confirm that the clinical suspicion of PCa is grounded (15, 16). Risk-stratification with the ERSPC-RC4 has been shown to avoid unnecessary MRI-scans in this setting (17, 18). After the performance of an MRI-scan, risk-based patient selection for (targeted) biopsy could help to avoid unnecessary biopsy procedures, especially in the absence of pre-MRI multivariable risk-stratification. In the present study, we aim to augment the multiple externally validated ERSPC-RC3 and ERSPC-RC4 with the overall PI-RADS score and potentially other relevant clinical information.

MATERIAL AND METHODS

Study population

A total of 1353 consecutive men with a clinical suspicion of PCa (no prior PCa diagnosis) who received multi-parametric MRI and subsequent TRUS-Bx and/or targeted biopsy (TBx) between 2012 - 2016 were included in the prospective institutional review board approved databases of 5 individual institutions in Düsseldorf (n=723), Rotterdam (n=178),

The Hague (*n*=210), Amsterdam (*n*=160) and Den Bosch (*n*=82). Subgroups of the institutional cohorts were reported previously (17, 19-21).

Multi-parametric MRI

All MRI-scans were performed on a 3-Tesla MRI-scanner using a pelvic phased-array coil. The mpMRI protocol consisted of T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) reconstructions, and dynamic contrast enhanced (DCE) imaging in four institutions (Düsseldorf, Rotterdam, The Hague and Amsterdam). In Den Bosch (*n*=82) a bi-parametric MRI protocol was used consisting of T2WI and DWI. The institutional radiologists who reviewed the MRI-scans all had years of experience in reading prostate MRI. All individual suspicious lesions were graded according to the PI-RADS score (22, 23). Since the time period for (MRI-)data collection was predominantly before publication of PI-RADSv2 (23), the majority of MRI's in the present study were graded according to PI-RADSv1 (22).

Prostate biopsy

The prostate biopsy protocol varied among the individual institutions. In all institutions MRI-TBx was performed of each PI-RADS ≥3 lesion. The technique used for MRI-TBx varied amongst institutions (table 1): the MRI in-bore technique, as well as the MRI-TRUS fusion and cognitive fusion techniques were used. A total of 961 out of the 1353 consecutive men received a TRUS-Bx, with (in case of PI-RADS ≥3) or without (in case of PI-RADS 1 – 2) additional MRI-TBx. The biopsy procedures were all performed by experienced operators and all biopsy specimens were graded by dedicated uro-pathologists. All Gleason score (GS) 3+3 PCa were classified as low-grade PCa, regardless of the maximum cancer core length. GS ≥3+4 PCa was classified as high-grade disease.

Adjustment of the ERSPC-RCs

The ERSPC-RC3 and ERSPC-RC4 are prediction models for PCa in sextant TRUS-Bx based on data of respectively 3624 men in the first screening round and 2896 men in the second screening round of the ERSPC Rotterdam (www.prostatecancer-riskcalculator.com) (6). Both the ERSPC-RC3 and ERSPC-RC4 use PSA, DRE (suspicious: no/yes), TRUS (suspicious: no/yes) and TRUS-measured prostate volume (continuous) as parameters. In addition, the ERSPC-RC4 takes the previous biopsy status (previous biopsy: no/yes) into account. The ERSPC-RC3+DRE and ERSPC-RC4+DRE are simplified models in which TRUS (suspicious: no/yes) is not included as a parameter and the prostate volume is used categorized (25ml, 40ml or 60ml) as can be assessed by DRE. The ERSPC-RC3(+DRE) and ERSPC-RC4(+DRE) calculate the risk of any grade PCa and the risk of high-grade (GS ≥3+4) and/or locally advanced (T-stage ≥2C) PCa. In the present study, we aimed to augment the ERSPC-RC3+DRE and ERSPC-RC4+DRE by incorporating the overall PI-RADS score, for the prediction of any

grade and high-grade (GS ≥3+4) PCa in extended (12-core) TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3). In addition, as the ERSPC-RC3+DRE and ERSPC-RC4+DRE are developed based on data of men aged 55 – 74 years, age was included as a potential predictor in order to comply with the larger age range of men in daily clinical practice. . Data from the 961 men from our cohort who received TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3) were used, of whom 504 biopsy naïve men were included in the adjusted MRI-ERSPC-RC3 and 457 previously biopsied men were included in the MRI-ERSPC-RC4.

Statistical analysis

The multiple imputation by chained equations (MICE) algorithm was used to substitute missing DRE values. The MRI-measured prostate volume, calculated by the ellipsoid formula (length x width x height x π/6), was categorized into the known volume classes of the ERSPC-RC3+DRE and ERSPC-RC4+DRE with cut-off values of <30 ml (25ml), 30 – 50 ml (40ml) and >50 ml (60ml). The original ERSPC-RCs were recalibrated (re-estimation of the intercept and slope of the linear predictor) to a clinical setting using data from the institutions in Rotterdam and Den Bosch (12, 17). Logistic regression analysis was performed to estimate the coefficients of the overall PI-RADS score and age in addition to the recalibrated ERSPC-RC3+DRE and ERSPC-RC4+DRE. The adjusted MRI-ERSPC-RC included the linear predictor of the original ERSPC-RCs as a covariate. Bootstrap resampling was used for internal validation of the MRI-ERSPC-RCs and the calibration was explored graphically by the construction of calibration plots. The predictive accuracy of the original ERSPC-RCs and the MRI-ERSPC-RCs was assessed by the area under the receiver operating characteristic curve (AUC) and compared with the DeLong test. Decision curve analysis was performed to assess and compare the clinical utility of the original ERSPC-RCs and the MRI-ERSPC-RCs. The clinical utility of the models is expressed by the net benefit ratio, which weighs the benefits of (high-grade) PCa detected against the harms of unnecessary biopsies performed (24, 25). Tables were constructed displaying the number and percentage of biopsies saved *vs* (high-grade) PCa missed at different risk thresholds to biopsy of the MRI-ERSPC-RCs. Statistical tests were two sided with the criterion of significance set at p <0.05. Statistical analyses were performed with R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Table 1 shows the patient characteristics of all 1353 men with a clinical suspicion of PCa who received mpMRI and subsequent biopsy between 2012 – 2016 in the 5 individual institutions. The median age, PSA and prostate volume were respectively 66 (IQR 60 – 71)

Table 1. Patient characteristics of all consecutive men with a suspicion of prostate cancer who received MRI and subsequent biopsy between 2012 - 2016 in Düsseldorf, Rotterdam, The Hague, Amsterdam and Den Bosch.

	Düsseldorf (*n* = 723)		**Rotterdam** (*n* = 178)		**The Hague** (*n* = 210)		**Amsterdam** (*n* = 160)		**Den Bosch** (*n* = 82)		**Total cohort** (*n* = 1353)	
	median	IQR	median	IQR	median	IQR	median	IQR	median	IQR	median	IQR
Age (years)	66.1	59.7 – 72.0	67.0	61.8 – 70.5	66.8	62.0 – 71.4	65.0	60.0 – 69.0	62.0	58.0 – 65.0	66.0	60.0 – 71.0
PSA (ng/ml)	8.6	6.0 – 12.8	11.0	8.1 – 17.0	9.4	6.8 – 15.2	6.4	4.9 – 9.2	6.6	5.7 – 10.0	8.7	6.1 – 12.9
Prostate volume (ml)	49.0	36.0 – 71.0	47.0	33.0 – 73.3	51.0	37.8 – 73.3	51.9	37.9 – 67.0	45.0	31.0 – 60.0	49.7	36.0 – 70.0
PSA density	0.17	0.12 – 0.26	0.24	0.15 – 0.36	0.19	0.12 – 0.28	0.13	0.09 – 0.19	0.15	0.11 – 0.23	0.17	0.12 – 0.27
	number	%	number	%	number	%	number	%	number	%	number	%
DRE												
Benign	202	28	136	76	101	48	111	69	58	71	608	45
Suspicious	133	18	42	24	56	27	49	31	24	29	304	22
Missing	388	54	0	0	53	25	0	0	0	0	441	33
Previous biopsy												
No	293	41	10	6	59	28	107	67	82	100	551	41
Yes	430	59	168	94	151	72	53	33	0	0	802	59
PI-RADS												
1 – 2	8	1	55	31	52	25	99	62	25	30	239	18
3	138	19	28	16	38	18	25	16	21	26	250	18
4	375	52	52	29	75	36	22	14	13	16	537	40
5	202	28	43	24	45	21	14	9	23	28	327	24
Biopsy procedure												
TRUS-Bx only	0	0	55	31	49	23	98	61	25	30	227	17
MRI-TBx only	206	29	62	35	124	59	0	0	0	0	392	29
TRUS-Bx + MRI-TBx	517	72	61	34	37	18	62	39	57	70	734	54
Included in MRI-ERSPC-RCs (TRUS-Bx ± MRI-TBx)	517	72	116	65	86	41	160	100	82	100	961	71

Table 1. Patient characteristics of all consecutive men with a suspicion of prostate cancer who received MRI and subsequent biopsy between 2012 - 2016 in Düsseldorf, Rotterdam, The Hague, Amsterdam and Den Bosch. (*continued*)

	Düsseldorf (*n* = 723)		**Rotterdam** (*n* = 178)		**The Hague** (*n* = 210)		**Amsterdam** (*n* = 160)		**Den Bosch** (*n* = 82)		**Total cohort** (*n* = 1353)	
	median	IQR	median	IQR	median	IQR	median	IQR	median	IQR	median	IQR
TBx method												
In-bore	240	33	0	0	122	58	0	0	0	0	362	27
Fusion	483	67	123	69	0	0	58	36	57	70	721	53
Cognitive	0	0	0	0	39	19	4	3	0	0	43	3
No MRI-TBx	0	0	55	31	49	23	98	61	25	30	227	17
Overall GS												
No PCa	365	50	67	38	108	51	82	51	38	46	660	49
GS 3+3 PCa	79	11	42	24	41	20	24	15	24	29	210	16
GS 3+4 PCa	130	18	45	25	33	16	30	19	7	9	245	18
GS 4+3 PCa	67	9	13	7	13	6	11	7	8	10	112	8
GS ≥4+4 PCa	82	11	11	6	15	7	13	8	5	6	126	9
Total	723	100	178	100	210	100	160	100	82	100	1353	100

IQR = interquartile range; PSA = prostate-specific antigen; DRE = digital rectal examination; PI-RADS = Prostate Imaging Reporting Reporting and Data System; TRUS-Bx = transrectal ultrasound-guided systematic biopsy; MRI-TBx = MRI-targeted biopsy; ERSPC-RCs = European Randomized study of Screening for Prostate Cancer Risk Calculators; GS = Gleason score; PCa = prostate cancer.

years, 8.7 (IQR 6.1 – 12.9) ng/ml and 49.7 (36.0 – 70.0) ml. DRE values were missing in 33% (441/1353) men. A total of 82% (1114/1353) men had an overall PI-RADS score ≥3. TRUS-Bx and MRI-TBx were performed with a median number of 12 cores (IQR 12 – 12) and 4 cores (IQR 3 – 6) per patient, respectively. MRI-TBx was performed using the in-bore technique in 32% (362/1126) men and using MRI-TRUS fusion and cognitive fusion in respectively 64% (721/1126) and 4% (43/1126) men. A total of 16% (210/1353) men had low-grade PCa and 36% (483/1353) men had high-grade PCa. The patient characteristics of the 504 biopsy naïve men who received TRUS-Bx ± MRI-TBx included in MRI-ERSPC-RC3 and the 457 previously biopsied men included in MRI-ERSPC-RC4 are shown in table 2 and 3, respectively. In the 504 biopsy naïve men included in MRI-ERSPC-RC3 the low-grade and high-grade PCa detection rates were 16% (81/504) and 42% (213/504), respectively (table 2). The low-grade and high-grade PCa detection rates in the 457 previously biopsied men included in MRI-ERSPC-RC4 were 14% (65/457) and 29% (132/457), respectively (table 3).

Tabel 2. Patient characteristics of men included in MRI-ERSPC-RC3: model for the prediction of any and high-grade PCa in TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3) in biopsy naïve men.

Patient characteristics of biopsy naïve men included in MRI-ERSPC-RC3 (*n* = 504)								
	No PCa (*n*=210; 42%)		**Any PCa** (*n*=294; 58%)		**GS 3+3 PCa** (*n*=81; 16%)		**GS ≥3+4 PCa** (*n*=213; 42%)	
	median	IQR	median	IQR	median	IQR	median	IQR
Age (years)	62.0	56.0 – 67.8	66.1	60.9 – 72.2	65.0	58.3 – 70.0	67.0	61.9 – 73.0
PSA (ng/ml)	6.1	4.8 – 7.8	7.3	5.2 – 10.8	6.5	4.7 – 10.1	7.7	5.5 – 11.0
Prostate volume (ml)	56.5	39.8 – 77.0	40.0	30.0 – 52.0	42.0	29.5 – 58.0	40.0	30.0 – 51.0
	number	%	number	%	number	%	number	%
DRE								
Benign	116	55	116	39	44	54	72	34
Suspicious	23	11	102	35	18	22	84	39
Missing	71	34	76	26	19	23	57	27
PI-RADS								
1 – 2	66	31	39	13	26	32	13	6
3	67	32	32	11	13	16	19	9
4	66	31	97	33	26	32	71	33
5	11	5	126	43	16	20	110	52
Total	210	100	294	100	81	100	213	100

IQR = interquartile range; PSA = prostate-specific antigen; DRE = digital rectal examination; PI-RADS = Prostate Imaging Reporting Reporting and Data System; ERSPC-RCs = European Randomized study of Screening for Prostate Cancer Risk Calculators; GS = Gleason score; PCa = prostate cancer.

Tabel 3. Patient characteristics of men included in MRI-ERSPC-RC4: model for the prediction of any and high-grade PCa in TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3) in previously biopsied men.

Patient characteristics of previously biopsied men included in MRI-ERSPC-RC4 (*n* = 457)								
	No PCa (*n*=260; 57%)		**Any PCa** (*n*=197; 43%)		**GS 3+3 PCa** (*n*=65; 14%)		**GS ≥3+4 PCa** (*n*=132; 29%)	
	median	IQR	median	IQR	median	IQR	median	IQR
Age (years)	65.4	61.1 – 69.4	68.0	62.9 – 72.0	65.9	58.2 – 69.9	68.0	65.0 – 72.8
PSA (ng/ml)	9.4	6.8 – 13.6	11.0	7.4 – 16.0	9.0	6.5 – 14.8	11.7	7.7 – 17.5
Prostate volume (ml)	63.9	48.0 – 88.8	42.0	30.0 – 60.6	48.0	29.0 – 65.1	41.0	30.2 – 55.9
	number	%	number	%	number	%	number	%
DRE								
Benign	123	47	104	53	45	69	59	45
Suspicious	51	20	54	27	10	15	44	33
Missing	86	33	39	20	10	15	29	22
PI-RADS								
1 – 2	106	41	24	12	20	31	4	3
3	56	22	16	8	9	14	7	5
4	78	30	98	50	26	40	72	55
5	20	8	59	30	10	15	49	37
Total	260	100	197	100	65	100	132	100

IQR = interquartile range; PSA = prostate-specific antigen; DRE = digital rectal examination; PI-RADS = Prostate Imaging Reporting Reporting and Data System; ERSPC-RCs = European Randomized study of Screening for Prostate Cancer Risk Calculators; GS = Gleason score; PCa = prostate cancer.

Predictive accuracy of the original and adjusted ERSPC-RCs

Both the overall PI-RADS score and age added significantly to the original ERSPC-RC3+DRE and ERSPC-RC4+DRE. The discriminative ability of the MRI-ERSPC-RCs was significantly higher for both any grade and high-grade PCa compared with the original ERSPC-RCs (Table 4). The MRI-ERSPC-RC3 had a significantly higher AUC for high-grade PCa of 0.84 (95%CI 0.81 – 0.88) compared to an AUC of 0.76 (95%CI 0.71 – 0.80, p <0.01) of the ERSPC-RC3+DRE. Similarly, the AUC for high-grade PCa of the MRI-ERSPC-RC4 was significantly higher compared to the ERSPC-RC4+DRE: AUC of 0.85 (95%CI 0.81 – 0.89) *vs* AUC of 0.74 (95%CI 0.69 – 0.79, p <0.01).

Table 4. Comparison of the predictive accuracy of the original ERSPC-RCs and MRI-ERSPC-RCs.

Comparison of the predictive accuracy of the original and MRI-adjusted ERSPC-RCs					
	ERSPC-RC+DRE		MRI-ERSPC-RC (addition of PI-RADS + Age)		
	AUC	95% CI	AUC	95% CI	*p*-value
Any grade prostate cancer					
Biopsy naïve: ERSPC-RC3 (*n* = 504)	0.779	0.738 – 0.819	0.839	0.805 – 0.872	0.02
Previously biopsied: ERSPC-RC4 (*n* = 457)	0.708	0.659 – 0.757	0.791	0.748 – 0.834	<0.01
All men: ERSPC-RC3/4 (*n* = 961)	0.756	0.725 – 0.786	0.823	0.797 – 0.849	<0.01
High-grade (GS ≥3+4) PCa					
Biopsy naïve: ERSPC-RC3 (*n* = 504)	0.757	0.714 – 0.799	0.843	0.808 – 0.878	<0.01
Previously biopsied: ERSPC-RC4 (*n* = 457)	0.742	0.693 – 0.791	0.850	0.813 – 0.887	<0.01
All men: ERSPC-RC3/4 (*n* = 961)	0.758	0.726 – 0.789	0.852	0.827 – 0.876	<0.01

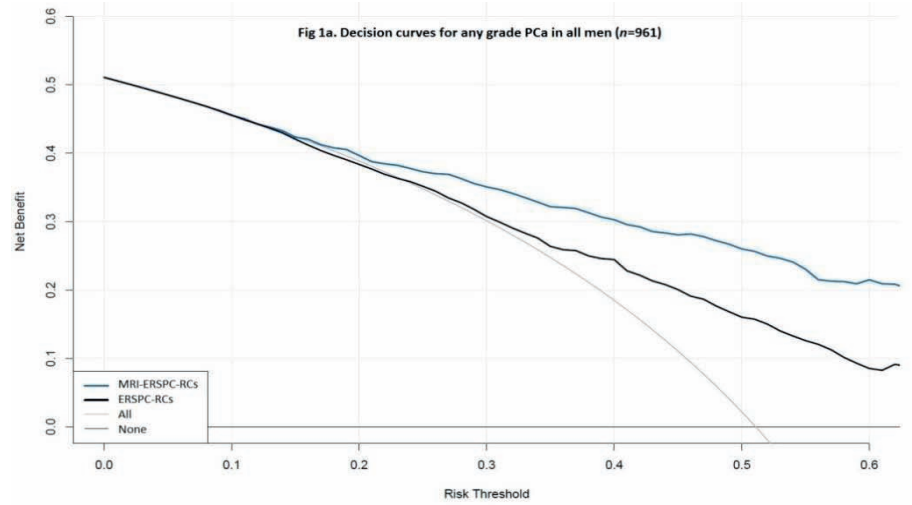
AUC = area under the receiver operating characteristic (ROC) curve; CI = confidence interval.

Decision curve analysis

Decision curve analysis showed improved performance of the MRI-ERSPC-RCs compared to the original ERSPC-RCs for both any grade and high-grade PCa (Figure 1a-b). For the MRI-ERSPC-RC3 net benefit (a potential net reduction in biopsies) compared to a biopsy-all strategy and the ERSPC-RC3+DRE was observed at a risk threshold ≥10% for high-grade PCa (Figure 1a). For the MRI-ERSPC-RC4 net benefit was observed at a risk threshold ≥5% for high-grade PCa (Figure 1b).

Biopsies saved vs (high-grade) PCa missed using the MRI-ERSPC-RCs

Table 5 depicts the number and percentage of biopsies saved and low- and high-grade PCa missed by applying different risk thresholds of the MRI-ERSPC-RC3 and MRI-ERSPC-RC4 for high-grade PCa in all 961 men used to construct both models. At a risk threshold to biopsy of ≥10%, 25% (237/961) biopsies and 23% (34/146) low-grade PCa diagnoses are saved, missing 4% (14/345) high-grade PCa.



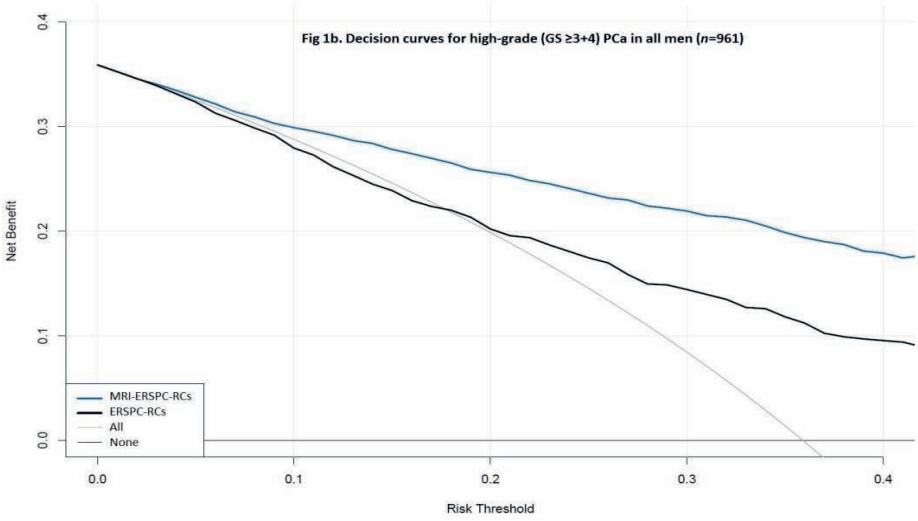


Figure 1A-B. Decision curves for any (Fig 1a) and high-grade (Fig 1b) PCa in TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3) of the original and MRI-adjusted ERSPC-RCs in all (biopsy naïve and previously biopsied) men.

Table 5. Biopsies saved *vs* prostate cancer detected/missed using different risk thresholds for high-grade (GS ≥3+4) PCa of the MRI-ERSPC-RCs(3or4) in all men (*n*=961)

Biopsies saved *vs* prostate cancer detected/missed using different MRI-ERSPC-RC(3or4) risk thresholds for high-grade (GS ≥3+4) PCa						
Risk threshold	(A) No. of men biopsied	(B) No. of biopsies saved (% of total A)	(C) No. of GS 3+3 PCa detected (% of A)	(D) No. of GS 3+3 PCa missed (% of total C)	(E) No. of GS ≥3+4 PCa detected (% of A)	(F) No. of GS ≥3+4 PCa missed (% of total E)
Total	961	-	146 (15.2%)	-	345 (35.9%)	-
3%	884	77 (8.0%)	135 (15.3%)	11 (7.5%)	344 (38.9%)	1 (0.3%)
5%	830	131 (13.6%)	128 (15.4%)	18 (12.3%)	341 (41.1%)	4 (1.2%)
10%	724	237 (24.7%)	112 (15.5%)	34 (23.3%)	331 (45.7%)	14 (4.1%)
15%	652	309 (32.2%)	107 (16.4%)	39 (26.7%)	325 (49.8%)	20 (5.8%)
20%	580	381 (39.6%)	90 (15.5%)	56 (38.4%)	313 (54.0%)	32 (9.3%)

DISCUSSION

Risk-based patient selection for TRUS-Bx has been adopted in daily clinical practice, either by clinical judgement or by the use of risk calculators. Using an objective multivariable risk calculator like the original ERSPC-RCs has been shown to reduce the percentage of unnecessary TRUS-Bx by 20 – 33% in several independent external validation studies (6-12). Nowadays, mpMRI is increasingly performed, especially in men with a sustained suspicion of PCa after previous negative TRUS-Bx (15, 16). The EAU PCa guideline panel recommends to risk-stratify before the performance of an MRI in previously biopsied men and it was previously shown that stratification based on the ERSPC-RC4 could avoid unnecessary MRI-scans in this setting (15-17). In the present study, we aimed to augment the original ERSPC-RCs by incorporating the overall PI-RADS score and age, showing that a multivariable risk-based approach could also be used to avoid unnecessary biopsy procedures after the performance of a pre-biopsy MRI. The original ERSPC-RC3+DRE and ERSPC-RC4+DRE already performed well in our cohort with an AUC for high-grade PCa of 0.76 (95%CI 0.71 – 0.80) and 0.74 (95%CI 0.69 – 0.79), respectively. Nevertheless, the MRI-ERSPC-RCs had a significantly higher discriminative ability for high-grade PCa (AUC of 0.84 (95%CI 0.81 – 0.88) and 0.85 (95%CI 0.81 – 0.89) for the MRI-ERSPC-RC3 and MRI-ERSPC-RC4, respectively) and decision curve analysis showed clear net benefit of the MRI-ERSPC-RCs, proving their ability to avoid unnecessary biopsy procedures even after risk-stratification pre-MRI with the original (recalibrated) ERSPC-RCs.

Obviously, the percentage of potentially avoidable biopsies after MRI is dependent on the composition of the cohort and thus on the degree of risk-stratification pre-MRI. Our cohort used to develop the MRI-ERSPC-RCs consisted of men with a high clinical suspicion of PCa, reflected by a high percentage of men with any grade PCa (51%; 491/961) and

high-grade PCa (36%; 345/961). Nevertheless, the MRI-ERSPC-RCs still would have avoided 25% of unnecessary biopsy procedures in our cohort using a ≥10% high-grade PCa risk threshold to biopsy, missing 4% of high-grade PCa. The good discriminative ability of the original ERSPC-RCs in our cohort (AUC for high-grade PCa of 0.76 (95%CI 0.71 – 0.80) and 0.74 (95%CI 0.69 – 0.79) for ERSPC-RC3+DRE and ERSPC-RC4+DRE, respectively) is consistent with the recently reported AUC's for high-grade PCa of 0.81 and 0.76 for respectively the ERSPC-RC3 and refitted ERSPC-RC4 in the large MRI study of Radtke et al. (26). Therefore, risk-based patient selection for mpMRI to avoid unnecessary MRI-scans using the original (recalibrated) ERSPC-RCs seems justified (17).

Next to the present study, two recent studies presented new PCa prediction models incorporating both clinical and MRI parameters (26, 27). Van Leeuwen et al. constructed a model based on data of 393 predominantly biopsy naïve (88%) men undergoing transperineal template mapping biopsies (median 30 cores) incorporating the same parameters as used in the MRI-ERSPC-RCs: i.e. PSA, DRE, prostate volume, previous biopsy status, overall PI-RADSv1 score and age (27). The model had an AUC for significant PCa, defined as GS ≥3+4 PCa with >5% grade 4 and/or ≥20% cores positive and/or ≥7 mm of PCa in any core, of no less than 0.88 (95%CI 0.85 – 0.92) in the construction cohort and 0.86 (95%CI 0.81 – 0.92) in a validation cohort of 198 men (27). Similar to the present study, using a significant PCa risk threshold to biopsy of ≥10% would have avoided 28% of biopsy procedures in the cohort of van Leeuwen et al., missing 3% of insignificant PCa (27). Radtke et al. also used the previously mentioned parameters included in the MRI-ERSPC-RCs to fit new risk models for any grade and high-grade (GS ≥3+4) PCa based on data of 660 biopsy naïve and 355 previously biopsied men who received transperineal template mapping biopsies (median 24 cores) + fusion MRI-TBx of all PI-RADSv1 ≥2 lesions (26). In accordance with the present study, the risk models of Radtke et al. including PI-RADSv1 and age performed significantly better than the probabilities of the original ERSPC-RCs, calculated manually per single patient online (www.prostatecancer-riskcalculator.com) (26). However, with decision curve analysis net benefit of these risk models was only observed beyond the ≥10% risk threshold for high-grade PCa (26).

Unlike the newly fitted models presented in the previously mentioned studies (26, 27), the MRI-ERSPC-RCs are constructed by augmenting the already multiple externally validated original ERSPC-RCs. After recalibration, the linear predictor of the original ERSPC-RCs was included as a covariate together with the overall PI-RADS score and age. The MRI-ERSPC-RCs do not predict (high-grade) PCa in transperineal template mapping biopsy, but rather the more commonly used extended (12-core) TRUS-Bx in combination with MRI-TBx in case of PI-RADS ≥3 lesions. Only the 961 who received a TRUS-Bx out of the total cohort 1353 men were included in the MRI-ERSPC-RCs as the EAU PCa guideline recommends to perform both TRUS-Bx and MRI-TBx (in case of suspicious lesions) after the performance of a pre-biopsy MRI (15, 16). After external validation, the MRI-ERSPC-RCs will become

available for use in clinical practice on the ERSPC-RC website: www.prostatecancer-riskcalculator.com.

Strength of our study is the inclusion of data from 5 different institutions (2 countries) using different targeted biopsy approaches. This makes our study results more generalizable, although it must be stated that no clear benefit of one targeted biopsy technique over another has been shown so far (28). To limit the number of parameters included in the MRI-ERSPC-RCs, thereby improving their clinical applicability, the ERSPC-RCs+DRE (models without TRUS outcome as a parameter) were augmented instead of the ERSPC-RCs (models including TRUS outcome as a parameter). Our study has several limitations, one being the fact that one third of cases had missing DRE values. These missing DRE values were imputed using the (MICE) algorithm. Another limitation is the fact that the majority of MRI-scans in our study were graded according to PI-RADSv1 (22), as the time period for (MRI-)data collection was predominantly before introduction of the PI-RADSv2 grading system (23), which might perform slightly better (29). A final limitation is the fact that bi-parametric instead of multi-parametric MRI was performed in 1 out of 5 institutions with the smallest subcohort ($n = 82$).

CONCLUSION

Multivariable risk-based patient selection for biopsy after mpMRI can avoid unnecessary systematic and/or targeted biopsies, even after risk-stratification pre-MRI. In the present study we augment the multiple externally validated ERSPC-RC-3 and ERSPC-RC-4 by incorporating the overall PI-RADS score and age. The MRI-ERSPC-RC3 and MRI-ERSPC-RC4 have improved discriminative ability and application of these models in our cohort of men with a high clinical suspicion of PCa would have avoided 25% of biopsy procedures, missing 4% of high-grade PCa.

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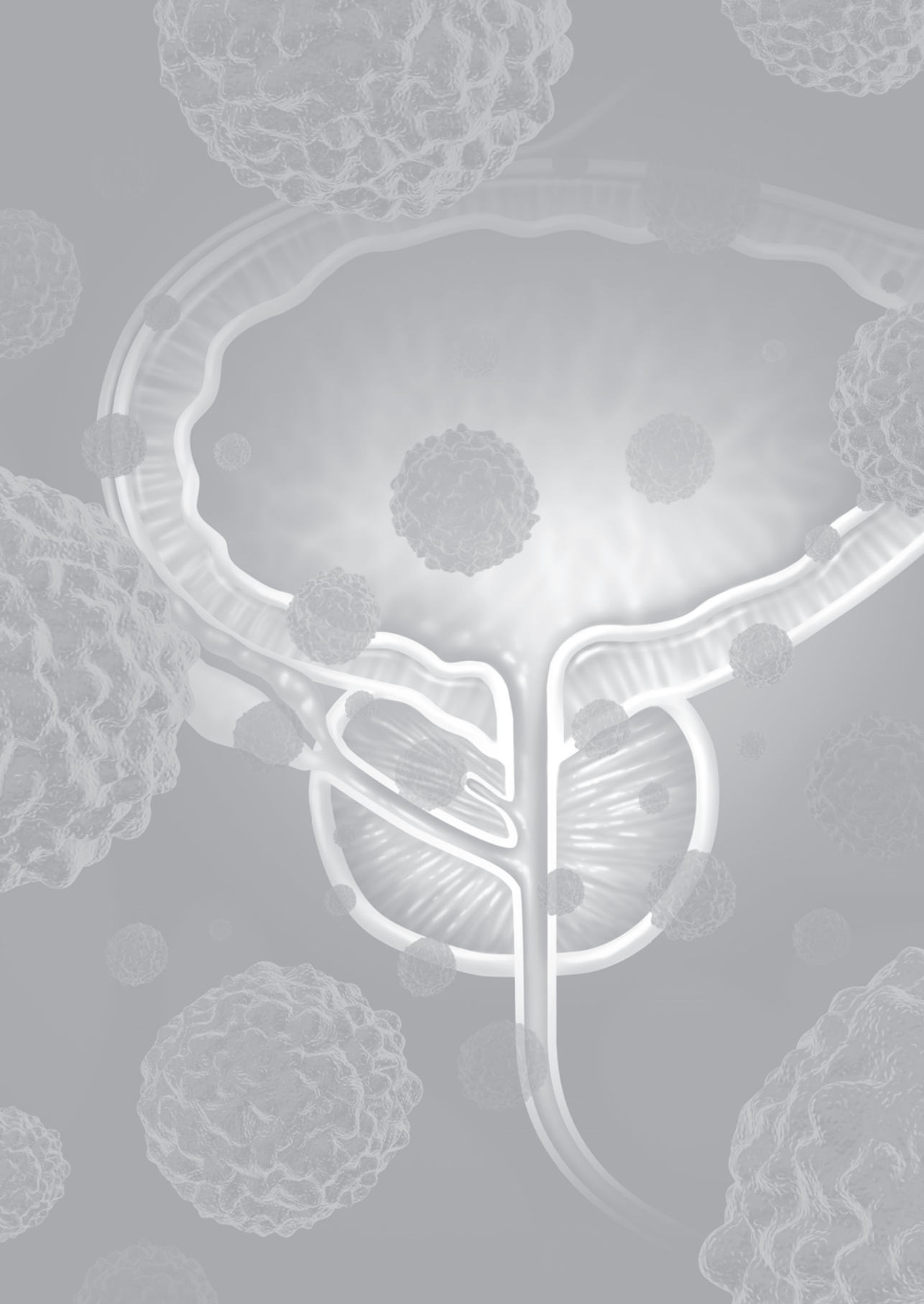
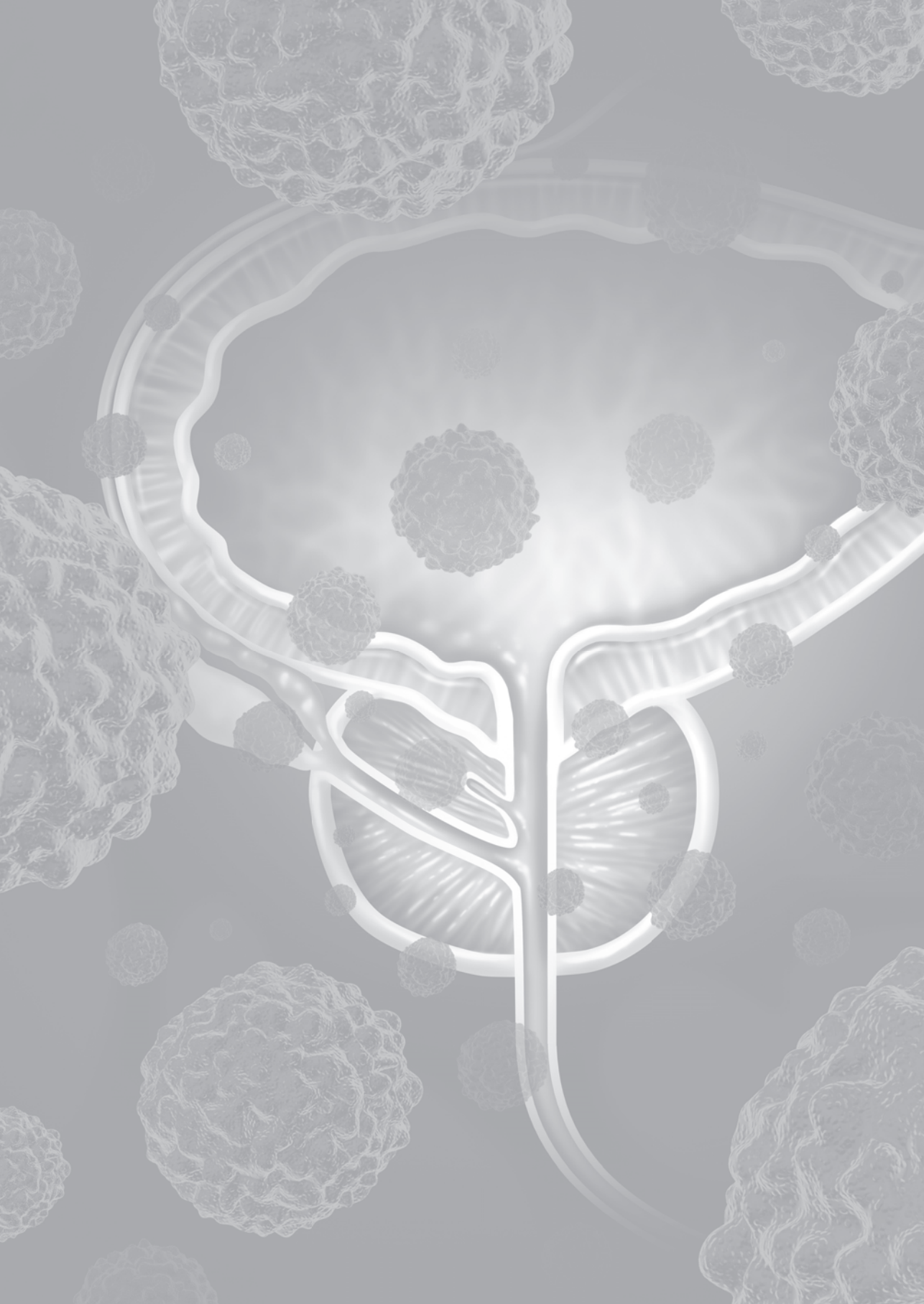


Part II

Active Surveillance



Chapter 6

Biopsy undergrading in men with Gleason score 6 and fatal prostate cancer in the European Randomized study of Screening for Prostate Cancer Rotterdam

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ABSTRACT

Objectives: A total of 15 men who died of prostate cancer had cT1/2 biopsy Gleason Score ≤6 prostate cancer at prevalence screening in the European Randomized study of Screening for Prostate Cancer Rotterdam. Our objective was to explain (part of) these prostate cancer deaths by undergrading with the classical Gleason score.

Methods: Biopsy specimens of 98 men with classical Gleason score ≤6 or 3+4=7 at prevalence screening in the European Randomized study of Screening for Prostate Cancer Rotterdam were retrospectively reviewed by two pathologists using the International Society of Urological Pathology 2014 modified Gleason score. These 98 men included 15 men with cT1/2 classical Gleason score ≤6 who died of prostate cancer (cases) and 83 randomly selected men with classical Gleason score ≤6 or 3+4=7 (controls). The primary outcome was the reclassification rate from classical Gleason score ≤6 to modified Gleason score 3+4=7 (grade group 2) stratified for prostate cancer death. The secondary outcome was the rate of cribriform/intraductal carcinoma in Gleason score-reclassified men stratified for prostate cancer death.

Results: A total of 79 out of 98 men had classical Gleason score ≤6 prostate cancer. A total of 8 out of 15 (53%) prostate cancer deaths with classical Gleason score ≤6 were reclassified to modified Gleason score 3+4=7, compared with 16 out of 64 (25%) men with non-fatal prostate cancer ($p = 0.017$). A total of 5 out of 8 (63%) Gleason score-reclassified men with fatal prostate cancer had cribriform/intraductal carcinoma, compared with 2 out of 16 (13%) Gleason score-reclassified men with non-fatal prostate cancer ($p = 0.011$).

Conclusions: Part of the prostate cancer deaths with Gleason score ≤6 at prevalence screening in the European Randomized study of Screening for Prostate Cancer Rotterdam could be explained by biopsy undergrading. This study confirms that the International Society of Urological Pathology 2014 modified Gleason score is more accurate for prognostic assessment based on prostate biopsy than the classical Gleason score.

INTRODUCTION

PSA-based prostate cancer (PCa) screening in the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam resulted in a 32% PCa-specific mortality reduction in the core age group of 55 – 69 years (1). During a median follow-up of 12.8 years, a total of 151 PCa deaths occurred in the screening arm (1). Remarkably, 22 (14.6%) of these 151 PCa deaths were diagnosed with Gleason score (GS) ≤6 PCa on sextant prostate biopsy in the prevalence (first) screening round. A total of 15 (68%) out of these 22 fatal PCa with GS ≤6 at prevalence screening had cT1/2-stage disease, and thus were classified as low-risk. As GS ≤6 PCa on radical prostatectomy (RP) is very unlikely to metastasize (2-4), a high-grade tumor component not detected by biopsy is most likely responsible for PCa death in these men. The high-grade tumor component could either have been missed due to insufficient tumor sampling by random sextant biopsy or due to undergrading of the biopsy specimens. Apart from human reading error, undergrading could have been caused by insufficiencies in the classical GS (cGS), used to grade the biopsy specimens in the prevalence screening round of the ERSPC Rotterdam (1993–1999). In 2005, the International Society of Urological Pathology (ISUP) modified GS (mGS) was adopted (5). Biopsy grading according to the ISUP 2005 mGS tends to decrease the number of G S≤6 PCa and increase the number of GS 3+4=7 PCa (6-9). Although challenged by some, it has been shown that prognostic prediction based on prostate biopsy is more accurate with the ISUP 2005 mGS as compared with the cGS (9-13). Recently, an updated GS was proposed based on the ISUP consensus conference in November 2014 (14, 15). The ISUP 2014 mGS significantly outperforms the ISUP 2005 mGS in terms of prognostic prediction (16). Hypothetically, part of the PCa deaths with biopsy GS≤6 at prevalence screening in the ERSPC Rotterdam could be explained by undergrading with the cGS. In the present study, we compared the reclassification rate from biopsy cGS ≤6 to ISUP 2014 mGS 3+4=7 (grade group 2) at prevalence screening in men who did or did not die of PCa to assess the rate of PCa deaths with GS ≤6 that could be explained by biopsy undergrading.

METHODS

ERSPC Rotterdam

The study population and protocol of the ERSPC Rotterdam have previously been described in detail (17). Starting in 1993, a total of 42.376 men aged 54 – 74 years were randomized to a screening or control arm in a 1:1 ratio. In the screening arm, men were offered PSA testing with a 4-year interval until the age of 75 years. Random sextant biopsy was initially offered to men with a PSA ≥4.0 ng/ml and/or abnormal digital rectal examination (DRE), later on it was offered to men with a PSA ≥3.0 ng/ml. The PCa-specific mortality was the

primary end-point of the ERSPC. The cause of death was assessed for all men with a PCa diagnosis (both in and outside the screening protocol) through linkage with the national cancer registry and subsequent patient chart review by an independent monitoring committee. Death as a result of a PCa intervention-related complication was classified as PCa death according to the Causes of Death Committee protocol. The study was approved by the institutional ethical review board (MEC 1994-152), and written informed consent with guarantee of confidentiality was obtained from the participants. For the current analysis, a follow-up until the end of 2012 was used, as follow-up and cause-of-death assessment was complete up to and including 2012.

Retrospective consensus review with the ISUP 2014 mGS

Until the end of 2012, a total of 15 men diagnosed with cT1/2 cGS ≤6 PCa in the prevalence screening round of the ERSPC Rotterdam (1993 – 1999) died of PCa (1). These men were selected as cases for the current case-control study. Subsequently, a computer-assisted random selection was performed of 85 controls out of all other men diagnosed at prevalence screening with cGS ≤6 or 3+4=7 PCa (n = 963). The randomly selected control group consisted of both men with cGS ≤6 and men with cGS 3+4=7, so that the uropathologists knew they would not solely review biopsy specimens originally graded as cGS ≤6. In 98 out of the 100 selected men the biopsy specimens were available for pathological review. In the 2 remaining men the biopsy specimens were no longer present in our biorepository. The 98 biopsy specimens, originally scored using the cGS, were reviewed independently by 2 expert uropathologists (THK, GJL) for grading with the ISUP 2014 mGS. One of the uropathologists (THK) originally graded all biopsy specimens during the prevalence screening round with the cGS. Both pathologists were blinded for the original cGS (6 or 3+4=7) and patient outcome during follow-up after the PCa diagnosis. After the pathologists independently graded all biopsy specimens, consensus on the mGS was reached in all cases after common re-evaluation and open discussion.

Statistical analysis

Clinical patient characteristics were compared between men who did or did not die of PCa. The interobserver agreement between the pathologists for the mGS (i.e. 6 or ≥3+4=7) was assessed both proportionally and with the Cohen's K statistic. The rates of reclassification from cGS ≤6 to mGS 3+4=7 (grade group 2) were compared in all 98 men after stratification for PCa death, biochemical recurrence (BCR) after initial treatment by RP or radiotherapy (RT) and the development of PCa metastasis during follow-up until the end of 2012. BCR was defined as 2 consecutive PSA measurements ≥0.2 ng/ml with an interval of 2 – 3 months after RP or a PSA ≥2.0 ng/ml above the PSA-nadir after RT. The distribution of the grade 4 growth patterns were compared between the GS upgraded men who died or did not die of PCa to determine a potentially higher rate of cribriform

and/or intraductal carcinoma (IDC) growth in men with fatal disease. Cribriform growth and IDC were combined for analysis as both entities are equally associated with poor clinical outcome, they often coexist and their morphological distinction is often difficult (18). Inter-group comparison of continuous and categorical data was carried out using the Mann-Whitney U test and χ^2 test, respectively. Statistical tests were 2-sided with the criterion of significance set at $p < 0.05$. SPSS for Windows (Version 21.0; IBM, Armonk, NY, USA) was used for the statistical analysis.

RESULTS

Patient characteristics at PCa diagnosis

The patient characteristics at diagnosis of the 98 selected men stratified for PCa death are shown in table 1. After stratification for PCa death there were no statistically significant differences in median age (67.7 *vs* 68.8 yrs), the proportion of men with a suspicious DRE (52% *vs* 53%) and the proportion of men who received active treatment with curative intent (91% *vs* 94%). The median serum PSA at diagnosis was significantly higher in men with fatal PCa (7.6 *vs* 5.0 ng/ml, $p = 0.007$). Furthermore, men with fatal PCa had a higher number of positive cores at sextant biopsy and higher maximum percentage of cancer core involvement. Although not statistically significant, the proportion of men receiving immediate RT was higher in the fatal PCa group (65% *vs* 42%), possibly reflecting higher-risk disease. In the non-fatal PCa group, 5 men received delayed active treatment after a median period of 3.5 yrs (IQR 1.3 – 4.2) of Watchful Waiting (WW): 4 men received RT while 1 man was treated by RP. Only 1 out of the 15 men with cT1/2 cGS ≤6 and PCa death during a median follow-up of 13.7 years (IQR 10.1 – 15.3) did not receive active treatment. Supporting Table 1 depicts the (not-revised) prostatectomy cGS of all 40 men who received RP at diagnosis.

Consensus review with the ISUP 2014 mGS

The expert pathologists individually agreed on the ISUP 2014 mGS (i.e. 6 or ≥3+4=7) in 84 out of 98 (86%) men. There was substantial interobserver agreement with a Cohen's κ of 0.70. After consensus was reached on the mGS in the discordant cases, a total of 24 out of 79 (30%) men were upgraded from biopsy cGS ≤6 to mGS 3+4=7 PCa (grade group 2). Biopsy revision of the 19 men with cGS 3+4=7 yielded downgrading to mGS 6 (grade group 1) in 2 out of 19 (10.5%) men and upgrading to mGS 4+3=7 (grade group 3) in 2 out of 19 (10.5%) men.

Table 1. Clinical patient characteristics.

		No Prostate cancer death (81 controls)		Prostate cancer death (15 cases + 2 controls)		
		Median	IQR	Median	IQR	*p*-value
Age at diagnosis (years)		67.7	62.0 – 70.8	68.8	63.1 – 71.6	0.306
PSA at diagnosis (ng/ml)		5.0	3.6 – 7.6	7.6	4.9 – 21.5	0.007
Maximum Cancer Core Involvement (%)		20	10 – 60	50	20 – 80	0.092
		n	%	*n*	%	*p*-value
Suspicious DRE		42	52	9	53	0.935
T-stage	T1C	39	48	8	47	0.666
	T2A	23	28	6	35	
	T2B	6	7	2	12	
	T2C	13	16	1	6	
Number positive cores	**1**	25	31	3	18	0.036
	2	29	36	5	29	
	3	14	17	1	6	
	≥4	13	16	8	47	
Classical Gleason Score	**≤6**	64	79	15	88	0.382
	3+4=7	17	21	2	12	
Active treatment		74	91	16	94	0.706
	RP	35	43	5	29	
	RT	34	42	11	65	
	Delayed RP/RT after WW	5	62	0	0	
Watchful Waiting		7	9	1	6	0.706
Total no. of men		81	100	17	100	

PSA = prostate-specific antigen, DRE = digital rectal examination, RP = radical prostatectomy, RT = radiotherapy, WW = Watchful Waiting, IQR = Interquartile range

GS reclassification rates stratified for BCR, metastases and PCa death

After stratification for PCa death, as shown in table 2, the GS reclassification rate from cGS ≤6 to mGS 3+4=7 was significantly higher in men with fatal PCa (53%) in comparison with men who did not die of PCa (25%, $p = 0.017$). Table 3 shows that 26 out of 85 (31%) men who were treated at diagnosis developed BCR during a median PSA follow-up of 8.9 yrs (IQR 5.6 – 12.9). Although statistically insignificant, the GS reclassification rate was higher in men who developed BCR (40%) as compared with men who did not (26%). The GS reclassification rate was also higher in men who developed PCa metastasis (46%) as compared with men who did not (27%, $p = 0.129$). As 2 men died of a PCa intervention-related complication before clinical metastases occurred, the number of PCa deaths (17) was higher than the number of men who developed PCa metastases (15). One man died of a cardiovascular complication that was initiated by RP. The other man had castration-

resistant PCa without clinical metastases, but died after an endoscopic intervention for refractory hematuria caused by radiation cystitis.

Table 2. Classical *vs.* Modified Gleason score after stratification for prostate cancer death.

		ISUP 2014 Modified Gleason score				% reclassification of classical GS*
		6 (G1)	3+4=7 (G2)	4+3=7 (G3)	Total	
Classical Gleason score	**No Prostate cancer death (n=81)**					
	≤ 6	48	16	0	64	25%
	3+4=7	2	14	1	17	18%
	Total	50	30	1	81	24%
	Prostate cancer death (n=17)					
	≤ 6	7	8	0	15	53%
	3+4=7	0	1	1	2	50%
	Total	7	9	1	17	53%
	*Reclassification can be both up- or downgrading					

ISUP = International Society of Urological Pathology, GS = Gleason Score, G = Grade group

Table 3. Classical *vs.* Modified Gleason score after stratification for biochemical recurrence and prostate cancer metastasis.

		ISUP 2014 Modified Gleason score				% reclassification of classical GS*
		6 (G1)	3+4=7 (G2)	4+3=7 (G3)	Total	
Classical Gleason score	**No Biochemical recurrence after initial curative therapy (n=59)**					
	≤ 6	34	12	0	46	26%
	3+4=7	2	11	0	13	15%
	Total	36	23	0	59	24%
	Biochemical recurrence after initial curative therapy (n=26)					
	≤ 6	12	8	0	20	40%
	3+4=7	0	4	2	6	33%
	Total	12	12	2	26	38%
	No Prostate cancer metastasis (n=83)					
	≤ 6	48	18	0	66	27%
	3+4=7	2	14	1	17	18%
	Total	50	32	1	83	25%
	Prostate cancer metastasis (n=15)					
	≤ 6	7	6	0	13	46%
	3+4=7	0	1	1	2	50%
	Total	7	7	1	15	47%
	*Reclassification can be both up- or downgrading					

ISUP = International Society of Urological Pathology, GS = Gleason Score, G = Grade group

Distribution of grade 4 growth patterns in GS reclassified men

Table 4 shows the distribution of the grade 4 growth patterns in all men with mGS ≥ 3+4=7 (grade group 2). The most common growth patterns in GS reclassified men were fused glands (17/24 men) and ill-formed glands (15/24 men). All men with IDC also had cribriform growth in their biopsy specimen. GS reclassified men with fatal PCa had significantly more cribriform/IDC growth as compared with men who did not die of PCa (63% *vs* 13%, $p = 0.011$).

Table 4. Distribution of grade 4 growth patterns in men reclassified to modified Gleason score 3+4=7.

Reclassified from cGS ≤ 6 to ISUP 2014 mGS 3+4=7					
	No Prostate cancer death		**Prostate cancer death**		
	n	%	*n*	%	*p*-value
Ill-formed	10	63	5	63	1.000
Fused	10	63	7	88	0.204
Glomeruloid	1	6	1	13	0.602
Cribriform	2	13	5	63	0.011
IDC	2	13	4	50	0.046
Cribriform / IDC	2	13	5	63	0.011
No. of men	16	100	8	100	
	median	IQR	median	IQR	*p*-value
% grade 4	7.5	5.0 – 27.5	15.5	8.0 – 20.0	0.256

cGS = classical Gleason score, ISUP = International Society of Urological Pathology, mGS = modified Gleason score, IDC = intraductal carcinoma, IQR = interquartile range

DISCUSSION

Although GS ≤6 PCa on RP is very unlikely to metastasize (2-4) a substantial number of 15 PCa deaths in the ERSPC Rotterdam were men diagnosed at prevalence screening with cT1/2 biopsy cGS ≤6 PCa (1). A high-grade tumor component not detected by (initial) pathological review of the biopsy specimens is most likely to be responsible for the PCa death in these men. As all but one of these men received active treatment, the main explanations for the "missed" high-grade tumor component could either be insufficient tumor sampling by sextant biopsy or undergrading of the biopsy specimens. In the present study, we showed that the reclassification rate from cGS ≤6 to mGS 3+4=7 (grade group 2) was significantly higher in men with fatal PCa (53%) compared with men who did not die of PCa (25%). This shows that a substantial part of the PCa deaths with GS ≤6 at prevalence screening in the ERSPC Rotterdam could be explained by biopsy undergrading.

In the ISUP 2005 mGS and subsequently the ISUP 2014 mGS the definition of Gleason pattern 3 was further specified, moving some architectural patterns from Gleason pattern

3 to the pattern 4 category, and as a consequence the definition of pattern 4 is expanded, causing a shift of PCa graded as biopsy GS ≤6 towards GS 3+4=7 (14, 19). After revision of biopsy specimens, upgrading to ISUP 2005 mGS 3+4=7 occurs in 19–45% of men originally diagnosed with cGS ≤6 (6-9). The upgrading rate of 30% in our study is in line with these previous findings. To our knowledge, we are the first to report on a higher GS upgrading rate in men who died of PCa. Although statistically not significant, the GS upgrading rate also tended to be higher in the present study in men who developed BCR and PCa metastasis. Previous studies reported on the superior prognostic prediction of the biopsy ISUP 2005 mGS as compared with the cGS, both for BCR after RP (9-11) and for PCa-specific survival in men on WW (12). Recent evidence suggests further improvement of prognostic prediction with the biopsy ISUP 2014 mGS (16). The findings of our study support that the ISUP 2014 mGS is a more accurate tool for prognostic assessment based on prostate biopsy than the cGS. As the main goal of the present study was to explain (part of) the PCa deaths in the ERSPC Rotterdam with GS ≤6 at prevalence screening by undergrading with the cGS, our study was not designed for a comparison between grading with the ISUP 2005 mGS and the ISUP 2014 mGS.

Although enabling a more accurate prognostic prediction, upfront grading with the ISUP 2014 mGS probably would not have affected the PCa death rate in our cohort from the pre-active surveillance era as 90 out of 98 (92%) men received active treatment with curative intent. Nowadays, active surveillance is increasingly implemented in biopsy GS ≤6 PCa. As the oncological safety of Active Surveillance in men with (limited) Gleason pattern 4 is not yet proven it is essential to select only those men with low-grade disease (20). The mGS, that was implemented ever since the rise of active surveillance as a treatment modality, probably allows a superior patient selection for active surveillance as compared with the cGS. In the near future, patients with (limited) Gleason pattern 4 could be selected for active surveillance based on the grade 4 growth pattern. Cribriform growth and IDC in prostate biopsy have been shown to be equally associated with a poor cancer-specific survival as compared with men without cribriform/IDC growth (18). The present study confirmed cribriform/IDC growth as a risk factor for PCa death, with a higher rate of cribriform/IDC growth in GS reclassified men with fatal PCa. Cribriform growth and IDC were combined for analysis as both entities often coexist and can be hard to distinguish. Combining cribriform growth and IDC does not alter the prognostic value and morphological distinction between the separate entities by additional immunohistochemistry is no longer needed.

Besides biopsy undergrading, undersampling by sextant biopsy is probably the most important cause of "missed" high-grade tumor components in the fatal PCa with GS ≤6 at prevalence screening. Extended systematic biopsy core schemes increase the PCa detection rate by a factor of 1.3 (21). Systematic biopsy insufficiently samples anterior tumors (22, 23), not only leading to underdetection but also undergrading of tumors. Upgrading

of biopsy GS ≤6 on RP occurs in approximately 40% of cases (24, 25). In our cohort a total of 7 men with cT1/2 cGS ≤ 6 and PCa death were not reclassified with the mGS. Three of these men were treated by RP. As shown in supplementary table 1, all 3 had a high-grade tumor component in the RP specimen (cGS 5+4, 3+5 and 4+3), indicating insufficient tumor sampling by random sextant biopsy. The development of a high-grade tumor component after the initial diagnosis during WW could not be responsible for the PCa death in the 15 men with cT1/2 cGS ≤6, since all but one of these men received active treatment (5 RP and 9 RT).

Besides grading with the ISUP 2014 mGS, GS upgrading could be caused by a general shift upwards of the perception of patterns (Gleason inflation) after the introduction of the mGS. Furthermore, pathological (double reading) revision of the biopsy specimens with correction of initial diagnostic errors could also yield GS upgrading. Highly variable levels of intraobserver (43 – 78%) and interobserver (36 – 81%) agreement of the GS have been reported (26-28). The 86% interobserver agreement in our study is in line with the approximately 80% interobserver agreement found in most studies using the mGS [10]. In the present study, consensus review was only carried out for the mGS. However, we would not expect a variation of interobserver cGS variability between subgroups after stratification for PCa death, nor would we expect a variation in Gleason inflation. Thus, the difference in the rate of upgrading to mGS 3+4=7 between men who did and did not die of PCa in our cohort is most likely primarily based on undergrading with the cGS.

The strength of this study lies in the double reading of the biopsy specimens and the accurate long-term follow-up. However, as we only had follow-up until the end of 2012, more PCa deaths might have occurred in our cohort afterwards. The present study is also limited by the fact that our small cohort included only a fraction of all cGS 3+3 and 3+4 PCa in the prevalence screening round of the ERSPC Rotterdam. Finally, the sextant prostate biopsy performed in our cohort detects less (significant) PCa as compared with extended biopsy core schemes used in current clinical practice.

Conflicts of Interest

None declared.

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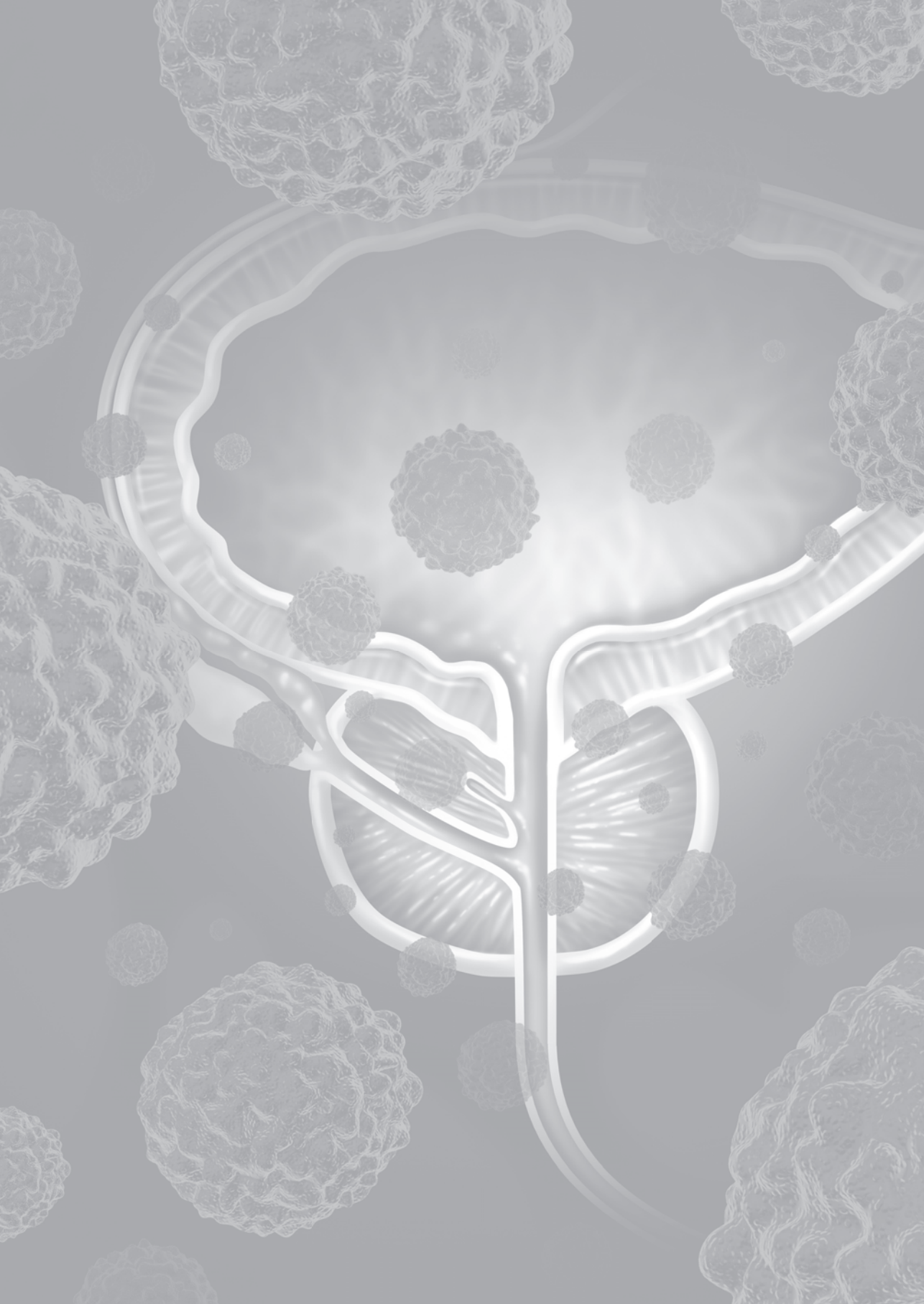
SUPPLEMENTARY MATERIAL

Supporting table 1. (Not-revised) Classical Gleason score of the Radical Prostatectomy specimens at initial diagnosis stratified for Prostate Cancer Death.

		Radical Prostatectomy Classical Gleason score		
		≤ 6	≥ 3+4=7	Total
Biopsy Modified Gleason score	**No Prostate cancer death (n=35)**			
	6	22	0	22
	≥ 3+4=7	7	6	13
	Total	29	6	35
	Prostate cancer death (n=5)			
	6	0	3	3
	≥ 3+4=7	2	0	2
	Total	2	3	5



Chapter 7

Compliance rates with the Prostate Cancer Research International: Active Surveillance (PRIAS) protocol and disease reclassification in noncompliers.

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ABSTRACT

Background: Men with prostate cancer on active surveillance are advised to follow strict follow-up schedules and switch to definitive treatment if risk reclassification occurs. However, some men might not adhere to these strict protocols.

Objective: To determine the number of non-compliers and disease reclassification rates in men not complying with the follow-up protocol of the Prostate cancer Research International: Active Surveillance (PRIAS) study.

Design, setting, and participants: 4547 men with low-risk prostate cancer were included and prospectively followed on active surveillance. Men were regularly examined using PSA, DRE, and repeat biopsies and advised to switch to definitive treatment if disease reclassification occurred (>cT2c, Gleason score >3+3, >2 cores positive, or PSA-doubling time (PSA-DT) 0-3 year).

Outcome measurements and statistical analysis: Rates of men not complying with the follow-up visits or recommendation to discontinue active surveillance were reported. Biopsy outcome (Gleason score >=7 or > 2 cores positive) between compliers and non-compliers was compared using cox proportional hazard analysis.

Results and limitations: The compliance rate with PSA visits was 91%. In contrast compliance rates with standard repeat biopsies decreased over time (81%, 60%, 53%, and 33% for 1, 4, 7, and 10 years after diagnosis respectively). Yearly repeat biopsies in men with faster rising PSA (PSA-DT 3-10 year) was low at less than 30%, although these men had higher upgrading rates at repeat biopsy (25-30% versus 16%). A PSA-DT of 0-3 year was the most common recommendation to discontinue, nevertheless 71% continued active surveillance. Men with PSADT 0-3 year were at higher risk of upgrading on repeat biopsy (HR 2.02; 95% CI 1.36-3.00) as compared to men without fast rising PSA.

Conclusion: Some men and their physician do not comply with an active surveillance follow-up protocol. Especially yearly repeat biopsies in men with fast rising PSA, are often ignored, as is the recommendation to discontinue active surveillance due to a very fast rising PSA. Although these men are at increased risk of having higher Gleason scores on repeat biopsy, the majority still presents favorable tumor characteristics. A fast rising PSA should therefore not be a recommendation to advice active treatment, but should rather serve as a criterion for stricter follow-up. In addition, we should aim to find ways of safely reducing the amount of biopsies to increase adherence to active surveillance protocols.

Patient summary: In this report we looked at the compliance with a large active surveillance protocol for low risk prostate cancer. We observed reluctance with yearly biopsies due to a fast rising PSA, despite a higher risk of disease progression. Further research should aim to safely reduce the amount of repeat biopsies in men on active surveillance, to increase protocol adherence.

INTRODUCTION

Active surveillance for prostate cancer is a treatment option aimed at reducing the negative side effects of radical treatment, while at the same time preserving the option for curative treatment. It does so by strictly following men and only offering curative treatment to those that show signs of disease progression / reclassification. However, optimal criteria for follow-up, inclusion and exclusion are currently still being investigated. Most common protocols include criteria based on a combination of PSA tests, digital rectal examinations (DRE), and repeated prostate biopsies to both include patients and define disease reclassification (1-6). Some men and their physicians might however choose to deviate from these strict protocols, ignoring either the follow-up schedule or the advice to switch to curative treatment.

The aim of the current analysis is to determine the number of men who do not comply with the protocol of the Prostate cancer Research International: Active Surveillance (PRIAS) study. The PRIAS study is currently the largest prospective study on active surveillance, including over 100 centers in 17 countries aimed to represent a real world situation (1). Furthermore, follow-up of men not complying with the approved protocol allows us to evaluate the protocol by investigating their intermediate term outcomes (i.e. Gleason score upgrading at repeat biopsy).

PATIENTS AND METHODS

In the PRIAS study men with low risk prostate cancer are prospectively followed on active surveillance (7). All centers enter data on inclusion and follow-up trough an online tool (www.prias-project.org), which automatically provides all recommendations for follow-up based on the protocol (7). Criteria for inclusion are: Gleason score <=3+3, <=cT2c, PSA <=10ng/ml, <= two cores positive for prostate cancer, PSA density <=0.2ng/ml/ml, and fitness for curative treatment. A minimum number of biopsy cores taken is advised based on prostate volume (prostate volume <40cm3: 8 cores, 40-60cm3: 10 cores, >60cm3: 12 cores), but is not a strict inclusion criterion. As of 2012 men with minimal Gleason score 3+4 disease (<=10% core involvement) can be included if aged >=70 year (n=24)(for follow-up all regular criteria apply except for Gleason score, which can be 3+4 on repeat biopsy).

Men are followed using PSA testing every 3 months the first 2 years and every 6 months thereafter. Digital rectal examination is advised every 6 months the first 2 years and every year thereafter. Repeat biopsies are done 1,4,7,10, and subsequent every 5 years after diagnosis. Yearly repeat biopsies are only advised if PSA doubling time (PSA-DT) is between 3 and 10 years. PSA-DT is calculated using all available PSA values since diagnosis by plot-

ting the base 2 logarithm of the PSA values against the time since diagnosis. The PSA-DT is then calculated as the reciprocal value of the slope of the regression line through these points. PSA-DT is only used if at least 4 PSA values are available. A bone scan is recommended if PSA >=20ng/ml. Criteria used to recommend a switch to definitive treatment are: Gleason score >3+3, >2 biopsy cores positive for prostate cancer, >cT2c, and a PSA-DT of 0-3 year (if at least 4 PSA values are available) on any of the follow-up visits (figure 1). Follow-up for the current analysis ended 31 December 2014.

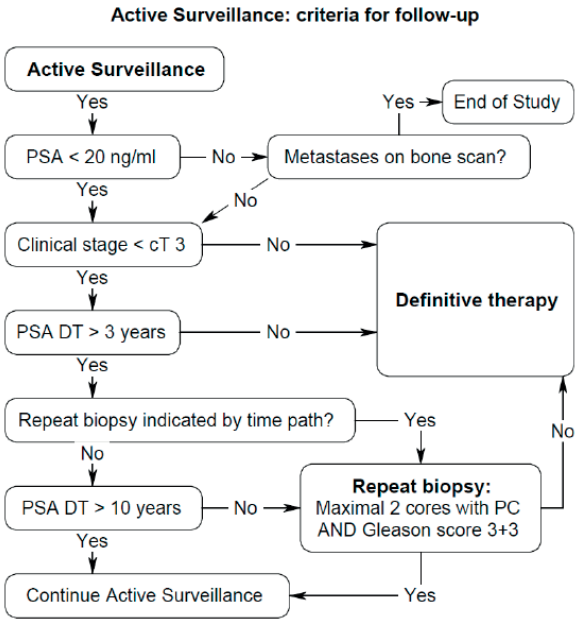
Figure 1A. Follow-up schedule of the PRIAS study

Time table

Year	*1*					*2*				*3*		*4*		*5*		*6*		*7*	
Month	*0***	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*30*	*36*	*42*	*48*	*54*	*60*	*66*	*72*	*78*	*84*
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Biopsy*	✓				✓								✓						✓
Evaluation	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓

* repeat biopsy: Standard after 1, 4, 7 and 10 year and subsequently every 5 years.
If PSA–DT is 0-10 years repeat biopsy every year is advised. No more than 1 biopsy per year should be performed
** Time of diagnosis

Figure 1B. Active surveillance: criteria for follow-up (old protocol until 2015)



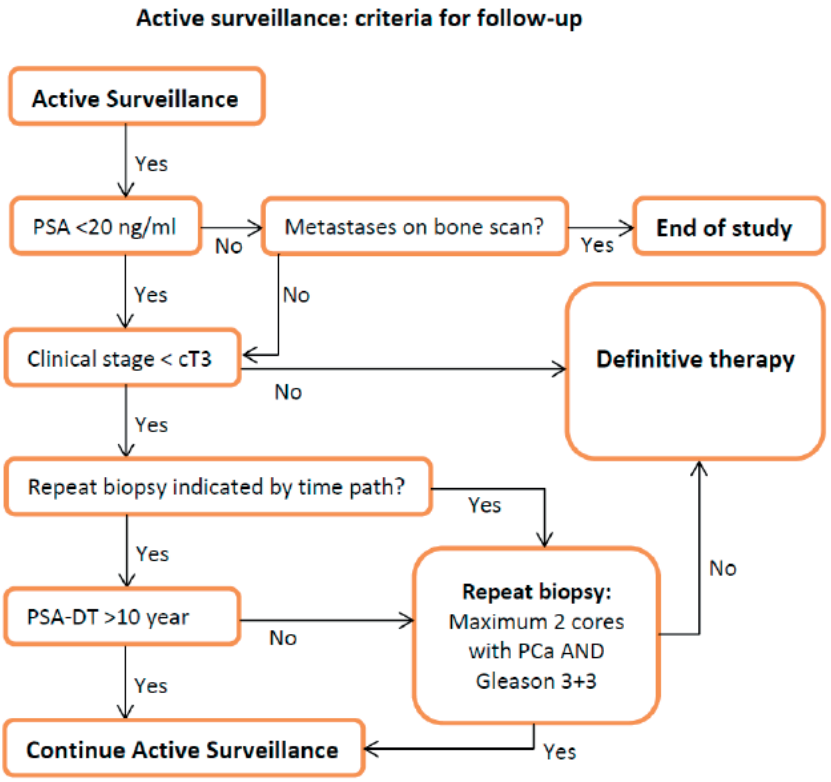


Figure 1C. Active surveillance: criteria for follow-up (new protocol)

Figure 1 – (A) Follow-up schedule for the PRIAS study. Month 0 represents the time of diagnosis. RBx is standard after 1, 4, 7, and 10 yr, and every 5 yr thereafter. If PSA-DT is 0–10 yr, RBx every year is advised. No more than one biopsy per year should be performed. (B,C) Follow-up criteria for the PRIAS study (B) up to 2015 and (C) after 2015. *PRIAS = Prostate Cancer Research International Active Surveillance; PSA = prostate-specific antigen; DRE = digital rectal examination; RBx = repeat biopsy; PSA-DT = PSA doubling time; PCa = prostate cancer.*

Compliance with the follow-up schedule was studied per year of being on active surveillance. Men were defined as being compliant with the PSA visits if in the first 2 years at least 3 PSA tests were done per year and at least 1 PSA test in the years thereafter. A biopsy 6 months before or after the designated time for the biopsy was classified as being compliant with that biopsy. Standard biopsies should have been done in year 1, 4, 7, and 10 in men with >1.5, >4.5, >7.5, and >10.5 years of follow-up respectively to classify as being compliant. Men with a PSA-DT of 3-10 years within the years with no scheduled standard repeat biopsy (years 2, 3, 5, 6, 8, 9 after inclusion, see figure 1) should have had a biopsy in that year. Two definitions were used for non-compliance with a protocol based reason to

discontinue active surveillance: at least 1 PSA visit or at least 1 biopsy after the protocol recommendation to discontinue.

Statistical analysis

Upgrading in men not complying with a recommendation to biopsy
The number of men with upgrading (Gleason score >6 or >2 cores positive) on the second standard repeat biopsy (year 4) was compared for men without a PSA-DT between 3 and 10 in the second and third year and men with a PSA-DT between 3 and 10 during that period, but who did not receive an early repeat biopsy, using the Chi-square test. In addition, a comparison was made with the number of men with upgrading on repeat biopsy in year 2 or 3 triggered by a PSA-DT between 3 and 10. For equal comparison all men had the first scheduled repeat biopsy in year 1.

Upgrading in men not complying with a recommendation to discontinue
As the number of previous biopsies during follow-up could influence upgrading rates we only reported upgrading rates on the second repeat biopsy during follow-up for men who ignored a recommendation to discontinue active surveillance on the first repeat biopsy during follow-up (either Gleason score >6 or > 2 cores positive) or ignored a recommendation to discontinue in-between the first and second repeat biopsy (due to a PSA-DT of 0-3 year). As comparison, upgrading rates on the second repeat biopsy during follow-up for men without a previous recommendation to discontinue were reported. As time between the first two biopsies could differ between these groups we conducted a cox proportional hazard analysis with correction for age, PSA and number of positive cores at the first repeat biopsy and PSA density at diagnosis to predict upgrading on the second repeat biopsy. For this analysis PSA-DT 0-3 was assumed to be at the time of the first repeat biopsy, as most PSA-DT 0-3 occurred within 1 year of the first repeat biopsy (8). For all analysis SPSS for windows (Version 21.0. Armonk, NY: IBM Corp.) was used.

RESULTS

Until the end of follow-up 4547 men were included and followed on active surveillance in the PRIAS study. As inclusion and follow-up is still ongoing, the median time on active surveillance for all men was only 1.5 years, but 750 men were followed for more than 4 years and 94 men for more than 7 years.

Compliance with PSA and biopsy visits

During follow-up 91% of patients complied with all PSA visits. After year 7 a slight decrease in compliance with the scheduled PSA visits was seen (figure 2). The rate of compliance with all advised biopsy visits was lower at 70%. Compliance rates with the standard biopsies (year 1, 4, 7, and 10) decreased over the years with 1867/2306 men (81%) complying with the 1 year repeat biopsy, 333/559 (60%) with the 4 year repeat biopsy, 27/51 (53%) with the 7 year repeat biopsy, and 1/3 men (33%) with the 10 year repeat biopsy. Overall compliance rates with the yearly repeat biopsies due to a PSA-DT of 3-10 years was low ranging from 226/702 men (24%) in year 2 to 1/11 men (9%) in year 8 (figure 2). Of 750 men with more than 4 years of follow-up, 222 (30%) complied with all advised biopsies.

Men with a biopsy advise in year 2 or 3 (due to a PSA-DT of 3-10 years) who did not comply, more often had upgrading (Gleason >6 and/or >2 cores positive) on repeat biopsy at year 4, as compared to men without a PSA-DT of 3-10 years in year 2 or 3 (25% versus 16% respectively, p=0.028). Men with a PSA-DT of 3-10 in year 2 and 3 who did have a biopsy in year 2 or 3, were upgraded in 27% and 30% of cases respectively (table 1). In year 7 50 men had a repeat biopsy. Of the 22 men that fully complied with the biopsy protocol 1 (5%) had a Gleason score >=7. Of the 28 that did not fully comply, 5 (18%) had a Gleason score >=7 (p=0.15).

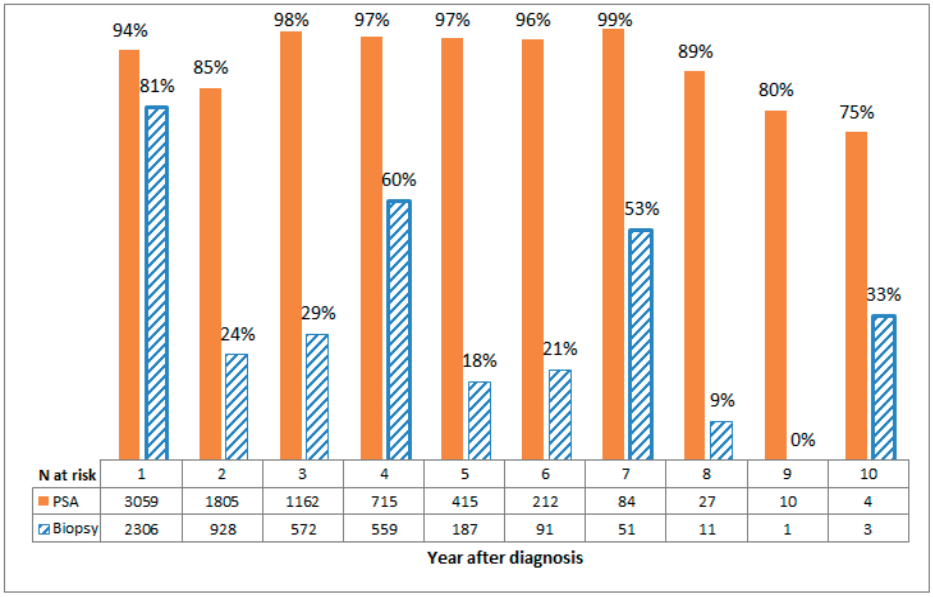


Figure 2. Percentage of men complying with prostate-specific antigen (PSA) testing and prostate biopsies among men on active surveillance per year (standard repeat biopsies are highlighted).

Table 1. Outcome in men complying and not complying with advice to undergo prostate biopsies.

	Group 1*		Group 2*		Group 3*		Group 4*	
Biopsies during follow-up	**PSA-DT 3-10**	**Bx**	**PSA-DT 3-10**	**Bx**	**PSA-DT 3-10**	**Bx**	**PSA-DT 3-10**	**Bx**
Year 1		Yes		Yes		Yes		Yes
Year 2	Yes	No	No	-	Yes	Yes	No	-
Year 3	Yes	No	No	-			Yes	Yes
Year 4		Yes		Yes				
Age at diagnosis, median (IQR)	64.9 (61.3-69.9)		65.9 (60.2-70.7)		64.4 (60.3-69)		64.5 (59.4-70.3)	
PSA at diagnosis, median (IQR)	5.1 (3.6-6.4)		5.7 (4.4-7.5)		5.4 (4.4-6.6)		5.5 (4.4-6.9)	
Outcome prostate biopsy in:	**Year 4**		**Year 4**		**Year 2**		**Year 3**	
no prostate cancer	58 (43%)		101 (47%)		61 (33%)		44 (37%)	
Gleason ≤6	56 (42%)		97 (45%)		100 (54%)		57 (48%)	
Gleason 3+4	15 (11%)		10 (5%)		18 (10%)		12 (10%)	
Gleason 4+3	3 (2%)		5 (2%)		3 (2%)		2 (2%)	
Gleason ≥8	2 (1%)		2 (1%)		4 (2%)		5 (4%)	
>2 cores positive	23 (17%)		25 (12%)		42 (23%)		28 (23%)	
Gleason >6 or >2 cores positive	34 (25%)[a]		34 (16%)		51 (27%)		36 (30%)	
Total	134 (100%)		215 (100%)		186 (100%)		120 (100%)	

*For comparison all men had a biopsy in year 1 and:
Group 1: Non-compliers: no biopsy in year 2 or 3 despite PSA-DT of 3-10 year in year 2 or 3
Group 2: Compliers: no recommendation for biopsy in year 2 or 3
Group 3: Compliers: PSA-DT of 3-10 year in year 2 and a biopsy in year 2
Group 4: Compliers: PSA-DT of 3-10 year in year 3 and a biopsy in year 3
[a]: $p = 0.028$ versus group 2.
PSA-DT = prostate-specific antigen doubling time; Bx = biopsy; IQR: interquartile range.

Compliance with recommendation to discontinue active surveillance

During follow-up 10 men had clinical stage >=T3 of which 2 continued AS (20%), 535 men had a Gleason score >6 at any repeat biopsy of which 96 continued AS (18%), 734 men had >2 cores positive for prostate cancer at any repeat biopsy of which 175 continued AS (24%), and 915 men had a PSA-DT of 0-3 year of which 651 continued AS (71%). The percentage of men continuing active surveillance were lower if a stricter definition was used (figure 3). Of all men who continued active surveillance despite a recommendation to discontinue 329 out of 839 (varying from 245/651 for PSA-DT of 0-3 year to 1/2 for clinical stage >=T3) eventually switched of active surveillance after a median follow-up of 1.0 year after their recommendation to discontinue, and 510 out of 839 are still on active surveillance for a median of 1.7 year.

Men who continued active surveillance, and subsequently had a second repeat biopsy, despite >2 cores positive for prostate cancer or a PSA-DT of 0-3 year more often had a Gleason score >6 (15% and 16% respectively), as compared to men without a recommendation to discontinue (11%, table 2). After correction for other variables and time between biopsies, both a PSA-DT between 0-3 and >2 cores positive on first repeat biopsy were significant predictors of upgrading on the second repeat biopsy (table 3).

Table 2. Outcome of second repeat biopsy in men continuing active surveillance despite protocol advice to switch to active treatment either at the first repeat biopsy (Gleason >6, >2 cores positive) or between first and second repeat biopsy (PSA-DT ≤3 year), compared with men adhering to the protocol (no protocol based reason to discontinue).

	No protocol advice to discontinue	Continuation despite protocol advice		
Biopsies during follow-up		**PSA-DT 0-3 year** [a]	**>2 cores positive with PCa** [b]	**Gleason score >6** [b]
Year 1	1st Bx	1st Bx	1st Bx	1st Bx
Year 2, 3, or 4	2nd Bx	2nd Bx	2nd Bx	2nd Bx
Age at diagnosis, median (IQR)	64.7 (59.8-69.5)	64.5 (60.6-69.9)	65.9 (59.9-70.3)	68.4 (62.1-71.5)
PSA at diagnosis, median (IQR)	5.6 (4.3-7)	5.1 (3.6-6.4)	4.9 (3.5-6.6)	5.6 (5-7.3)
Time from first to second repeat biopsy, median (IQR)	2.2 (1.1-3.0)	1.5 (1.0-2.9)	1.3 (1.0-2.9)	0.5 (0.5-1.9)
Time between PSA-DT 0-3 and second repeat biopsy, median (IQR)	-	1.4 (1.0-2.6)	-	-
Outcome second repeat biopsy				
no PCa	267 (43%)	81 (37%)	4 (12%)	1 (8%)
Gleason ≤6	283 (46%)	103 (47%)	24 (73%)	4 (33%)
Gleason 3+4	45 (7%)	21 (10%)	2 (6%)	6 (50%)
Gleason 4+3	10 (2%)	6 (3%)	1 (3%)	0 (0%)
Gleason ≥8	11 (2%)	8 (4%)	2 (6%)	1 (8%)
>2 cores positive	83 (13%)	12 (5%)	15 (45%)	5 (42%)
Gleason >6 or >2 cores positive	120 (19%)	64 (29%)	18 (55%)	7 (58%)
Total	616 (100%)	219 (100%)	33 (100%)	12 (100%)

[a] In year 1, 2, 3 or 4.

[b] In year 1.

Bx = biopsy; PSA = prostate-specific antigen; PSA-DT = PSA doubling time; IQR = interquartile range; PCa: prostate cancer

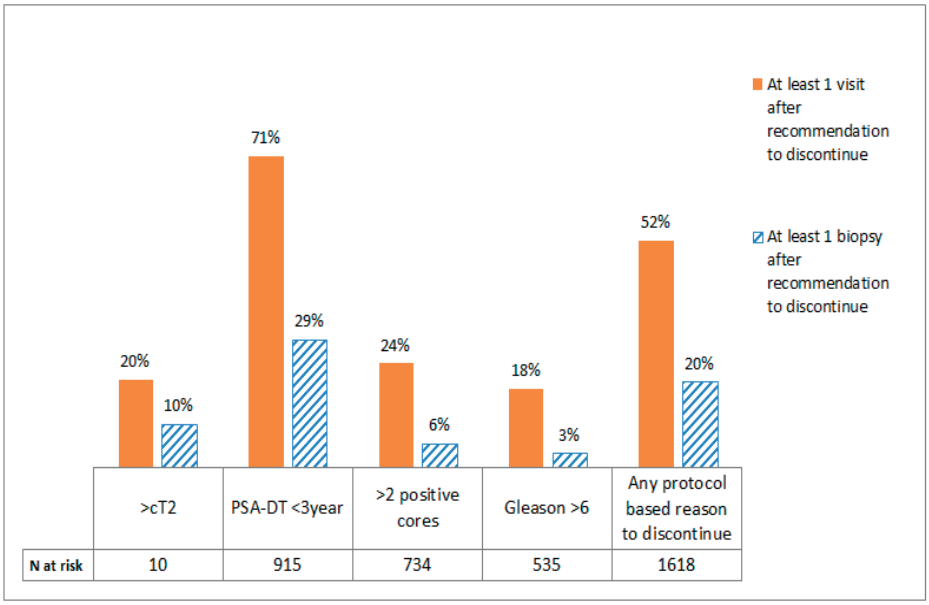


Figure 3. Percentage of men not complying with protocol reasons for discontinuation of active surveillance.

Table 3. Multivariable cox proportional hazards model predicting upgrading (Gleason >6 and/or >2 cores positive) at the second repeat biopsy during follow-up.

	HR (95% CI)	*p*-value
Age first repeat biopsy	1.00 (0.98 – 1.02)	0.9
PSA first repeat biopsy	1.00 (0.93 – 1.07)	>0.9
PSA second repeat biopsy	1.05 (0.99 – 1.11)	0.078
PSA density at diagnosis (0.1 increase)	1.26 (0.88 – 1.82)	0.2
Gleason >6 first repeat biopsy (but continued active surveillance)	3.59 (1.62 – 7.98)	0.002
Number of positive cores first repeat biopsy		<0.001
0	Reference	
1	2.12 (1.48 – 3.03)	<0.001
2	3.19 (2.22 – 4.59)	<0.001
≥3 (but continued active surveillance)	4.32 (2.43 – 7.66)	<0.001
PSA-DT between first and second repeat biopsy		0.002
Always >10 years or negative	Reference	
At least once from 10-3 years	1.45 (1.02 – 2.08)	0.039
At least once from 3-0 years (but continued active surveillance)	2.02 (1.36 – 3.00)	<0.001

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; PSA-DT: PSA doubling time

DISCUSSION

The PRIAS study is currently the largest active surveillance study worldwide. It was aimed to provide a real world representation of active surveillance outside the more strictly controlled academic centers, by including both academic, non-academic and private practices across 17 countries and 4 continents. We observed a substantial proportion of men who did not comply with the repeat biopsies schedule. Especially the yearly biopsies due to a faster rising PSA were often ignored. PSA kinetics were in addition regularly put aside as recommendation to discontinue active surveillance. Both men ignoring the follow-up schedule and criteria for discontinuation of active surveillance were at increased risk of disease upgrading. Although a substantial number still presented with favorable disease characteristics on repeat biopsy.

We observed a clear decrease over time in the percentage of men receiving the standard repeat biopsies, from 81% in the first year, 60% and 53% in the fourth and seventh year, to 33% in the tenth year of follow-up. Although not recorded as standard, several common reasons for not complying with these standard repeat biopsies were recorded. Some examples included "patient does not want biopsy", "PSA stable", "no signs of disease progression on previous biopsy" or "complications on last biopsy". This seems to indicate that the repeat biopsies might put a substantial strain on men. As compared to PSA testing, which was most often strictly complied with, biopsies are considered uncomfortable. In addition, several complications are recorded such as pain, hematuria, or even sepsis (9). These complications will result in some men declining repeat biopsies (10). Furthermore, increasing age (median age at diagnosis, 4, 7, and 10 year was 65.8, 69.5, 72.2, and 76.0 respectively) or previous negative biopsies combined with unchanging PSA values, might reassure both physicians and patients of stable disease which might not become clinically significant. This assumptions seems to be confirmed by biopsy results in men with a negative PSA-DT or a PSA-DT >10 years. In these men a biopsy 4 years after diagnosis showed Gleason score >6 in only 8% (group 2, table 1). This questions whether yearly biopsies for everyone, as used in some active surveillance studies (2, 11, 12), are justified. As active surveillance is primarily aimed at reducing the side effects of aggressive treatment to improve quality of life, one might argue that the small portion of men that might benefit from yearly biopsies does not outweigh the additional burden and its possible reduction of quality of life. Especially in men with a slow rising PSA (PSA-DT negative of >10 years) the risk of upgrading was low, which could trigger some patients and their physicians to switch to a watchful waiting strategy, avoiding further biopsies.

Men with a PSA-DT of 3-10 year do seem to have a higher risk of having higher grade and extent of disease. In year 2 and 3 approximately 30% of men with a biopsy due to a PSA-DT of 3-10 year were upgraded (Gleason >6 or >2 cores positive). Men who ignored the biopsy advise in year 2 or 3 seemed to have a similar rate of upgrading if biopsied

in year 4. This indicates that for 10-15% of men ignoring the recommendation to have a repeat biopsy based on PSA kinetics, upgrading is delayed by 1-2 year. Despite the increased risk, which was published before (1, 13), many men do not have yearly biopsies. It seems important that during theoretical design of active surveillance follow-up schedules, practical adoption and compliance should not be disregarded. Instead we need to develop follow-up schedules that are acceptable to those who follow it. Less harmful ways of monitoring tumor progression, such as MRI (14), might be incorporated in the protocol design to improve compliance. In the PRIAS study we initiated a side study to investigate if replacing yearly biopsies in men with fast rising PSA by MRI with targeted biopsies in case of visible tumor progression could substantially reduce the amount of biopsies (protocol available on www.prias-project.org). Even if such an approach will delay active treatment for some, the reduced strains of follow-up might outweigh the harms.

Of the 4 protocol based recommendations to discontinue active surveillance, a PSA-DT for 0-3 year occurred most frequently. At the same time this was the recommendation most often ignored. More than 70% of men (or perhaps more likely their physicians) did not comply with the recommendation to discontinue active surveillance. More men presented with a Gleason score >6 in this group as compare to men not having a PSA-DT of 0-3 years. The higher risk of upgrading remained after correction for other variables. This correlation between PSA-DT and biopsy outcome was reported before in the PRIAS study (1, 13), but not in another study (15). Differences could be due to variances in study population or to the relatively small numbers in the later study (15). If looked at the outcome on radical prostatectomy of men who did discontinue active surveillance, 29% of men who discontinued due to a low PSA-DT only had unfavorable outcomes (defined as Gleason >=4+3 or cT3-4 disease)(16). Low PSA-DT was also found to be a strong predictor of biochemical recurrence after radical treatment (6). However, despite these higher risks, a substantial part of men still had favorable disease characteristics. As many men might thus be excluded from active surveillance without having true unfavorable disease, and many men and their physicians did not follow the advice to discontinue, the recommendation to discontinue active surveillance if PSA-DT is 0-3 years was removed from the PRIAS protocol as of 2015 (see figure 1 for new follow-up schedule). Instead more frequent (yearly) repeated biopsies, preferably sampling the anterior transition zone, are advised as with a PSA-DT of 3-10 years. If available and MRI with targeted biopsies could be done to rule out large anterior tumors in men with fast rising PSA.

Another recommendation to discontinue active surveillance that occurred frequently and was sometimes ignored was >2 cores positive for prostate cancer. These men had higher rates of Gleason score >6 at repeat biopsy than men with only 1 or 2 cores positive. However, a previous analysis indicated that a substantial part of men had Gleason 6 prostate cancer if subsequently treated with radical prostatectomy (16). As metastasis in men with true Gleason 6 disease, irrespective of tumor volume, seems very rare (17, 18), the

number of cores positive for prostate cancer might currently only function as a surrogate for higher grade disease. If targeted biopsies could (partially) eliminate this undergrading problem, determining the extent of the tumor might become obsolete in the future. In the PRIAS MRI side study the number of cores is therefore omitted as a criterion to recommend active treatment (protocol available on www.prias-project.org).

Outcome in the current analysis was defined as the outcome on repeat biopsy. Although this allows for a comparison of compliers and non-compliers the effect on more definitive outcomes (e.g. prostate specific death) could currently not be assessed, as no such events were reported yet. Longer follow-up is warranted to assess the effect of non-compliance on definitive outcomes.

CONCLUSION

Some men with low risk prostate cancer on active surveillance do not comply with the schedule for follow-up and recommendations to switch to active treatment. Repeat biopsies, especially yearly biopsies in men with fast rising PSA, are often ignored, as is the recommendation to discontinue active surveillance due to a very fast rising PSA. Although these men are at increased risk of having higher Gleason scores on repeat biopsy, the majority still presents favorable tumor characteristics. A fast rising PSA should therefore not be a recommendation to advice active treatment, but should rather serve as a criterion for stricter follow-up. In addition, reducing the amount of yearly biopsies might increase the amount of men complying with the active surveillance protocol.

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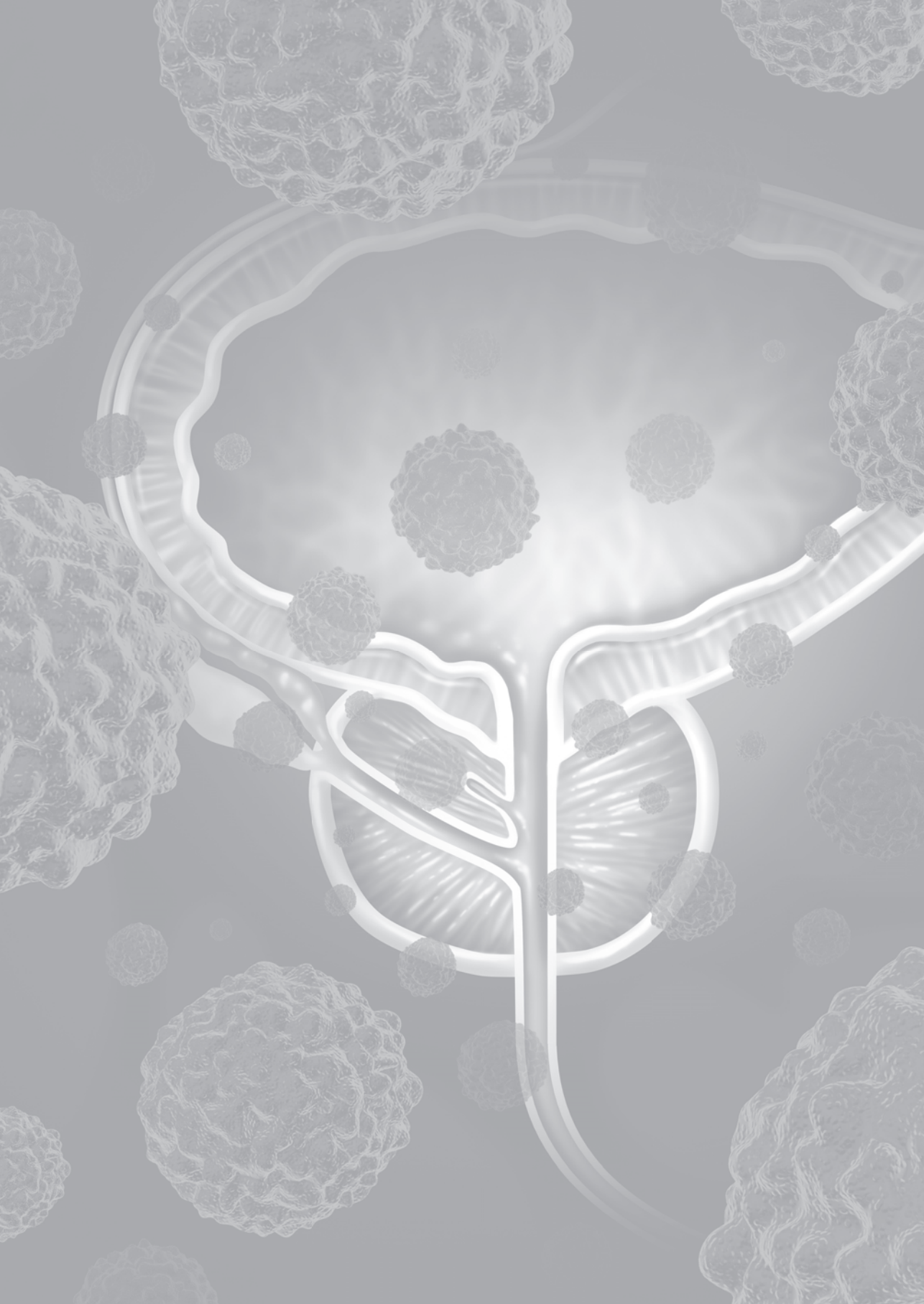

Chapter 8

Risk-stratification based on magnetic resonance imaging and prostate-specific antigen density may reduce unnecessary follow-up biopsy procedures in men on active surveillance for low-risk prostate cancer

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ABSTRACT

Objectives: To assess the value of risk-stratification based on magnetic resonance imaging (MRI) and prostate-specific antigen density (PSA-D) in reducing unnecessary biopsies without missing Gleason pattern 4 prostate cancer in men on active surveillance.

Patients and methods: In all, 210 men on active surveillance with Gleason score 3+3 prostate cancer received a first MRI and if indicated (Prostate Imaging Reporting and Data System (PI-RADS) score ≥3) targeted biopsy (TBx) using MRI-transrectal ultrasonography (TRUS) fusion. The MRI was performed 3 months after diagnosis (group A: n = 97), at confirmatory biopsy (group B: n = 39) or at surveillance biopsy after one or more repeat TRUS-guided systematic biopsies (TRUS-Bx) (group C: n = 74). The primary outcome was upgrading to Gleason score ≥3+4 prostate cancer based on MRI ± TBx in groups A, B and C. Biopsy outcomes were stratified for the overall PI-RADS score and PSA-D to identify a subgroup of men in whom a biopsy could have been avoided as no Gleason score upgrading was detected.

Results: In all, 134/210 (64%) men had a positive MRI and 51/210 (24%) men Gleason score upgrading based on MRI-TBx. The percentage of Gleason score upgrading based on MRI-TBx was 23% (22/97), 23% (9/39) and 27% (20/74) in respectively groups A, B and C. Additional Gleason score upgrading detected by TRUS-Bx occurred in 8% (3/39) of men in group B and 6% (1/17) of men who received TRUS-Bx in group C. No Gleason score upgrading was detected by MRI-TBx in men with a PI-RADS score of 3 and a PSA-D <0.15 ng/ml^2 (n = 15), nor by TRUS-Bx in men with a PI-RADS score of 1 – 3 and PSA-D <0.15 ng/ml^2 (n = 15).

Conclusion: At least one out of five men on active surveillance with Gleason score 3+3 prostate cancer at diagnostic TRUS-Bx show Gleason score upgrading based on first MRI ± TBx at baseline, confirmatory or surveillance biopsy. Men with a PI-RADS score of 1 - 3 and PSA-D <0.15 ng/ml^2 did not show Gleason score upgrading at MRI ± TBx or TRUS-Bx at each time point of surveillance. Thus risk-stratification based on PI-RADS and PSA-D may reduce unnecessary follow-up biopsy procedures in men on active surveillance.

INTRODUCTION

Active surveillance is a widely used strategy for low-risk prostate cancer (PCa) with proven oncological safety at long-term follow-up (1, 2). However, the repeatedly performed transrectal ultrasound-guided systematic biopsies (TRUS-Bx) during follow-up are burdening, causing low compliance and in addition can cause infectious complications (3-5). Follow-up compliance is essential for the oncological safety of active surveillance, thus strategies are needed to reduce unnecessary biopsies. Magnetic resonance imaging (MRI) is increasingly used in men on active surveillance and could help to select those men who need a repeat biopsy. An MRI ± targeted biopsy (TBx) strategy could reduce the number of follow-up biopsies by omitting TRUS-Bx in the absence of suspicious lesions (one third of men on active surveillance) and potentially even MRI-TBx in the absence of radiological progression of a known lesion (6-8). However, little is known of the performance of MRI ± TBx during follow-up after the confirmatory biopsy. It can be hypothesized that the high-grade (Gleason score (GS) ≥3+4) PCa detection rate of MRI ± TBx is low at surveillance biopsy as a significant proportion of men have already been reclassified based on the confirmatory biopsy (2). In addition, MRI ± TBx is known to miss high-grade PCa detected by TRUS-Bx in 4 – 14% of men at confirmatory biopsy (6, 9-16). In the present study we aim to assess the percentage of men with GS upgrading (GS ≥3+4) based on the outcome of MRI ± TBx in our prospective cohort of men on active surveillance who received their first MRI at baseline 3 months after diagnosis, at time of the confirmatory (first repeat) biopsy or at surveillance biopsy after one or more prior repeat biopsies. Furthermore, we stratified biopsy outcomes for the overall Prostate Imaging Reporting and Data System (PI-RADS) score and PSA density, known predictors of GS upgrading, with the aim to selectively identify those men that may not benefit from MRI-TBx and/or additional TRUS-Bx.

PATIENTS AND METHODS

Study population

From November 2013 until November 2016 a total of 216 consecutive men on active surveillance for low-grade (GS 3+3) PCa received a first multi-parametric MRI ± TBx at our tertiary referral center. On request of the referring urologist the MRI ± TBx could be combined with an additional TRUS-Bx. A total of 6 of the 216 men were excluded in the current study, as they had a positive MRI but did not receive MRI-TBx. The remaining 210 men were included in the current study, as the only exclusion criterion was the presence of high-grade (GS ≥3+4) PCa. A total of 111/210 (53%) men were participants of the Prostate cancer Research: International Active Surveillance (PRIAS) study (www.prias-project.org), an international web-based active surveillance study with strict criteria for inclusion at

diagnosis (GS 3+3, T-stage ≤cT2C, PSA ≤10 ng/ml, ≤2 positive cores, PSA density <0.2 ng/ml^2) and follow-up (17). Within the MRI-PRIAS side study an MRI ± TBx is performed at baseline 3 months after diagnosis and during every repeat TRUS-Bx scheduled at 1, 4, 7 and 10 years after diagnosis (Figure 1). Inclusion in the MRI-PRIAS side study is however also possible after one or more repeat TRUS-Bx. The only reclassification criterion in the MRI-PRIAS side study is the presence of high-grade PCa at repeat (targeted) biopsy. The remaining 99/210 (47%) men in the present study had low-grade PCa but were followed-up outside of the PRIAS protocol, as they did not meet the strict PRIAS inclusion criteria (PSA >10 ng/ml and/or >2 positive TRUS-Bx cores) or were referred from a center not participating in PRIAS. All relevant data were included in our prospective, institutional review board approved database.

Multi-parametric MRI

The institutional mpMRI protocol included T2-weighted imaging (T2WI), dynamic contrast-enhanced (DCE) imaging and diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) reconstructions, as previously described (18), according to the PI-RADS version 2 guidelines (19). MRI was performed on a 3-T system (Discovery MR750, General Electric Healthcare, Chicago, USA) using a 32-channel pelvic phased-array coil. All MRIs were reviewed by one urogenital radiologist (IS) with over 4 years of prostate MRI experience at the start of this study. Individual lesions were scored according to the PI-RADSv2 5-point likelihood scale for significant PCa (19). MRIs were classified as positive in cases of one or more PI-RADS ≥3 lesions.

MRI-targeted biopsy

All men with a positive MRI received MRI-TBx. The MRI-TRUS fusion technique was used (UroStation™, Koelis, Meylan, France) to perform MRI-TBx of all suspicious lesions. MRI lesions were targeted with 2 – 4 cores. An additional TRUS-Bx (8 – 12 cores) was performed in all men at confirmatory biopsy and in a subset of men at surveillance biopsy on request of the referring urologist. The biopsy procedures were performed by three operators (AA, F-JD, LB) who had managed approximately 50 cases at the beginning of this study.

Pathological review of biopsy specimens

One expert uro-pathologist (GL) reviewed all biopsy specimens according to the International Society of Urological Pathology (ISUP) 2014 modified GS (20). GS upgrading was defined as any GS ≥3+4 PCa found by MRI ± TBx and/or TRUS-Bx.

Study design

Men were stratified into 3 groups according to timing of the MRI using the MRI-PRIAS follow-up scheme (figure 1); i.e. MRI at baseline 3 months after diagnosis (group A), at

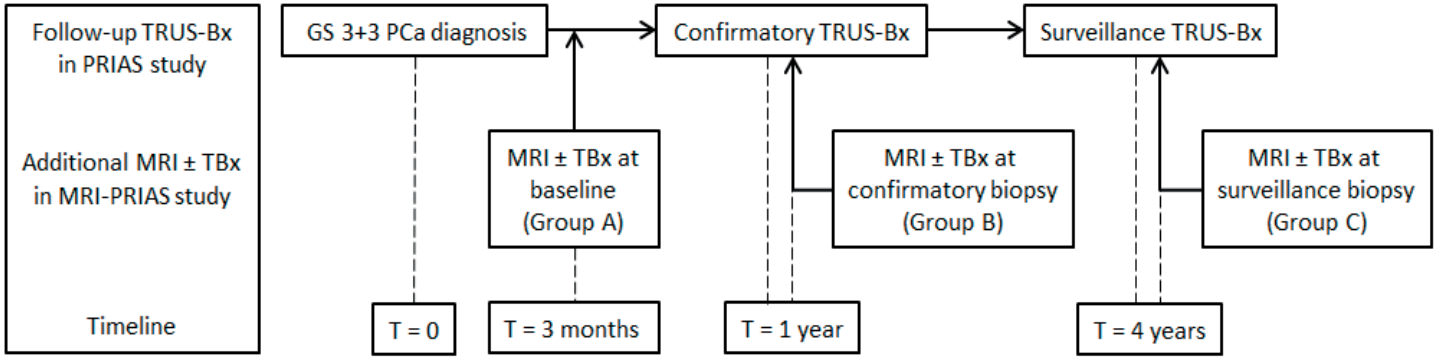

Figure 1. Timeline of repeat biopsies in the classical PRIAS study and MRI's in the MRI-PRIAS side study *TRUS-Bx = transrectal ultrasound-guided systematic biopsy, PRIAS = Prostate Cancer Research: International Active Surveillance, MRI = magnetic resonance imaging, TBx = targeted biopsy, GS = Gleason score, PCa = prostate cancer*

confirmatory TRUS-Bx 1 year after diagnosis (group B) or at surveillance biopsy after one or more prior repeat TRUS-Bx (group C). The primary objective of our study was to compare the percentage of men with GS upgrading based on MRI-TBx in groups A, B and C. The secondary objective was the identification of a subgroup of men, after stratification by PI-RADS score and PSA density, in whom the percentage of GS upgrading based on MRI-TBx is very low or absent. The tertiary objective was the identification of a subgroup of men in whom the percentage of GS upgrading based on TRUS-Bx is very low or absent.

Statistical analysis

Statistically significant differences in continuous patient characteristics at time of diagnosis and at time of MRI were assessed with the Kruskal-Wallis test, while the χ^2 test for trend was used to test for differences in categorical patient characteristics and the GS upgrading rates between groups (A, B and C). In accordance with the Standards of Reporting for MRI-Targeted biopsy studies (START) recommendations cross tabulation of biopsy outcomes was performed in the subgroup of men in groups B + C who received additional TRUS-Bx to compare the percentage of GS upgrading detected by MRI ± TBx *vs* TRUS-Bx (21). MRI-TBx and TRUS-Bx outcomes were stratified for the overall PI-RADS score and PSA density as these parameters are known to be strong predictors of GS upgrading (22-24). The previously described PSA density threshold of 0.15 ng/ml^2 was used for stratification (24-27). Histograms of the stratified biopsy outcomes were constructed to visualize in which subgroup of men GS upgrading did not occur. The PSA density was calculated using the MRI-measured prostate volume. The MRI-measured volume was calculated by the prolate ellipsoid formula (length x width x height x π/6). Statistical tests were two-sided with the criterion of significance set at p <0.05. Statistical analyses were performed with SPSS for Windows (Version 21.0. IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics at prostate cancer diagnosis and at time of MRI

In all, 210 men on active surveillance for GS 3+3 PCa received a first MRI in our institution. The median age and median PSA level at diagnosis of GS 3+3 PCa were respectively 65 years (IQR 60 – 70) and 7.0 ng/ml (IQR 5.2 – 9.6) (table 1). A total of 37/210 (18%) men had more than 2 positive TRUS-Bx cores at diagnosis. A total of 97/210 (46%) men received MRI at baseline (Group A), while 39/210 (19%) men received their first MRI at confirmatory biopsy (Group B) and 74/210 (35%) men at surveillance biopsy (Group C). The percentage of men with only one positive TRUS-Bx core at diagnosis was significantly higher in Group C (65%) as compared to Group A (45%) and Group B (46%). Other patient characteristics at diagnosis did not significantly differ between the groups. At the time of the first MRI, men

Table 1. Patient characteristics at diagnosis of low-grade prostate cancer

Patient characteristics at diagnosis of low-grade prostate cancer										
		Group A MRI at Baseline		**Group B** MRI at confirmatory biopsy		**Group C** MRI at surveillance biopsy			**Total Cohort**	
		median	IQR	median	IQR	median	IQR	*p*-value	median	IQR
Age (yrs)		66.3	60.8 – 71.5	65.1	59.0 – 70.5	63.4	58.1 – 67.8	0.016	65.4	59.2 – 69.5
PSA (ng/ml)		7.2	5.6 – 10.1	6.2	5.3 – 8.6	6.8	4.8 – 9.3	0.122	7.0	5.2 – 9.6
Number of cores at diagnostic TRUS-Bx		9	8 – 12	8	8 – 11	8	8 – 10	0.134	8	8 – 11
		number	%	number	%	number	%	*p*-value	number	%
DRE	T1C	76	78	30	77	63	85	0.446	169	81
	T2A	21	22	9	23	11	15	0.446	41	20
Positive cores at TRUS-Bx	1	44	45	18	46	48	65	0.028	110	52
	2	28	29	11	28	14	19	0.298	53	25
	≥3	21	22	7	18	9	12	0.272	37	18
	Unknown	2	2	2	5	2	3	0.621	6	3
	TURP	2	2	1	3	1	1	0.894	4	2
Total		97	100	39	100	74	100		210	100

PSA = prostate-specific antigen, TRUS-Bx = transrectal ultrasound-guided systematic biopsy, TURP = transurethral resection of the prostate, DRE = digital rectal examination, IQR = interquartile range, MRI = Magnetic Resonance Imaging

in Group C had a significantly higher median PSA level (9.5 ng/ml) as compared to men in Group A (7.7 ng/ml) and Group B (7.1 ng/ml). Men in Group B tended to have a lower median PSA density (0.13 ng/ml^2) as compared to men in Group A (0.18 ng/ml^2) and group C (0.17 ng/ml^2) (table 2).

Percentage of Gleason score upgrading according to the timing of the MRI

A total of 134/210 (64%) men had a positive MRI and a total of 51/210 (24%) men were upgraded to GS ≥3+4 PCa based on MRI-TBx (table 3). The percentage of GS upgrading based on MRI-TBx was similar in Group A (23%, 22/97), Group B (23%, 9/39) and Group C (27%, 20/74). The percentage of GS ≥4+3 PCa found by MRI-TBx was significantly higher in Group C (15%, 11/74) as compared to in Group A (3%, 3/97) and Group B (3%, 1/39). The high-grade tumor was located in the peripheral zone in 39/51 (76%) GS upgraded men and in the transitional zone in 11/51 (22%) upgraded men, while one man had high-grade PCa in both posterior and anterior MRI-TBx.

Identification of a subgroup of men who may not benefit from MRI-targeted biopsy

Figure 2 shows a histogram of GS upgrading based on MRI-TBx stratified for PI-RADS and PSA density. In the group of men with a PSA density <0.15 ng/ml^2 no GS upgrading occurred based on MRI-TBx in case of PI-RADS 3 (n = 15). In case of PI-RADS 4 and a PSA density <0.15 ng/ml^2 3 out of 26 (12%) men showed GS upgrading based on MRI-TBx. In men with PI-RADS 5, the percentage of GS upgrading was high both in case of a PSA density <0.15 ng/ml^2 (83%, 5/6) and a PSA density ≥0.15 ng/ml^2 (74%, 17/23).

Identification of a subgroup of men who may not benefit from TRUS-guided systematic biopsy

Additional GS upgrading (not detected by MRI-TBx) occurred in 3 out of 39 (8%) men who received TRUS-Bx at confirmatory biopsy and 1 out of 17 (6%) who received TRUS-Bx at surveillance biopsy. The cross tabulation of MRI ± TBx outcomes *vs* TRUS-Bx outcomes in men in Group B + C is shown in table 4. The percentage of GS ≥3+4 PCa detected by MRI ± TBx (79%, 15/19) and TRUS-Bx (74%, 14/19) was comparable. In all 10 men who upgraded based on both MRI-TBx and TRUS-Bx positive cores for high-grade PCa of both biopsy approaches were located in the same quadrant of the peripheral zone. Figure 3 shows a histogram of GS upgrading based on TRUS-Bx stratified for PI-RADS score and PSA density <0.15 ng/ml^2. No GS upgrading occurred based on TRUS-Bx in men with PI-RADS 1 – 3 and PSA density <0.15 ng/ml^2 (n = 15).

Table 2. Patient characteristics at time of the first MRI

Patient characteristics at time of the first MRI										
		Group A MRI at Baseline		**Group B** MRI at confirmatory biopsy		**Group C** MRI at surveillance biopsy			**Total Cohort**	
		median	IQR	median	IQR	median	IQR	*p*-value	median	IQR
Age (yrs)		66.5	61.1 – 71.7	66.8	62.2 – 70.9	67.0	61.2 – 71.7	0.860	66.8	61.2 – 71.7
Time since diagnosis (yrs)		0.3	0.2 – 0.4	1.1	0.9 – 1.3	3.7	2.1 – 5.7	<0.001	0.9	0.3 – 2.8
PSA (ng/ml)		7.7	5.5 – 10.0	7.1	5.2 – 8.3	9.5	5.2 – 14.1	0.031	7.8	5.4 – 11.7
Prostate volume (ml)		37.0	28.0 – 58.5	48.0	34.0 – 64.0	47.0	35.8 – 66.0	0.025	45.0	30.8 – 61.0
PSA density (ng/ml^2)		0.18	0.12 – 0.28	0.13	0.08 – 0.24	0.17	0.11 – 0.31	0.081	0.18	0.11 – 0.28
		number	%	number	%	number	%	*p*-value	number	%
DRE	T1C	78	80	28	72	55	74	0.471	161	77
	T2A	12	12	7	18	14	19	0.463	33	16
	≥T2B	7	7	4	10	5	7	0.784	16	8
Total		97	100	39	100	74	100		210	100

MRI = magnetic resonance imaging, PSA = prostate-specific antigen, IQR = interquartile range, DRE = digital rectal examination

Table 3. Biopsy outcomes stratified for timing of the first MRI

	Biopsy outcomes at first MRI								
	Group A MRI at Baseline		**Group B** MRI at confirmatory biopsy		**Group C** MRI at surveillance biopsy			**Total Cohort**	
	number	%	number	%	number	%	*p*-value	number	%
Men receiving MRI ± TBx	97	100	39	100	74	100	/	210	100
Negative MRI (no TBx)	37	38	12	31	27	36	0.719	76	36
No GS upgrading in TBx	38	39	18	46	27	36	0.604	83	40
GS upgrading in TBx	22	23	9	23	20	27	0.791	51	24
GS 3+4 PCa	19	20	8	21	9	12	0.366	36	17
GS ≥4+3 PCa	3	3	1	3	11	15	0.006	15	7
Men receiving additional TRUS-Bx	/	/	39	100	17	100	/	56	100
No additional GS upgrading in TRUS-Bx	/	/	36	92	16	94	0.809	52	93
Additional GS upgrading in TRUS-Bx	/	/	3	8	1	6	0.809	4	7
GS 3+4 PCa	/	/	2	5	0	0	0.342	2	4
GS ≥4+3 PCa	/	/	1	3	1	6	0.538	2	4

MRI = magnetic resonance imaging, TBx = targeted biopsy, TRUS-Bx = transrectal ultrasound-guided systematic biopsy, IQR = interquartile range, PI-RADS = prostate imaging reporting and data system, GS = Gleason score, PCa = prostate cancer

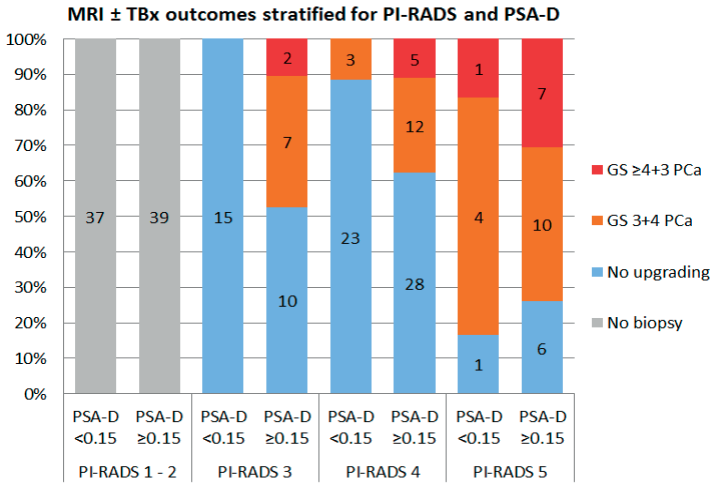

Figure 2. MRI-targeted biopsy outcomes stratified for the overall PI-RADS score and PSA density *MRI = magnetic resonance imaging, TBx = targeted biopsy, PI-RADS = prostate imaging reporting and data system, PSA-D = PSA density, GS = Gleason score, PCa = prostate cancer*

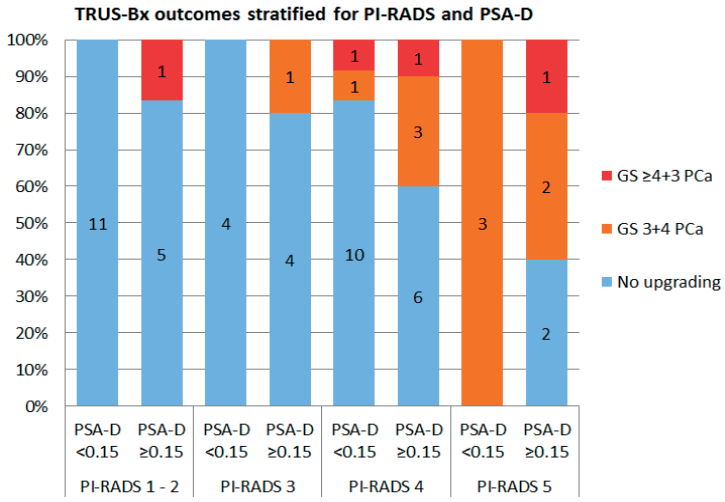

Figure 3. TRUS-guided systematic biopsy outcomes stratified for the overall PI-RADS score and PSA density *TRUS-Bx = Transrectal Ultrasound-guided systematic biopsy, PI-RADS = prostate imaging reporting and data system, PSA-D = PSA density, GS = Gleason score, PCa = prostate cancer*

DISCUSSION

Repeated TRUS-Bx in men on active surveillance are often considered burdening, causing a drastic decline in biopsy compliance with longer follow-up (3, 4). However, compliance with follow-up testing is needed for the detection of initially missed high-grade PCa that has the potential to metastasize. Therefore, strategies are needed to reduce unnecessary biopsies and select only those men who need a repeat biopsy. MRI is increasingly implemented in men on active surveillance and an MRI ± TBx strategy omitting repeat TRUS-Bx could reduce both the number of follow-up biopsies, as well as the number of cores per biopsy procedure. However, MRI ± TBx is known to miss high-grade PCa detected by TRUS-Bx at confirmatory biopsy (6, 9-16). Moreover, a recent study showed a significantly lower percentage of GS upgrading based on MRI ± TBx as compared to TRUS-Bx in a cohort of 103 men at surveillance biopsy (28). In contrast, we surprisingly showed a similar percentage of GS upgrading based on MRI ± TBx after one or more repeat biopsies (27%; group C) as compared to at baseline (23%; group A) and confirmatory biopsy (23%; group B). MRI ± TBx missed high-grade PCa detected by TRUS-Bx in 3 out of 39 (8%) men at confirmatory and 1 out of 17 (6%) men at surveillance biopsy.

The stable percentage of GS upgrading at different time points in our study is consistent with the stable percentage of reclassification (≠GS upgrading) of approximately 25% found at each repeat TRUS-Bx in the PRIAS study (2). The slightly higher percentage of GS ≥3+4 PCa (27%) and significantly higher percentage of GS ≥4+3 PCa (15%) in MRI-TBx in

Table 4. MRI ± TBx *vs.* TRUS-Bx outcomes in the subgroup of men receiving TRUS-Bx

MRI ± TBx *vs.* TRUS-Bx outcomes at confirmatory biopsy (group B)							
		Negative MRI	MRI-TBx				
			No PCa	GS 3+3 PCa	GS 3+4 PCa	GS ≥4+3 PCa	Total
TRUS-Bx	No PCa	4	5	1	**0**	**0**	10
	GS 3+3 PCa	7	2	8	**3**	**0**	20
	GS 3+4 PCa	**0**	**1**	**1**	5	0	7
	GS ≥4+3 PCa	**1**	**0**	**0**	0	1	2
	Total	12	8	10	8	1	39
MRI ± TBx *vs.* TRUS-Bx outcomes at surveillance biopsy (subgroup of group C)							
		Negative MRI	MRI-TBx				
			No PCa	GS 3+3 PCa	GS 3+4 PCa	GS ≥4+3 PCa	Total
TRUS-Bx	No PCa	2	0	0	**0**	**0**	2
	GS 3+3 PCa	3	1	4	**0**	**2**	10
	GS 3+4 PCa	**0**	**0**	**0**	3	0	3
	GS ≥4+3 PCa	**0**	**0**	**1**	0	1	2
	Total	5	1	5	3	3	17
MRI ± TBx *vs.* TRUS-Bx outcomes in all men (group B + subgroup of group C)							
		Negative MRI	MRI-TBx				
			No PCa	GS 3+3 PCa	GS 3+4 PCa	GS ≥4+3 PCa	Total
TRUS-Bx	No PCa	6	5	1	**0**	**0**	12
	GS 3+3 PCa	10	3	12	**3**	**2**	30
	GS 3+4 PCa	**0**	**1**	**1**	8	0	10
	GS ≥4+3 PCa	**1**	**0**	**1**	0	2	4
	Total	17	9	15	11	4	56

MRI = magnetic resonance imaging, MRI-TBx = MRI-targeted biopsy, TRUS-Bx = transrectal ultrasound-guided systematic biopsy, PCa = prostate cancer, GS = Gleason score

group C as compared to in group A and B could be due to (selection for MRI of men with) a higher risk of upgrading, translated by a higher median PSA density. In line with our study, several studies reported MRI ± TBx missing high-grade PCa in 4 - 9% of men on active surveillance (6, 11-16). Two recent studies using an extended 14-core TRUS-Bx scheme even reported a percentage of 12 - 14% of men in whom MRI ± TBx missed high-grade PCa (9, 10). A follow-up strategy with only MRI ± TBx thus inevitably misses high-grade PCa detected by TRUS-Bx. The question is whether the benefit of a reduction of one third of follow-up biopsy procedures and a significant reduction of cores per procedure outweighs the harm of missing a high-grade PCa in 4 - 14% of men at a specific time point during follow-up on active surveillance. Answering this question one has to keep in mind that these missed high-grade PCa might be detected later on during follow-up without missing the window of curability (29). Furthermore, one has to keep in mind that the previously

reported excellent long-term disease-specific survival of men on active surveillance is based on follow-up with TRUS-Bx only (1). This long-term disease-specific survival is not expected to be worse with an MRI ± TBx strategy as the previously reported sensitivity of MRI ± TBx for high-grade PCa (71 - 89%) is at least equal as compared to the sensitivity of TRUS-Bx (63 - 76%) (6, 9, 14-16).

Although MRI seems to be helpful in patient selection for repeat biopsy, solely implementing an MRI ± TBx follow-up strategy does not seem to be sufficient as high-grade PCa would be missed and two thirds of men would still need to be biopsied. Recently, two robust models for the prediction of GS upgrading at repeat TRUS-Bx were presented based on large datasets of men on active surveillance who did not receive MRI (30, 31). A multivariable risk-based approach in the presence of MRI seems the way forward to reduce unnecessary biopsies (18). Walton Diaz et al. presented an acceptably discriminating prediction model (AUC 0.71) incorporating MRI parameters for the prediction of high-grade PCa at confirmatory MRI-TBx + TRUS-Bx (32). In a validation cohort of 85 men this model would have saved 27 – 68% of biopsies, with a corresponding NPV of 91 – 81% for high-grade PCa (15). Satasivam et al. presented a prediction model incorporating MRI and clinical variables with good discriminative ability (AUC 0.85) for GS upgrading at confirmatory TRUS-Bx (11). Validation of this model is needed to prove its ability to reduce unnecessary biopsies. Interestingly, the strongest predictor for GS upgrading in this model is the PSA density. PSA density was already known to be predictive for GS upgrading at repeat TRUS-Bx in the absence of MRI (33, 34). More recently, it was shown that PSA density remains a strong predictor for GS upgrading when combined with the PI-RADS score in men on active surveillance who received MRI (22-24). After stratification for the overall PI-RADS score and PSA density using the previously described cut-off of 0.15 ng/ml^2 (24-27) no GS upgrading was found based on MRI-TBx in men with a PI-RADS score 3 and PSA density <0.15 ng/ml^2, nor at additional TRUS-Bx in men with PI-RADS 1 – 3 and PSA density <0.15 ng/ml^2. In line with our findings Washino et al. showed no GS upgrading based on MRI-TBx + TRUS-Bx in biopsy naïve men with PIRADS 1 – 3 and PSA-density <0.15 ng/ml^2 (27). This suggests that men on active surveillance with PI-RADS 1 – 3 and PSA-density <0.15 ng/ml^2 may not benefit from a follow-up biopsy. Obviously, the percentage of avoided biopsy procedures by omitting repeat biopsy in these men depends on the characteristics of the active surveillance cohort. In our cohort 49% (37/76) of men with PI-RADS 1 – 2 and 44% (15/34) of men with PI-RADS 3 had a PSA density <0.15 ng/ml^2. Hopefully, a robust prediction model incorporating PI-RADS and PSA density will be available in the near future to enable risk-based patient selection for repeat biopsy rather than simply stratifying patients based on these clinical parameters. Such a prediction model could be built from the large dataset of the Movember GAP3 project (35).

While the risk of developing metastasis and PCa death is significantly higher in men on active surveillance with GS 3+4 as compared to GS 3+3 PCa, men with GS 4+3 PCa have

the highest risk of clinical progression with longer follow-up (36). Therefore, active surveillance in men with GS ≥3+4 PCa cannot be considered standard of care yet (37). As in most other institutions, patients in our institution with GS ≥3+4 PCa are generally not enrolled in an active surveillance program and the finding of upgrading to any GS ≥3+4 PCa during follow-up usually means switch to active treatment with curative intent. Nevertheless, the high GS upgrading and/or reclassification rates of men on active surveillance trigger the need to extend the active surveillance inclusion and follow-up criteria and (limited) GS 3+4 disease is nowadays considered suitable for active surveillance by some. In the near future, selection of men with GS 3+4 PCa for active surveillance could be based on the prognostic predictors of clinical disease progression cribriform and/or intraductal carcinoma growth and the percentage of grade 4 disease (20, 38, 39).

A major strength of the present study is that is represents the true clinical setting. Men in our prospective cohort were referred from 8 different peripheral institutions and did not all fulfill the strict inclusion criteria of the PRIAS study (www.prias-project.org). Our study is mainly limited by the fact that only a subgroup of men at surveillance biopsy received an additional TRUS-Bx next to the MRI ± TBx (17/74, 23%), making it hard to draw conclusions from the comparison between both biopsy strategies. However, our findings from this comparison were in line with several previous studies. Furthermore, all men who received a first MRI were included in our study, regardless of time since diagnosis of low-grade PCa. The percentages of GS upgrading based on MRI ± TBx could be different in men who have received a previous MRI ± TBx (22, 23). Finally, multi-parametric MRI used in the present study, consisting of T2WI, DWI and DCE imaging is not yet widely available. Bi-parametric MRI (T2WI + DWI) is more feasible and less expensive and could therefore help to widely implement MRI in men on active surveillance. Within PI-RADS version 2 the DCE images are used to differentiate between PI-RADS 3 or 4 lesions in the peripheral zone (19). Only 4 out of 71 (6%) men in the present study with an overall PI-RADS score 4 would have been classified as having a suspicion score of 3 based on bi-parametric MRI, 3 of whom had high-grade PCa in MRI-TBx. However, as all 4 men had a PSA density ≥0.15 ng/ml^2 the conclusion of the present study (i.e. MRI-TBx may be avoided in men with PI-RADS 3 and PSA density <0.15 ng/ml^2) remains unchanged with the use of bi-parametric MRI.

In conclusion, at least one out of five men with GS 3+3 PCa at diagnostic TRUS-Bx in our present cohort had GS upgrading based on first MRI ± TBx at baseline, confirmatory or surveillance biopsy. Men with PI-RADS 1 - 3 and a PSA density <0.15 ng/ml^2 did not show GS upgrading at MRI ± TBx or TRUS-Bx at each time point of surveillance. Therefore, risk-stratification based on PI-RADS and PSA density may reduce unnecessary follow-up biopsy procedures in men on active surveillance.

Conflict of Interest

None declared.

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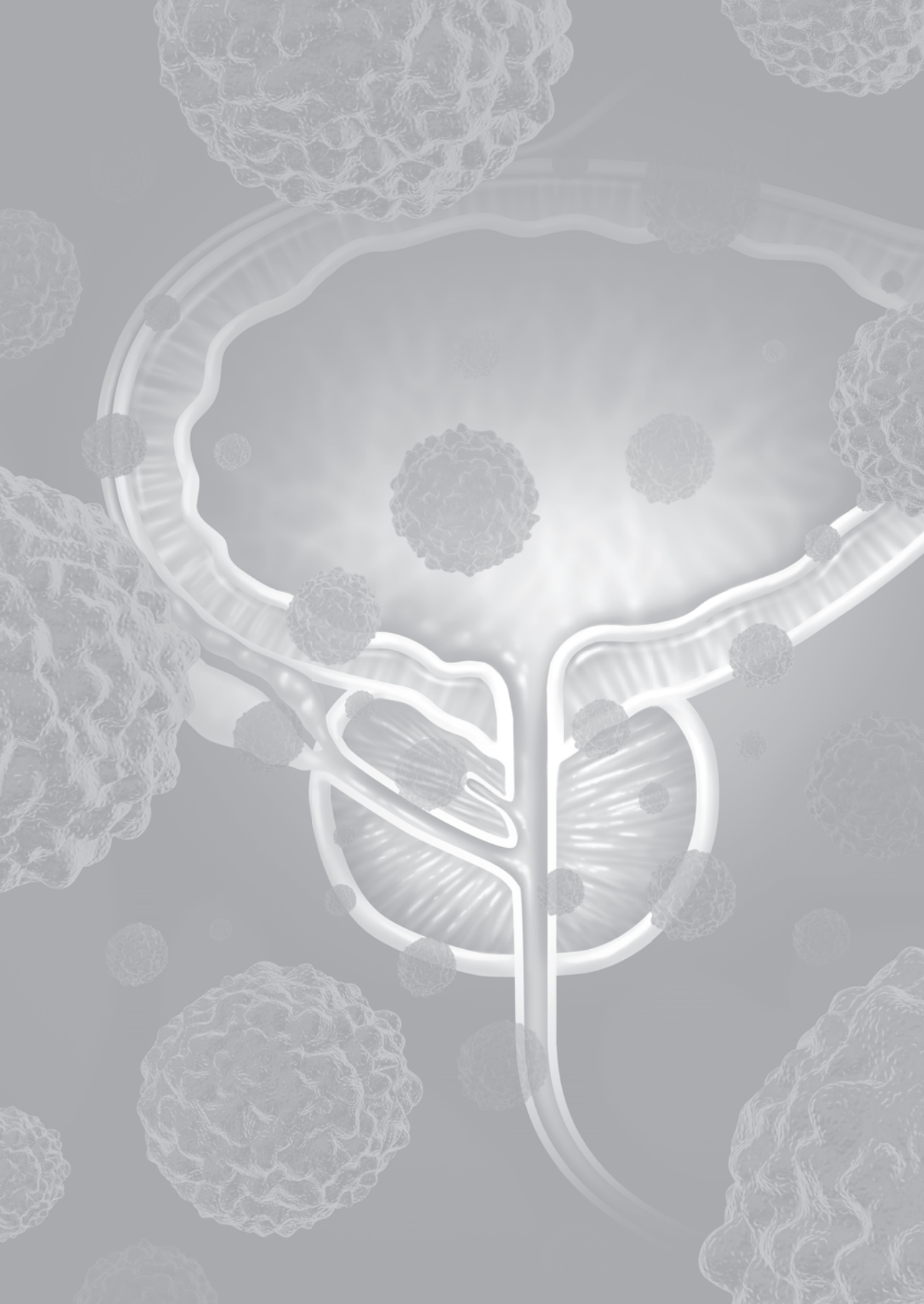

Chapter 9

General discussion

As stated in the introduction section (Chapter 1) there are two main objectives of this thesis. The first objective is to study how a reduction of the harms of PSA-based prostate cancer screening can be established without affecting the benefit (Part 1). The second objective is to study how current protocols on active surveillance can be improved (Part 2). Several research questions regarding these objectives will be answered in this general discussion. In addition, future perspectives will be discussed.

PART 1: CAN WE REDUCE THE HARMS OF PROSTATE CANCER SCREENING WITHOUT AFFECTING THE BENEFIT OF A REDUCTION OF METASTATIC DISEASE AND PROSTATE CANCER MORTALITY?

Can we select those men who may benefit from screening and refrain from screening in those who may not benefit?

Since the introduction of opportunistic PSA-based prostate cancer screening in the early 1990's the incidence of metastatic disease has decreased by half in the United States (1). PSA-based screening reduces the chance of dying from prostate cancer by 50% when comparing men screened multiple times between the age of 55 – 74 years to those men not screened at all (2). The men that truly benefit from screening are those in whom a prostate cancer is detected (and subsequently treated) that otherwise would have certainly caused metastatic disease or death. Looking at the data from the large randomized trials (RCT) it is safe to conclude that most men within the age range 50 – 74 years do not benefit from screening. No less than a 1000 men need to be screened to prevent 1 – 2 prostate cancer deaths and 3 cases of metastatic disease at 13 years of follow-up (3, 4). Lifetime estimates on the basis of the RCT data show that 100 men need to be screened and 5 men need to be diagnosed with prostate cancer to prevent 1 prostate cancer death (5). Ideally, we should only screen those men who will actually benefit and refrain from screening in those who will not, thereby preventing the screening-related harms of unnecessary testing and overdiagnosis. Unfortunately, upfront selection of those men who will benefit from screening is impossible. Besides the fact that we are not able to predict whether someone harbors a prostate cancer with the potential to metastasize before screening that individual, it is impossible to predict whether the events of prostate cancer metastases and death will occur before the competing risk of death from another cause. To date, we are able to identify certain groups of men with an elevated risk of prostate cancer (death) in which PSA-based screening is most likely more beneficial. Examples are men with a positive family history and men from African descent (6-8). Furthermore, we are able to identify men with screen-detected prostate cancer who may (in potential) benefit from the early detection based on the histological characteristics of the tumor and the estimated life expectancy. Due to their potential to cause metastatic disease, Gleason ≥3+4 prostate cancers are often

considered clinically significant. The detection of such clinically significant tumors in men with a life expectancy long enough to develop metastases could be considered a surrogate of benefit of PSA-based screening. Similarly, the detection of a clinically insignificant tumor (often defined as Gleason 3+3 prostate cancer) could be considered a surrogate of overdiagnosis, although a higher-grade tumor component is easily undersampled and grade progression of non-aggressive cancers does occur (9-12). Naturally, the harm of an unnecessary biopsy is evident in case of a benign outcome of that biopsy. The net-benefit effect of PSA-based screening within a specific population can be expressed as the ratio of these surrogates of benefit and harm of screening. Obviously, prostate cancer screening should only be considered in those populations in whom a positive benefit-to-harm ratio could be achieved. This benefit-to-harm ratio is dependent on the weight (or importance) that is adjudged to the benefit and harms of screening. For example, for the individual of 60 years who regards his chance of dying from prostate cancer being reduced by only 20% (i.e. from 3% to 2.4%) as far more important than a 60% chance of being confronted with a prostate cancer diagnosis that in potential would not have hurt him if not detected (with subsequent potential consequences for the quality of life) his benefit-to-harm ratio of PSA-based screening will be positive. Therefore, virtually all international guidelines recommend to engage in the process of shared-decision making when dealing with the individual (Chapter 2).

Improvement of the benefit-to-harm ratio of PSA-based screening on a population level can either be achieved by an increase in benefit or a decrease of the harms. Ideally, prostate cancer screening would reduce the disease-specific mortality to 0% instead of 50%. Although a 0% prostate cancer mortality caused by screening is wishful thinking, the relative mortality reduction achieved in the European Randomized study of Screening for Prostate Cancer may very well be increased by several adjustments to the screening protocol used (in most centers) within this study. Examples of these adjustments will be discussed in detail in the next sections of the general discussion and an optimal screening strategy will be proposed. An increase in the relative reduction of metastatic disease and prostate cancer mortality could be achieved by screening within a wider age range compared to the core age of 55 – 69 years in the ERSPC study (13). Furthermore, an increase in benefit of screening could be established by narrowing the 4 year screening interval as used in most centers in the ERSPC (14). Finally, the benefit of screening could most likely be increased by adjusting the PSA and sextant TRUS-guided systematic biopsy screening algorithm, thereby detecting clinically significant prostate cancer at an earlier stage and hence increase the chance of cure. Additional kallikrein biomarkers next to PSA have the potential to increase the specificity for clinically significant prostate cancer. Also, the sextant TRUS-guided systematic biopsy could be replaced by an extended 12-core TRUS-biopsy scheme and even include MRI-targeted biopsy cores (Chapter 3).

Within which age range should we screen?

The ERSPC provided level 1 evidence for a relative mortality reduction caused by PSA-based screening in the core age group of 55 – 69 years (3). Besides a further improvement in the screening algorithm within this age range it could very well be that outside this age range men can benefit from prostate cancer screening. A recent analysis from the Göteborg trial showed a similar prostate cancer-specific mortality reduction at 17-years of follow-up in men aged 50 - 54 years compared to the ERSPC core age group of 55 - 69 years (13). The age cut-off of 50 years for men at normal risk of prostate cancer (no family history and not from African descent) is already implemented in the prostate cancer screening guidelines of several associations, such as the European Association of Urology and the American Urological Association (Chapter 2). In men aged under 50 years (symptomatic) prostate cancer is rare and there is no direct evidence for a screening-induced mortality reduction within this age category. Nevertheless, as a baseline PSA value in men aged 45 – 49 years has been shown to be predictive of prostate cancer metastases several decades later (15), some guidelines include the measurement of baseline PSA in men at normal risk aged under 50 years (Chapter 2).

Next to the age to start prostate cancer screening, the age to stop is also subject of debate. There is currently still no level 1 evidence for a screening-induced mortality reduction in men aged ≥70 years. As men become older their life expectancy decreases and the benefit that can be achieved by early detection of prostate cancer therefore becomes less. Microsimulation screening analysis (MISCAN) has shown that any benefit of PSA-based screening in men aged ≥70 years is offset by a reduction in their quality of life (5, 16). Nevertheless, men aged ≥70 years, often with multiple comorbidities, are frequently screened in daily practice in the United States (17, 18). In Europe, a similar trend can be observed. A Swedish study in showed a high prevalence (up to 46%) of PSA testing in men aged 70 – 79 years in Stockholm County (19). In the United Kingdom, Italy and the Netherlands PSA testing by general practitioners has been shown to be skewed towards men above 70 years (20-22). As the median life expectancy of Western men still increases and the incidence of aggressive prostate cancer increases with age, some men ≥70 years may benefit from early detection (23-25). As stated previously, this is only the case in men with a life expectancy long enough for a clinically significant prostate cancer to become symptomatic if left untreated. Both the European Association of Urology and the American Urological Association guidelines now state that men with a life expectancy ≥10 – 15 years should be considered for PSA-based screening rather than applying an absolute age criterion (26, 27) (Chapter 2).

The median life expectancy of Dutch men aged 70 years and 75 years is 14.6 years and 11.2 years, respectively (28). The median life expectancy of Dutch men requesting to be screened within this age category may actually be higher than the average median life

expectancy (healthy screenee effect) (29, 30). Therefore, it is safe to state that a large proportion of men aged 70 – 75 in the Netherlands meet the criteria of the European Association of Urology and the American Urological Association guidelines and are eligible for PSA-based screening. In Chapter 3 it was shown that Dutch men within this age category (71 – 75 years) often harbor clinically significant prostate cancer, even after being repeatedly screened. As the median life expectancy of Dutch men aged 80 years is still 8.1 years (28), a highly selected subgroup of Dutch men aged 75 – 80 years might even benefit from screening. Naturally, life expectancy is not just dependent on age but also on comorbidities (31). Unfortunately, the confidence interval of a life expectancy estimation becomes wider as the life expectancy itself increases. The 10 year life expectancy as estimated by clinicians has been shown to be pessimistic and not very accurate (29). The 10 year life expectancy as predicted by available models and calculators unfortunately provides only modest improvement in accuracy and it is unclear whether these models provide any advantages over the available government life tables (29). Moreover, not only the estimated life expectancy but also the quality of life should be taken into account. Finally, the availability of a biomarker with increased specificity compared to PSA, which could help to selectively identify elderly men with aggressive prostate cancer, could significantly increase the net-benefit ratio of screening in men aged ≥75 years.

With which interval should we screen?

In Rotterdam as well as in most other centers within the ERSPC study men were screened with PSA with intervals of 4 years (32). However, in the Swedish section of the ERSPC study men were screened with intervals of only 2 years (33). Screening with 2 year instead of 4 year intervals resulted in a 40% relative reduction of prostate cancers detected in an advanced stage and, on the other hand, an increased detection of low-risk prostate cancers (14). Unfortunately, this cannot be translated directly into an increase in cancer-specific mortality reduction. A rough estimation based on the difference in prostate cancer mortality between the Rotterdam and Göteborg sections of the ERSPC indicates that using a 2 year instead of 4 year screening interval could result in a 10% higher relative cancer-specific mortality reduction (32, 33). Consequently, the EAU guideline recommends a 2 year screening interval in men initially at risk based on the baseline PSA value (26). As clinically significant interval cancers even occur with a 2 year screening interval, one could argue that a 1 year screening interval could provide additional benefit, especially in men with a high baseline PSA. As a treatment delay for up to 1 year in general has a relatively limited effect on the oncological outcome (34), a screening interval shorter than 1 year does not seem to be beneficial. Based on data suggesting it could be safe to prolong the screening interval to up to 8 years in case of a very low baseline PSA (15), the European Association of Urology guidelines panel suggests a risk-based approach to determine the screening interval in men with a low baseline PSA (26). In the optimal screening strategy

within this general discussion, a screening interval of 2 years is proposed. A one year screening interval can be used on indication in case of a high prostate cancer risk but benign outcome on biopsy.

PSA threshold to biopsy

An increase in the detection of clinically significant prostate cancer could be established by lowering the PSA threshold to biopsy (35). In most men in the ERSPC study a PSA cut-off value to biopsy of 3.0 ng/ml was used. However, it was previously shown that a total of 14% and 2% of men with a PSA below 3.0 ng/ml harbor any grade and high-grade (Gleason ≥3+4) prostate cancer, respectively (36). Within a small pilot study in the 10th screening round of the Göteborg trial a total of 11% and 5% of men with a PSA of 1.8 – 3.0 ng/ml had any grade and high-grade prostate cancer, respectively (35). Lowering the PSA threshold to biopsy increases the sensitivity, but also decreases the specificity, meaning that it increases the percentage of unnecessary prostate biopsies (36, 37). Moreover, the ratio between clinically significant and insignificant prostate cancers is more unfavorable as the PSA threshold to biopsy is lower (36). In addition, a large proportion of those clinically significant prostate cancers missed in men with a PSA below 3.0 ng/ml could probably be detected at subsequent screening without losing the window of curability, under the condition that the screening interval is not too wide.

Extended TRUS-biopsy and multiparametric MRI

In the ERSPC study the classical sextant TRUS-guided systematic biopsy was used for the detection of prostate cancer. It is known that clinically significant prostate cancer can be missed due to undersampling by TRUS-guided systematic biopsy. The TRUS-biopsy is especially poor at sampling the anterior, midline and apex region of the prostate (38, 39). Recently, the PROstate MR Imaging Study (PROMIS) showed that the sensitivity of a 10 – 12 core TRUS-biopsy for high-grade (Gleason ≥3+4) PCa in biopsy naïve men was as low as 48% with transperineal template mapping biopsy as the reference standard (40). Adding additional cores to the (sextant) TRUS-biopsy scheme increases the prostate cancer detection but does not necessarily improve the ratio between clinically significant and insignificant prostate cancers detected (41, 42). In Chapter 3 we showed that performing a 12-core TRUS-biopsy instead of a sextant TRUS-biopsy in repeatedly screened men aged 71 – 75 years only increased the low-grade prostate cancer detection, not the high-grade prostate cancer detection. Nowadays, multiparametric MRI is increasingly used due to its high negative predictive value for clinically significant prostate cancer of approximately 90% (40, 43, 44). The previously mentioned PROMIS study showed a significantly higher sensitivity for high-grade (Gleason ≥3+4) prostate cancer of multiparametric MRI in biopsy naïve of 88% compared to a 48% sensitivity of TRUS-biopsy (40). A targeted biopsy can be performed of suspicious lesions on MRI. In a clinical setting, an MRI with targeted

biopsy strategy instead of TRUS-biopsy strategy detects less clinically insignificant prostate cancer, while the detection of clinically significant prostate cancer by an MRI with targeted biopsy strategy is at least equal with fewer biopsy cores needed (45, 46). This was confirmed in a population-based screening setting in Chapter 3: while TRUS-biopsy and MRI with targeted biopsy had a similar sensitivity for high-grade prostate cancer of 79% and 71% respectively, the sensitivity of TRUS-biopsy for low-grade prostate cancer was considerably higher (89%) compared to MRI with targeted biopsy (23%). MRI-targeted biopsy seems to particularly detect more clinically significant prostate cancer in previously biopsied men (45-47). The performance of the MRI-targeted versus TRUS-biopsy strategy in biopsy naïve men is currently investigated in a randomized fashion in the ongoing multicenter PRECISION trial (48). Although MRI and targeted biopsy seems to outperform TRUS-biopsy in a clinical setting (40, 45, 46), most experts agree that MRI-targeted biopsy currently does not replace TRUS-biopsy as it still misses 10 – 20% of clinically significant prostate cancers (40, 45, 46). Therefore, a combined approach of both TRUS-biopsy and MRI-targeted biopsy (in case of a positive MRI) is recommended by the European Association of Urology guidelines panel after the performance of a pre-biopsy MRI (26, 44). However, as shown in Chapter 3 the combined approach of TRUS-biopsy and MRI-targeted biopsy does not only detect 10 – 20% more clinically significant prostate cancer but also drastically increases the detection of clinically insignificant prostate cancer. Nevertheless, the biopsy procedure in the optimal screening strategy of this general discussion consists of a 10 – 12 core TRUS-biopsy combined with an MRI-targeted biopsy in case of suspicious lesions.

Should we continue screening in previously biopsied men?

Naturally, the chance of harboring (clinically significant) prostate cancer decreases after the performance of a biopsy with benign outcome. Whereas 25% of men who received a sextant TRUS-biopsy in the first screening round of the ERSPC Rotterdam were diagnosed with prostate cancer, only 12% of previously biopsied men in round 2 and 15% of previously biopsied men in round 3 harbored prostate cancer (49). Moreover, the ratio between significant and insignificant disease detected is less favorable after a previous negative biopsy. Although 44% of men diagnosed with prostate cancer in the first screening round of the ERSPC Rotterdam had clinically significant disease, the percentage of clinically significant disease in previously biopsied men in screening round 2 and 3 was only 21% and 16%, respectively (49). Similarly, in Chapter 3 we showed that 25% of the previously biopsied men in the fifth screening round of the ERSPC Rotterdam harbored prostate cancer and that only 20% of those prostate cancers were high-grade. Thus, after a previous biopsy the chance of having prostate cancer at repeat biopsy is decreased by approximately 50%, as well as the chance of a detected prostate cancer being clinically significant. This indicates that men should be carefully selected for repeat biopsy. Nevertheless, as some previ-

ously biopsied men still harbor clinically significant prostate cancer, even after 4 previous screens (Chapter 3), repeat screening could be beneficial at least for some of these men. A study from the Rotterdam section of the ERSPC showed a 0.03% prostate cancer mortality at 11 years of follow-up in men biopsied at initial screening, compared to a 0.35% prostate cancer mortality in whole screening arm (50). This suggests that the chance of dying from prostate cancer at 11 years of follow-up is reduced by more than 90% after being biopsied (50). Therefore, the absolute mortality reduction that can be achieved by screening after a previous negative biopsy is limited. This emphasizes the need for a risk-based approach to select those men for repeat screening after a previous biopsy who may still benefit and refrain from screening in those who may not. A recent study using data from the Danish Prostate Cancer Registry showed that the 20 year cumulative prostate cancer mortality in men with a negative initial biopsy and PSA ≤10 ng/ml was only 0.7%, compared to 3.6% and 17.6% in men with a negative initial biopsy and PSA 10 – 20 ng/ml and PSA >20 ng/ml, respectively (51).

Although our understanding of whom may benefit from PSA-based prostate cancer screening has improved over the years, it seems that we have not succeeded up to day to increase the screening-induced benefit without also increasing the harms. All of the previously discussed measures that would increase the detection of clinically significant prostate cancer would also increase unnecessary testing and the detection of clinically insignificant disease. A better approach to improve the benefit-to-harm ratio of PSA-based prostate cancer screening would be to drastically reduce the harms, preferably while maintaining the currently established benefit. This could be achieved by the implementation of multivariable risk-stratification and magnetic resonance imaging.

Can we select those men who need a biopsy using currently available prediction models, thereby avoiding unnecessary biopsies and overdiagnosis?

Multivariable risk-based patient selection for TRUS-biopsy

A screening algorithm with a PSA threshold of 3.0 ng/ml to perform a TRUS-biopsy results in a benign outcome in 60 – 75% of biopsied men (41, 49) and up to half of the detected prostate cancers being clinically insignificant (52). Patient selection for TRUS-biopsy based on their actual risk of (high-grade) prostate cancer, can reduce the percentage of unnecessary biopsies and cause a more favorable significant-to-insignificant ratio of prostate cancers detected. Several prostate cancer prediction models are available (53, 54), the web-based risk calculators from the Prostate Cancer Prevention Trial (PCPT-RC) and the Rotterdam section of the ERPSC (ERSPC-RCs) being well externally validated and most frequently used in daily practice. In addition to PSA, the PCPT-RC includes the digital rectal examination (DRE), age, ethnicity, family history and number of previous negative

biopsies (55). The parameters in the ERSPC-RCs are PSA, DRE, prostate volume (assessed by DRE or TRUS), TRUS and previous biopsy status (56). The ERSPC-RCs have been shown to outperform the PCPT-RC in several external validation studies (57-60), most likely due to the inclusion of prostate volume in the models (61, 62). A meta-analysis showed a significantly higher predictive accuracy of the ERSPC-RC3 as compared to the PCPT-RC with an AUC for TRUS-biopsy detected prostate cancer of 0.79 (95%CI 0.77 – 0.81) and 0.66 (95%CI 0.63 – 0.68), respectively (54). Application of the ERSPC-RC3 doubles the sensitivity of PSA testing (44% instead of 21%) without losing specificity (54). Patient selection for TRUS-biopsy based on a specific risk cut-off for (high-grade) prostate cancer of the ERSPC-RCs has been shown to reduce the percentage of unnecessary biopsy procedures by 20 – 33% in multiple external validation studies (56, 59, 61-67). A screening algorithm with a PSA threshold to biopsy of 4.0 instead of 3.0 ng/ml results in a similar reduction of biopsy procedures but misses considerably more clinically significant prostate cancer as compared to an ERSPC-RC based screening algorithm. Therefore, the Dutch General Practitioners guideline was adapted in 2014, lowering the PSA cut-off for referral to the urologist from 4.0 to 3.0 ng/ml, with the remark that the urologist should risk-stratify before TRUS-biopsy using the ERSPC-RC (68, 69).

Both the PCPT-RC and the ERSPC-RC3 have been updated. The PCPT-RC 2.0 was adjusted for the prediction of low-grade and high-grade prostate cancer (instead of any grade prostate cancer), incorporating the percentage free PSA as a parameter (70). More recently, the ERSPC-RC3 was adjusted for the prediction of low-risk (defined as Gleason ≤3+4 without cribriform and/or intraductal carcinoma) and high-risk (Gleason 3+4 with cribriform and/or intraductal carcinoma or Gleason ≥4+3) prostate cancer, incorporating age in the model (71). In addition, improvements have been made in the biomarker field. Two novel kallikrein assays, the Prostate Health Index (([–2]proPSA / freePSA) × √PSA) and the 4Kscore (panel of total PSA, free PSA, intact PSA and hK2), have been introduced with the intend to avoid unnecessary biopsies in men with a PSA of 2 – 10 ng/ml (72, 73). The PHI and 4Kscore have a similar discriminative ability, although there is a lack of comparative studies up to day (74). Very recently, a novel marker called the IsoPSA was added to the line of kallikrein assays. This structure-based assay detects both known and unknown PSA isoforms and showed promising results in a multicenter cohort of 261 men (75). Although the novel kallikrein markers outperform PSA and have a similar discriminative ability as compared to multivariable risk calculators (75-78), their added value to the prediction of those risk calculators is relatively limited, questioning whether these kallikrein markers are worthy of their additional costs. The inclusion of new genetic markers in prediction models, although potentially even more expensive, may further improve the results of multivariable risk-stratification (79, 80).

Multivariable risk-based patient selection for MRI

Besides avoiding unnecessary TRUS-biopsies, multivariable risk-stratification could also avoid the performance of unnecessary pre-biopsy MRIs. The European Association of Urology guidelines panel recommends to risk-stratify as an initial step before the performance of a pre-biopsy MRI in order to confirm that the clinical suspicion of prostate cancer is grounded (26, 44). In Chapter 3, men in the fifth screening round of the ERSPC Rotterdam were retrospectively stratified based on the ERSPC-RC4. In this repeatedly screened cohort of men aged 71 – 75 years, it was shown that upfront stratification using the ERSPC-RC4 would have avoided no less than 67% of sextant TRUS-biopsies and 65% of pre-biopsy MRIs with 12-core TRUS-biopsies (± targeted biopsies). Although a screening algorithm with upfront risk-stratification and the performance of 12-core TRUS-biopsy would have avoided two-thirds of biopsy procedures and low-grade prostate cancer diagnoses, it also would have missed 29% of high-grade prostate cancers as detected by the performance of MRI and 12-core TRUS-biopsy (± targeted biopsy) in all men. A screening strategy with upfront risk-stratification and the combined performance of MRI and 12-core TRUS-biopsy (± targeted biopsy) is considered the optimal strategy, as it would have avoided two-thirds of biopsy procedures and low-grade PCa diagnoses, missing only 17% of high-grade prostate cancers. The high-grade prostate cancer detection rate with this optimal screening algorithm was higher as compared to a 12-core TRUS-biopsy in all men approach (13% *vs* 12%). In Chapter 4, the ERSPC-RC4 was applied retrospectively to a clinical cohort of 122 previously biopsied men with a sustained suspicion of prostate cancer who received MRI and targeted biopsy in the presence of PI-RADS ≥3 lesions. It was shown that upfront stratification based on the ERSPC-RC4 would have avoided the performance of 51% of pre-biopsy MRIs and 25% of low-grade prostate cancers as detected by targeted biopsy, missing only 10% of high-grade prostate cancer. Due to the higher prostate cancer detection of MRI-targeted biopsy compared to (sextant) TRUS-biopsy, particularly in men with a previous negative biopsy, calibration showed a systematic underestimation of the ERSPC-RC4 of the (high-grade) prostate cancer risk. Therefore, it was concluded that recalibration to a clinical setting with extended TRUS-biopsy and MRI-targeted biopsy could further improve the performance of the model. In chapter 5, the ERSPC-RC3(+DRE) and ERSPC-RC4(+DRE) were recalibrated to the clinical setting based on data from men from Rotterdam and Den Bosch. The recalibrated ERSPC-RC3 and ERSPC-RC4 performed well in a multicenter cohort of 961 men who received MRI and 12-core TRUS-biopsy (± targeted biopsy) with an AUC for high-grade prostate cancer of 0.76 (95%CI 0.71 – 0.80) and 0.74 (95%CI 0.69 – 0.79), respectively. This is in line with a German study showing an AUC for high-grade prostate of 0.81 and 0.76 of the ERSPC-RC3 and refitted ERSPC-RC4 in a cohort of 1015 men who received transperineal template mapping biopsy and MRI-targeted biopsy (81). Therefore, it can be concluded that multivariable risk-stratification with the (recalibrated) ERSPC-RCs could help to avoid unnecessary, costly MRIs. To validate

this finding, the prospective multicenter MR PROPER (MRI of the Prostate with Prior Risk-assessment) study will be conducted in the Netherlands comparing the (high-grade) prostate cancer detection after ERSPC-RC based stratification of TRUS-biopsy with MRI-targeted biopsy, as well as the cost-effectiveness and the quality of life.

Based on the current evidence it can be concluded that multivariable risk-stratification, preferably with the ERSPC-RC, should be performed before selecting men for biopsy in order to reduce overdiagnosis, unnecessary biopsy procedures and even MRI's. Therefore, multivariable risk-stratification is an essential part of the optimal screening strategy as proposed in this general discussion.

Can magnetic resonance imaging help to improve currently available prediction models?

Apart from upfront risk-stratification pre-MRI to avoid unnecessary MRI-scans, multivariable risk-stratification could also be used to avoid unnecessary (targeted) biopsy procedures after the performance of an MRI. Obviously, the added benefit of risk-stratification after the performance of an MRI depends on the degree of risk-stratification (none, based on clinical judgement or multivariable risk-stratification) pre-MRI. Recently, two new prostate cancer prediction models were developed, incorporating the clinical parameters as included in the ERSPC-RCs (PSA, DRE, prostate volume and previous biopsy status) as well as age and the PI-RADS score (81, 82). Van Leeuwen et al. constructed a model based on data of 393 predominantly biopsy naïve men who received transperineal template mapping biopsy (82). The model had an AUC for clinically significant prostate cancer, defined as Gleason ≥3+4 PCa with >5% grade 4 and/or ≥20% cores positive and/or ≥7 mm of prostate cancer in any core, of no less than 0.88 (95%CI 0.85 – 0.92) in the construction cohort and 0.86 (95%CI 0.81 – 0.92) in a validation cohort of 198 men (82). Using a significant prostate cancer risk threshold to biopsy of ≥10% would have avoided 28% of biopsy procedures in their cohort, missing 3% of clinically insignificant prostate cancer (82). Radtke et al. also used the previously mentioned parameters to construct new risk models for any grade and high-grade (Gleason ≥3+4) prostate cancer based on data of 660 biopsy naïve and 355 previously biopsied men who received transperineal template mapping biopsy + MRI-targeted biopsy (81). The risk models of Radtke et al., including PI-RADS and age, performed significantly better than the original ERSPC-RC3 and ERSPC-RC4 (81). However, with decision curve analysis net benefit of these risk models was only observed beyond the ≥10% risk threshold for high-grade prostate cancer (81). In Chapter 5, we constructed MRI-ERSPC-RCs based on data of 504 biopsy naïve and 457 previously biopsied men from 5 institutions in Germany and the Netherlands who received MRI and 12-core TRUS-biopsy (± targeted biopsy). Unlike the newly developed models in the previously mentioned studies (81, 82), the MRI-ERSPC-RCs were constructed by augmenting the already multiple validated original ERSPC-RCs. After recalibration, the linear predictor

of the original ERSPC-RCs was included as a covariate together with the PI-RADS score and age. In accordance with the risk models of Radtke et al. (81), the MRI-ERSPC-RCs performed significantly better than the original ERSPC-RCs: the AUC for high-grade PCa was 0.84 (95%CI 0.81 – 0.88) and 0.85 (95%CI 0.81 – 0.89) for the MRI-ERSPC-RC3 and MRI-ERSPC-RC4 respectively, compared to an AUC of 0.76 (95%CI 0.71 – 0.80) and 0.74 (95%CI 0.69 – 0.79) for the original ERSPC-RC3+DRE and ERSPC-RC4+DRE, respectively. Moreover, decision curve analysis showed clear net benefit of the MRI-ERSPC-RCs, proving their ability to avoid unnecessary biopsy procedures even after risk-stratification pre-MRI with the original (recalibrated) ERSPC-RCs. Using a ≥10% high-grade prostate cancer risk threshold of the MRI-ERSPC-RCs to biopsy would have avoided 25% of biopsy procedures in our multi-institutional cohort of 961 men, missing 4% of high-grade prostate cancers. External validation of the MRI-ERSPC-RCs is needed before application in daily clinical practice.

Conclusion

In PSA-based prostate cancer screening a positive benefit-to-harm ratio is mandatory. Improvement in this benefit-to-harm ratio can be achieved either by increasing the benefit or reducing the harms. Increasing the benefit (i.e. reducing the incidence of metastatic disease and cancer-specific mortality) could be achieved by a wider age range to screen (i.e. 50 – 75 years instead of 55 – 69 years for men at normal risk), screening more intensely (i.e. narrowing the screening interval), use of a lower PSA threshold to biopsy or new kallikrein markers (i.e. PHI, 4K-score or IsoPSA), or increasing the clinically significant prostate cancer detection of the biopsy (i.e. increasing the number of biopsy cores or targeting the cores). Unfortunately, measures to improve the benefit of prostate cancer screening usually also increase the harms (i.e. unnecessary testing and overdiagnosis of clinically insignificant disease). On the other hand, certain measures to reduce the harms of screening, such as stopping screening in men with a life expectancy less than 10 years and stricter selection of previously biopsied men for repeat screening and biopsy, do not necessarily reduce the benefit of screening. The optimal screening strategy as proposed in this general discussion (figure 1) includes upfront multivariable risk-stratification followed by multiparametric MRI and the combined performance of TRUS-biopsy and MRI-targeted biopsy (in the presence of PI-RADS ≥3 lesions), as it significantly reduces the harms of screening without affecting the benefit. Multivariable risk-stratification after MRI may in potential add to this screening algorithm.

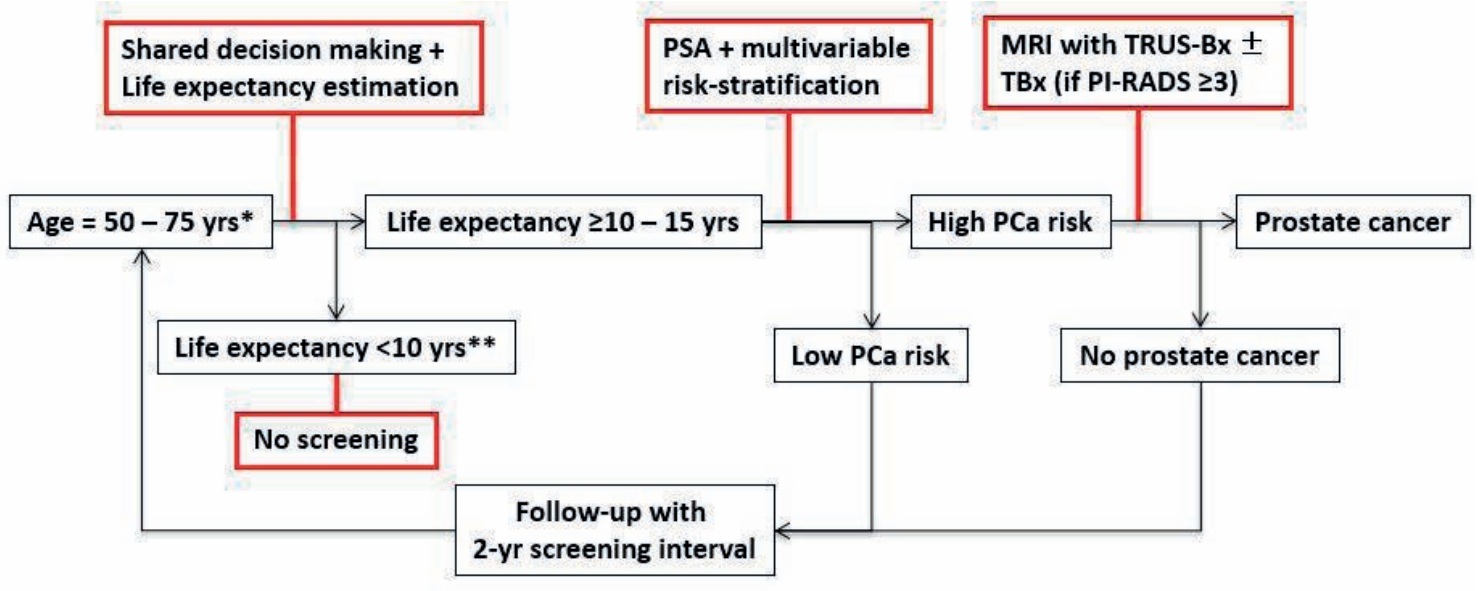

Figure 1. Screening strategy with measures to reduce the harms without affecting the benefit *PCa = prostate cancer; TRUS-Bx = transrectal ultrasound-guided systematic biopsy; TBx = targeted biopsy; PI-RADS = Prostate Imaging Reporting and Data System; *in highly selected men aged <50 years (familial predisposition, African descent) or aged >75 years (with life expectancy ≥10 years) screening can be beneficial; **life expectancy estimation is based on either a calculator or government life table ***measures to reduce the harms of screening, without affecting the benefit, are shown in a text box with red outline.*

Future perspectives

The European Association of Urology guidelines still only recommend a pre-biopsy MRI in men with a sustained suspicion of prostate cancer after a previous negative biopsy (26, 44). Nevertheless, some expert group are already in favor of performing a pre-biopsy MRI in biopsy naïve men (40, 48). Drawbacks of performing a pre-biopsy MRI in biopsy naïve men are the additional costs, as well as a current lack of logistical capacity and radiologists and urologists with expertise in prostate MRI and targeted biopsy. One modelling study from Nijmegen suggested that a diagnostic pathway with pre-biopsy MRI and in-bore targeted biopsy instead of a TRUS-biopsy driven diagnostic pathway could be cost-effective in the Netherlands (83). A more recent modelling study from the same group suggested that an MRI-TRUS fusion biopsy diagnostic pathway, compared to a TRUS-biopsy and in-bore targeted biopsy pathway, is the most cost-effective (84). Although adding MRI and fusion targeted cores to the TRUS-biopsy increases the costs of the diagnostic procedure, the improved accuracy of the diagnosis would result in cost-effectiveness of the diagnostic pathway (84). It must be stated that the outcomes of these modelling studies are very dependent on the input of the models (i.e. assumptions), such the costs for a multiparametric MRI. In the Netherlands, the costs for a multiparametric MRI of the prostate are currently only €317,- (as per January 2017) (84), whereas the costs of a multiparametric MRI in the United States are considerably higher. The costs of prostate MRI can be reduced by performing bi-parametric (T2-weighted imaging and Diffusion Weighted Imaging) instead of multiparametric MRI, as the dynamic contrast-enhanced images add little to the diagnostic accuracy of the multiparametric MRI (85). Naturally, the costs of an MRI-TRUS fusion biopsy diagnostic pathway (as well the TRUS-biopsy pathway) can be substantially reduced by upfront multivariable risk-stratification. The reduction of unnecessary MRIs and biopsies achieved by multivariable risk-stratification is probably approximately 33% in a clinical setting with biopsy naïve men, up to 50% in a clinical setting with previously biopsied men (Chapter 4) and even 66% in a population-based setting with repeatedly screened men (Chapter 3). The lack of logistical capacity and expert radiologists and urologists are perhaps even larger drawbacks than the costs associated with the performance of a pre-biopsy MRI in all biopsy naïve men. The equipment for an MRI-driven diagnostic pathway (i.e. MRI-scanners and fusion biopsy devices) is not yet widely accessible globally and should be expanded in those centers that already implement these techniques. The radiologists and urologists with expertise in multiparametric MRI and targeted prostate biopsy are still relatively scarce and for a drastic increase in the demand of expertise large scale training programs will have to be conducted. The European Association of Urology is currently initiating such a training program for urologists in collaboration with experts from University College London Hospital. Thus, although there are reasonable drawbacks of an MRI-driven diagnostic pathway, these drawbacks can be overcome at least partially.

The pre-biopsy MRI is here to stay and will be increasingly implemented in the near future, not only in previously biopsied men but also in biopsy naïve men.

Another subject of debate is whether PSA-based prostate cancer screening will continue to be conducted in the opportunistic setting or whether organized PSA-based screening should be implemented in the (near) future. It has become clear that opportunistic PSA-based screening as conducted in current clinical practice is relatively ineffective, despite the fact that the drawbacks of screening are well known (16, 86). An analysis from the Göteborg trial showed an increasing incidence of prostate cancer caused by both opportunistic and organized screening, but an opportunistic screening-induced relative disease-specific mortality reduction of only 12% compared to 42% for organized screening (87). Opportunistic PSA-based screening results in significantly more overdiagnosed prostate cancers, with almost twice the number of men needed to be diagnosed (23 *vs* 13) to avoid one prostate cancer death (87). The ineffectiveness of opportunistic screening is caused by the fact that it is often not according to best protocol as provided by the evidence. A systematic review showed a large variation in the degree of follow-up (i.e. repeat PSA testing) by general practitioners after a normal PSA test internationally (88). In the Netherlands, follow-up PSA testing by general practitioners after an initial normal PSA (<4.0 ng/ml) has been shown to be as low as 19% (22). Similarly, only 52% of Dutch men with an elevated initial PSA (4 – 10 ng/ml) at the general practitioner receive a follow-up test (22). Perhaps most importantly, men with an elevated PSA are often not referred by the general practitioner to the urologist (for prostate biopsy), both in the Netherlands and internationally (22, 88). Finally, wide scale opportunistic screening takes place internationally of men with little or no chance of benefit based on their age and comorbidities (17-21). In the Netherlands, half of men who receive an initial PSA test is aged ≥70years, of whom half are aged ≥80 years (22). The screening of older men with comorbidities is one of the important reasons for loss in quality-adjusted life years (QALYs) and thus low net benefit op PSA-based opportunistic screening in Microsimulation screening analysis (MISCAN) (16). The only way to improve the poor benefit-to-harm ratio of current widespread opportunistic screening is to make sure that screening will be performed in an organized fashion according to a protocol based on the best available evidence. Although offering PSA-based prostate cancer screening in an organized setting is controversy, the fact that the US Preventive Services Task Force (USPSTF) recently changed their level-D recommendation (89) (i.e. recommendation against screening) on prostate cancer screening to a level-C recommendation (90) (i.e. individualized decision making on screening) may indicate a changing landscape. Practically, organized PSA-based screening would mean removal of screening from the office of the general practitioner (and urologist) and transferring it to specialized facilities (despite the logistical and financial drawbacks associated). Whether such organized screening should then be available only for those who

choose to be screened (after the process of shared decision making) or be actively offered in a population-based program is another subject of debate. At 13 years of follow-up, the number needed to screen and number needed to diagnose to prevent one prostate cancer death in the ERSPC study is 781 and 27 respectively (3), which is below the number needed to screen in breast cancer trials (91). On a life time basis, an estimated total of 100 men need to be screened and 5 men need to be diagnosed to prevent one prostate cancer death (5). Microsimulation SCreening Analysis (MISCAN) based on the ERSPC data showed that a population-based screening program could be cost-effective when limited to two or three PSA screens (with subsequent sextant TRUS-biopsy if elevated) between the ages of 55 – 59 years (92). However, the estimated relative cancer-specific mortality reduction on a lifetime basis with this screening strategy was only 13% (92). New modelling studies, estimating the benefit-to-harm ratio and cost-effectiveness of PSA-based screening when taking into account multivariable risk-stratification and multiparametric MRI, can help determine whether a Dutch population-based prostate cancer screening program is indicated in the (near) future. A setting in which regional care paths are transparent, shared by all levels of health care including general practitioners, and followed within a quality control program, might be the optimal feasible setting for exploring the level of implementation and the outcome of prostate cancer screening (93, 94). There is opportunity to follow this idea in the years to come.

PART 2: CAN WE IMPROVE CURRENT PROTOCOLS ON ACTIVE SURVEILLANCE FOR CLINICALLY INSIGNIFICANT PROSTATE CANCER?

Can we selectively identify those men who are suitable for surveillance based on magnetic resonance imaging and the prostate cancer growth pattern?

Active surveillance is a strategy to reduce overtreatment of tumors with a low potential of causing morbidity and/or mortality if left untreated, thereby improving the quality of life of men diagnosed with low-risk prostate cancer (95, 96). Nowadays, over 40% of men with low-risk prostate cancer in the US are enrolled in an active surveillance program (97). In Sweden, the use of active surveillance in men with very low-risk prostate cancer increased from 57% in 2009 to 91% in 2014 (98, 99). Similarly, the use of active surveillance in Swedish men with low-risk prostate cancer increased from 40% in 2009 to 74% in 2014 (98, 99). Active surveillance has been shown to be a safe strategy for carefully selected men. The disease-specific survival of large cohorts with long-term follow-up from Toronto and Johns Hopkins (US) was 98 – 100% and 94 – 99% at 10 years and 15 years of follow-up, respectively (100, 101). The global Prostate cancer Research International: Active Surveillance (PRIAS) study, coordinated from the Erasmus University Medical Center, is the largest observational active surveillance cohort worldwide. To date, PRIAS has included over

6.500 patients in over 20 countries. Also in PRIAS, an excellent 10 year disease-specific mortality (<1%) is observed (102). Apparently, within the available follow-up data men who harbor disease with metastatic potential are adequately filtered out after diagnosis (patient inclusion) or during follow-up using eligibility criteria for surveillance. According to most guidelines and protocols men with a T-stage ≤2, a Gleason score 3+3 with ≤2 positive biopsy cores and a PSA <10 ng/ml are suitable for active surveillance (103). Unfortunately, many newly diagnosed prostate cancer patients do not meet these strict eligibility criteria, although only a subgroup would develop metastatic disease if left untreated. Furthermore, although initially considered suitable for surveillance, many men experience disease reclassification during follow-up and have to switch to active therapy after all.

In the Toronto and Johns Hopkins cohort the disease reclassification rates were 24 – 35% and 36 – 49 % at 5 and 10 years of follow-up, respectively (100, 101). In PRIAS, no less than 60% of men initially considered suitable for surveillance has received some form of active treatment after 10 years of follow-up (102). A substantial proportion of 10 – 20% of men in these large active surveillance cohorts reclassify at confirmatory biopsy only one year after diagnosis (100-102). Although disease reclassification on follow-up biopsy is the most common trigger for active treatment, other triggers are PSA-kinetics and patient choice, often driven by anxiety (104).

The fact that a high percentage of men is not considered suitable for active surveillance at diagnosis or reclassifies early during follow-up indicates the need of more flexible eligibility criteria. In general, the eligibility criteria could be broadened by the inclusion of higher volume Gleason 3+3 disease and/or higher-grade (i.e. Gleason ≥3+4) disease.

Retrospective studies have shown that "true Gleason 3+3 disease", i.e. Gleason 3+3 prostate cancer according to the ISUP 2014 modified Gleason score on radical prostatectomy specimen, virtually does not metastasize and therefore does not cause disease-specific mortality (105-107). Therefore, active treatment of "true Gleason 3+3 disease" with curative intent, regardless of the tumor volume, could be regarded as overtreatment per definition. Unfortunately, the diagnosis of "true Gleason 3+3 disease" can only be ascertained with certainty after a radical prostatectomy has been performed. Up to now, treatment selection (i.e. active surveillance or active treatment with curative intent) is often only based on the histological outcome of the TRUS-guided systematic biopsy, although upgrading of the TRUS-biopsy Gleason score on radical prostatectomy specimen occurs in 25 – 40% of cases (108-110). The multi-parametric MRI can help to improve the correlation between the biopsy Gleason score and the "true Gleason score" by guiding the biopsy operator to the location of the tumor. This can result in a more accurate characterization of the tumor at diagnosis, and thus a better selection of men who are suitable for active surveillance. In Chapter 8, a total of 23% of men who were originally considered suitable for active surveillance based on the diagnostic TRUS-biopsy Gleason score 3+3 was reclassified (Gleason score ≥3+4) based on a baseline MRI ± targeted biopsy. The improved patient selection

for surveillance by the performance of a baseline MRI ± targeted biopsy and inherent reclassification of a subgroup of men results in a higher percentage of men who remain on surveillance during follow-up. The high NPV (approximately 90%) of multi-parametric MRI for high-grade disease tackles the sampling error of the diagnostic TRUS-biopsy (109). Proportionally, reclassification during follow-up will more often be caused by the relatively rare phenomenon of true grade progression (1 – 3% per person per year) (10, 11). The partial elimination of the TRUS-biopsy sampling error by the performance of MRI ± targeted biopsy allows to no longer use tumor volume (i.e. number of positive biopsy cores; percentage of biopsy core involvement) of Gleason 3+3 disease as a surrogate for higher grade disease. Thus, a baseline MRI ± targeted biopsy can early identify men with higher-grade disease who are not suitable for surveillance, but on the other hand can confirm suitability of men with high-volume Gleason 3+3 disease. A baseline MRI ± targeted biopsy is already recommended by the UK NICE guideline and should be performed, if accessible, in all men with Gleason 3+3 disease on diagnostic TRUS-biopsy who are considered for active surveillance.

As indicated earlier, more men could be considered for active surveillance if Gleason score 3+4 disease would not be a strict exclusion criterion. In the ProtecT trial men were randomized between active monitoring, surgery and radiotherapy, regardless of their biopsy Gleason score, with an allocation of approximately 550 men in each treatment arm (111). A total of 23% of men in the ProtecT study had biopsy Gleason ≥3+4 disease (111). Data from this RCT show that twice as many men in the active monitoring arm developed metastatic disease at a median follow-up of 10 years as compared to the surgery and radiotherapy arm (111), indicating that active surveillance is usually not the preferred treatment strategy in men with Gleason ≥3+4 prostate cancer. This is confirmed by long-term follow-up data from the Toronto active surveillance cohort which includes a total of 128 men (out of 945) with Gleason 3+4/4+3 disease due to less stringent inclusion criteria at the beginning of their study (112). The cumulative incidence of metastatic disease at 15 years of follow-up in men with Gleason 3+4 and 4+3 disease was no less than 16% and 37%, respectively (112). Based on these data active surveillance in all men with TRUS-biopsy Gleason 3+4 prostate cancer is not to be recommended, let alone in men with Gleason 4+3 disease. Nevertheless, some men with (limited) Gleason 3+4 prostate cancer might be good candidates for surveillance. Gleason grade 4 disease is heterogeneous, consisting of various histological growth patterns (ill-formed, fused, cribriform and glomeruloid) (113). Apart from the percentage of grade 4 disease, both the cribriform growth pattern (114-118) as well as intraductal carcinoma (IDC) (118-123) have been shown to be associated with poor clinical outcome after treatment compared to the other grade 4 growth patterns. Retrospective analysis of men in the ERSPC Rotterdam first screening round showed a comparable 15-year cancer-specific survival of men with biopsy Gleason 3+3 disease

(99%) and men with biopsy Gleason 3+4 disease without cribriform/intraductal growth (96%), while a significantly poorer 15-year cancer-specific survival of 85% was observed in men with Gleason 3+4 disease and cribriform/intraductal growth (124). In chapter 6, the percentage of cribriform/intraductal growth was significantly higher in the Gleason score reclassified men (after pathological revision) in the ERSPC Rotterdam first screening who died of the disease (63%) as compared to those who did not die of the disease (13%). Moreover, the median percentage of Grade 4 disease in the Gleason score reclassified men who died of the disease was also higher (16%) compared to those who did not die of the disease (8%). Therefore, biopsy Gleason 3+4 prostate cancer without cribriform/ intraductal growth and a low percentage of grade 4 disease (≤10%) could be considered favorable Gleason 3+4 prostate cancer, and hence suitable for active surveillance. As of 2012, the PRIAS study allows for the inclusion of men with minimal Gleason 3+4 disease (≤10% core involvement) if aged ≥70 years.

In conclusion, it seems that we have taken some steps in improving patient selection for active surveillance by the use of baseline MRI and identification of favorable Gleason grade 4 growth patterns. Hopefully, long-term follow-up data will confirm this improved patient selection by showing lower disease reclassification rates or even higher disease-specific survival rates as compared to current TRUS-biopsy based data.

Do men on active surveillance comply with current strict follow-up protocols, including repeated biopsies, and if not, what are the reasons for non-compliance?

Most guidelines and protocols on active surveillance recommend repeated PSA measurements every 3 – 6 months during follow-up, a confirmatory TRUS-biopsy within the first year after diagnosis and a surveillance biopsy every 1 – 3 years afterwards (103). Triggers for disease reclassification in most protocols are a PSA-DT <3 years, >2 positive biopsy cores and/or Gleason score ≥3+4 prostate cancer (103). In Chapter 7, the compliance with the follow-up protocol of the PRIAS study was analyzed. The compliance with PSA testing was persistently high (>90%) during follow-up, presumably due to the non-invasive characteristics of the PSA test. In contrast, a drastic decline of the compliance with protocol-based follow-up biopsies was observed over time, from 81% at confirmatory biopsy to only 33% at surveillance biopsy 10 years after diagnosis. The low biopsy compliance is probably due to the invasive features of the prostate biopsy and could be either driven by patient, doctor or both. Complaints caused by a previous biopsy, such as hematuria, hematospermia and pain, certainly effect the compliance at follow-up biopsy (125). An analysis from the PRIAS study showed that men who have experienced complaints at diagnostic or first repeat biopsy more often do not comply with a follow-up biopsy (21%) compared to men without complaints at prior biopsy (12%) (125). Reassuring PSA-values

and pathological outcome at prior biopsy can also trigger both the patient and doctor not to comply with a protocol-based follow-up biopsy. Anyhow, the low biopsy compliance during follow-up seems to indicate that repeat biopsies are considered burdening for patients and that strategies are needed to safely reduce the number of follow-up biopsies in order to increase adherence to the protocol. That being said, the long-term cancer-specific survival in PRIAS (>99% at 10-yr of follow-up) can already be regarded as excellent despite the low biopsy compliance, questioning the importance of follow-up biopsies in general. Follow-up biopsies may even be of less importance after improved patient selection for surveillance by the performance of a baseline MRI (± targeted biopsy).

Similar to the low compliance with follow-up biopsies, the compliance with the recommendation to discontinue surveillance based on a PSA-DT <3 years in the PRIAS study was poor (29%), although these men were at higher risk of disease reclassification. The compliance with the recommendation to discontinue surveillance based on >2 positive biopsy cores was substantially higher (76%). Together, the PSA-DT <3 years and >2 positive cores recommendations comprised more than 50% of all recommendations to switch to active treatment in the PRIAS study. Nevertheless, approximately 50% of these men still harbor "true Gleason 3+3 disease" on radical prostatectomy (102), indicating that these recommendations to trigger active treatment are far from perfect. Therefore, the PRIAS protocol was adapted stating that these recommendations (i.e. PSA-DT <3 years and >2 positive cores) should trigger an MRI ± targeted biopsy (inclusion in the MRI side study) instead of immediate active treatment with curative intent. The number of biopsy cores positive for Gleason 3+3 disease is no longer restricted in men on surveillance as long as an MRI ± targeted biopsy has been performed.

Can we selectively identify those men who need a follow-up biopsy using magnetic resonance imaging, avoiding unnecessary biopsies in men at low risk of reclassification?

As previously indicated, strategies are needed to safely reduce the number of follow-up biopsies, thereby increasing protocol adherence. Ideally, we should only perform a follow-up biopsy in men with an elevated risk of disease reclassification and refrain from follow-up biopsies in men at low-risk. The multi-parametric MRI can help to identify men with an elevated risk of disease reclassification by detecting lesions suspicious for high-grade prostate cancer. A strategy with the performance of only MRI ± targeted biopsy, omitting follow-up TRUS-biopsies, could avoid follow-up biopsy procedures in the approximately 33% of men on active surveillance who do not harbor a cancer-suspicious lesion on MRI (109). However, an MRI ± targeted biopsy strategy is known to miss approximately 10% of high-grade prostate cancers detected by TRUS-biopsy and therefore does not seem to be sufficient (126-133). A better strategy would be to risk-stratify based on both MRI and clinical parameters and to perform only a follow-up biopsy (i.e. TRUS-biopsy + MRI-targeted

biopsy) in case of an elevated risk of disease reclassification. In Chapter 8, a total of 210 men on active surveillance who received a first multi-parametric MRI at different time points during follow-up were retrospectively stratified based on the PI-RADS score and PSA-density. In accordance with a prior study of Washino et al. in biopsy naïve men (134), no Gleason score upgrading in TRUS-biopsy ± MRI-targeted biopsy was observed in men with PI-RADS 1 – 3 and a PSA-density <0.15 ng/mL^2. This risk-based approach could safely avoid up to 50% of follow-up biopsy procedures in men with PI-RADS 1 – 3.

In men on active surveillance who have received consecutive (two or more) multi-parametric MRI-scans, the decision to perform a follow-up biopsy could be based on the presence of cancer-suspicious alterations on the present scan in comparison with a prior MRI (126, 135). Unfortunately, published data on men on active surveillance who have received consecutive MRI-scans are currently still lacking. A specialized task force has recently developed the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations for reporting of prostate MRI in men on active surveillance. These PRECISE recommendations will facilitate data collection in order to define "radiologic progression" in men who have received sequential MRI's (136).

Thus, (repeated) MRI can be used to select men for follow-up biopsy and avoid unnecessary biopsies in men at low-risk of disease reclassification. However, multi-parametric MRI is costly and not yet widely available. Furthermore, the importance of follow-biopsies in general is questionable, given the excellent long-term disease-specific survival in the absence of compliance with follow-up biopsies. Therefore, one could argue not to intensify the follow-up of most men on active surveillance with (repeated) MRI-scans, but rather to minimize the follow-up (i.e. less to zero biopsies and MRI's), especially if a baseline MRI has been performed at diagnosis.

Conclusion

A high percentage of men is not considered suitable for active surveillance at diagnosis or reclassifies at short-term follow-up. This indicates the need for more accurate eligibility criteria. A baseline MRI after diagnosis of low-risk prostate cancer helps to early identify men who harbor higher-grade disease, and on the other hand, helps to safely include men on active surveillance with higher-volume low-grade disease. In addition, the histological growth pattern of grade 4 disease could be helpful to identify men with low-volume Gleason 3+4 prostate cancer who are suitable for active surveillance. The low biopsy compliance during follow-up on active surveillance indicates the need for strategies to reduce unnecessary follow-up biopsies in those men selected for surveillance based on the traditional diagnostic TRUS-biopsy. The multi-parametric MRI, together with clinical parameters such as the PSA-density, can help to identify those men who need a follow-up biopsy and safely avoid a biopsy in those with a low-risk of disease reclassification.

Future perspectives

Recently, two prediction models for disease reclassification at follow-up TRUS biopsy have been developed based on large datasets (137, 138). In the near future, follow-up of men on active surveillance will be personalized using dynamic risk prediction models that incorporate both repeated measurements of clinical and radiological parameters, as perhaps newly validated biomarkers and assays, such as Prolaris (139) and Oncotype DX (140). These dynamic prediction models should certainly also take into account the patient comorbidity and life expectancy, as the individual on active surveillance for prostate cancer still has a 10 fold higher risk of dying from other causes (100). The Movember-GAP3 project can provide the necessary data having the availability of approximately 40% of all men on active surveillance globally (141). The increasing performance of sequential multiparametric MRI-scans in men on active surveillance could provide the evidence for follow-up with MRI only, omitting repeat biopsies in the absence of radiological progression. Finally, recent level-I evidence for the effectiveness of vascular-targeted photodynamic therapy in delaying disease progression could trigger an increasing use of focal therapy instead of active surveillance in specific cases (142).

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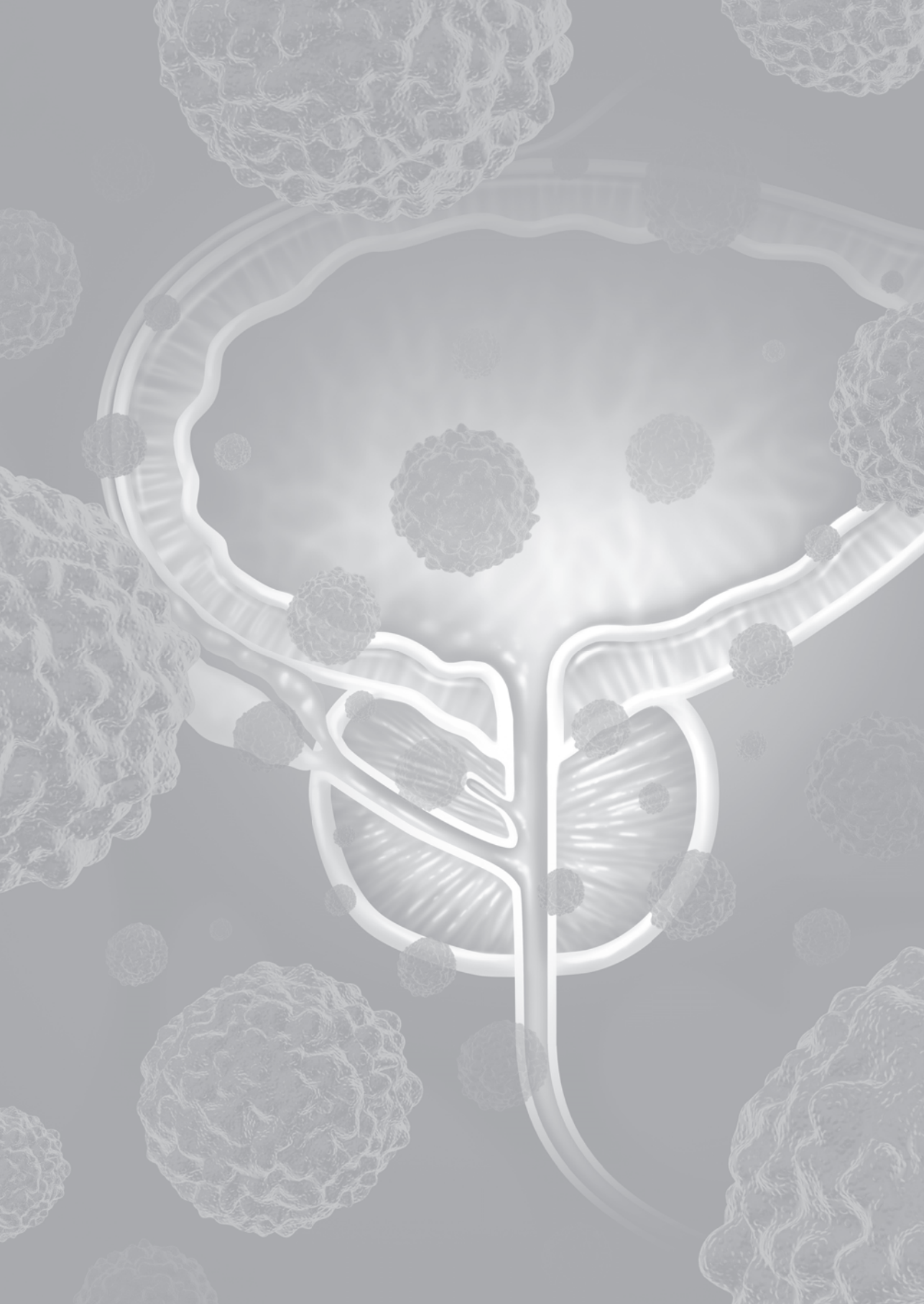

Part III

Appendices

SUMMARY

Chapter 1 (General Introduction) gives an overview of the pathophysiology, epidemiology, diagnosis and grading of prostate cancer. The history of PSA-based prostate cancer screening is discussed, as well as its benefits (i.e. cancer-specific morbidity and mortality reduction) and its harms (i.e. unnecessary testing and overdiagnosis of insignificant prostate cancer). The concepts of prediction models, multi-parametric MRI and active surveillance for low-risk prostate cancer are introduced. Several research questions are formulated, which are answered in **Chapter 9** (General Discussion).

Part I Screening

A comprehensive overview of the history of PSA-based prostate cancer screening is given in **Chapter 2**. All prostate cancer screening studies are discussed, including the two largest trials: the European Randomized study of Screening for Prostate cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian (PLCO) trial. Subsequently, an overview is given of the recommendations of current guidelines on prostate cancer screening. The major drawbacks of screening (i.e. unnecessary biopsies and overdiagnosis of insignificant cancer) are discussed. It is emphasized that these drawbacks may be overcome (partially) in the future by the combined implementation of magnetic resonance imaging, new biomarkers and multivariable risk-stratification.

The harms of population-based prostate cancer screening generally outweigh the benefit of a mortality reduction, particularly in men aged ≥70 years with a relatively limited life expectancy. The benefit-to-harm ratio of screening in these men can be improved by the implementation of multivariable risk-stratification and MRI. In **Chapter 3** it is shown that a significant proportion (13%) of the 337 men biopsied in the fifth screening round of the ERSPC Rotterdam (age between 71 – 75 years) harbored high-grade (Gleason score ≥3+4) prostate cancer. Given the fact that these men have a median life expectancy of approximately 13 years, some of them may still benefit from the early detection and subsequent treatment of prostate cancer. A screening strategy with upfront multivariable risk-stratification using the ERSPC-risk calculator and the combined performance of MRI (+/- targeted biopsy) and transrectal ultrasound-guided systematic biopsy (TRUS-biopsy) seems to be the optimal strategy, as it would have avoided two-thirds of biopsy procedures and insignificant prostate cancer diagnoses in our cohort, while maintaining the high-grade prostate cancer detection rate of a TRUS-biopsy all men approach.

According to the European Association of Urology prostate cancer guidelines a prebiopsy MRI is only indicated in case of a sustained suspicion of prostate cancer, usually based on PSA(-kinetics), after a negative TRUS-biopsy. However, not all men with a sustained clinical suspicion of prostate cancer after a negative TRUS-biopsy harbor (high-grade) prostate cancer. Multivariable risk-based patient selection for multi-parametric MRI

could help to avoid the performance of unnecessary, costly MRI-scans. In **Chapter 4** it is shown that risk-stratification based on the ERSPC-risk calculator(4) would have avoided the performance of 50% of MRI-scans in a clinical cohort of 122 men, missing 10% of high-grade prostate cancers. It is concluded that further improvement could be achieved by adjusting the ERSPC-risk calculator(4), which is constructed based on 6-core TRUS-biopsy data from a screening cohort, to the clinical setting with 10 – 12 core TRUS-biopsy and MRI (+/-targeted biopsy).

Multivariable risk-stratification is to be preferred before the performance of a multi-parametric MRI in order to avoid unnecessary MRI-scans. Nevertheless, the discriminative ability of prediction models with clinical parameters can be improved by the incorporation of MRI parameters such as the PI-RADS score, thereby helping to avoid unnecessary biopsy procedures after the performance of an MRI-scan. In **Chapter 5**, the ERSPC-risk calculator 3 and 4 are adjusted for the prediction of any-grade and high-grade prostate cancer in 12-core TRUS-biopsy +/- MRI-targeted biopsy using data from a multi-institutional cohort of 961 men. Application of the improved MRI-ERSPC risk calculators in our cohort would have avoided 25% of biopsy procedures, missing 4% of high-grade prostate cancers.

Part II Active surveillance

Men with localized high-grade (Gleason score ≥3+4) prostate cancer are usually treated with curative intent (i.e. radical prostatectomy or radiotherapy), as their cancer has the potential to metastasize and cause disease-related morbidity and mortality. In contrast, men with localized low-grade (Gleason score 3+3) prostate cancer are often followed-up on active surveillance as "true Gleason 3+3 disease" does not metastasize. Nevertheless, in the Rotterdam section of the ERSPC study a total of 15 men diagnosed in the first screening round with biopsy cT1/2 Gleason score 3+3 prostate cancer eventually died of the disease. In **Chapter 6**, pathological revision of the biopsy specimens revealed a higher-grade tumor component according to the contemporary Gleason score in half of these men. Furthermore, it was shown that the cribriform Gleason grade 4 growth pattern and intraductal carcinoma are associated with prostate cancer death and may therefore be used for patient selection for active surveillance.

Men on active surveillance are usually followed-up according to a strict protocol with repeated measurements of the PSA-level and follow-up biopsies. A strict follow-up scheme and repeated biopsies in particular could be burdening for patients on surveillance. In **Chapter 7** the compliance with PSA measurements and follow-up biopsies is assessed in the largest active surveillance study worldwide: the Prostate cancer Research: International Active Surveillance (PRIAS) study. While the compliance with PSA testing was persistently high (>90%) during follow-up, a drastic decline of the compliance with follow-up biopsies was observed over time, from 81% at confirmatory biopsy to only 33% at surveillance biopsy 10 years after diagnosis. This seems to indicate that repeat biopsies

are considered burdening for patients and that strategies are needed to safely reduce the number of follow-up biopsies in order to increase adherence to the protocol.

Multi-parametric MRI is increasingly used in men on active surveillance. MRI at diagnosis could help to improve the selection of men with low-risk prostate cancer who are suitable for surveillance. Furthermore, MRI could be helpful to safely reduce the number of follow-up biopsy procedures. In **Chapter 8**, a similar disease reclassification rate (Gleason score ≥3+4) of approximately 25% was observed at diagnosis, at first repeat biopsy (1 year after diagnosis) and at surveillance biopsy (4 years after diagnosis) in a cohort of 210 men on active surveillance who received a first MRI +/- targeted biopsy. No disease reclassification occurred in men with a PI-RADS score 1 – 3 and a low PSA-density (<0.15 ng/mL^2). Thus, risk-stratification based on the PI-RADS score and PSA-density could help to safely reduce the number of follow-up biopsies in men on active surveillance.

SAMENVATTING

In **Hoofdstuk 1** (Algemene Introductie) wordt een overzicht gegeven van de pathofysiologie, epidemiologie, diagnose en gradering van prostaatkanker. De geschiedenis van prostaatkanker screening met behulp van PSA wordt bediscussieerd, evenals de voordelen (i.e. reductie van kanker-specifieke morbiditeit en mortaliteit) en nadelen (i.e. onnodige onderzoeken en overdiagnose van insignificante tumoren) van screening. De begrippen "predictiemodellen, multi-parametrische MRI en active surveillance voor laagrisico prostaatkanker' worden geïntroduceerd. Er worden meerdere onderzoeksvragen geformuleerd, dewelke worden beantwoord in **Hoofdstuk 9** (Algemene Discussie).

Deel I Screening

In **Hoofdstuk 2** wordt een uitgebreid overzicht gegeven van de geschiedenis van prostaatkanker screening met behulp van PSA. Alle prostaatkanker screening studies worden bediscussieerd, waaronder de twee grootste studies: de "European Randomized study of Screening for Prostate Cancer (ERSPC)" en de "Prostate, Lung, Colorectal and Ovarian (PLCO)" studie. Vervolgens wordt er een overzicht gegeven van de aanbevelingen uit de huidige richtlijnen voor prostaatkanker screening. De nadelen van screening (i.e. onnodige biopten en overdiagnose van insignificante tumoren) worden bediscussieerd. Er wordt benadrukt dat deze nadelen in de toekomst (gedeeltelijk) kunnen worden overwonnen door de gecombineerde implementatie van MRI, nieuwe biomarkers en multivariabele risico-stratificatie.

Over het algemeen weegt het voordeel van een mortaliteitsreductie niet op tegen de nadelen van prostaatkanker screening op populatieniveau, met name niet bij mannen met een leeftijd ≥70 jaar en dus een relatief beperkte levensverwachting. De verhouding tussen de voordelen en nadelen van screening bij deze mannen kan worden verbeterd door multivariabele risico-stratificatie en MRI te implementeren. In **Hoofdstuk 3** wordt aangetoond dat een significant percentage (13%) van de 337 gebiopteerde mannen in de vijfde screening ronde van de ERSPC Rotterdam (leeftijd tussen de 71 – 75 jaar) hooggradig (Gleason score ≥3+4) prostaatkanker heeft. Gezien het feit dat deze mannen een mediane levensverwachting van ongeveer 13 jaar hebben, hebben sommigen nog baat bij de vroege detectie en daaropvolgende behandeling van prostaatkanker. Een screening strategie met op voorhand multivariabele risico-stratificatie gebruikmakende van de ERSPC-risico calculator en het gecombineerd verrichten van zowel MRI (+/- gerichte biopsie) als transrectale echogeleide systematische biopsie (TRUS-biopsie) lijkt de optimale screening strategie te zijn. Met deze strategie zou namelijk twee derde van de bioptprocedures en diagnoses van insignificant prostaatkanker in ons cohort zijn voorkomen, terwijl de detectie van hooggradig prostaatkanker gelijk zou blijven aan wanneer alle mannen een TRUS-biopsie zouden krijgen.

Volgens de prostaatkanker richtlijn van de Europese Vereniging voor Urologie (EAU) is een MRI vóór het verrichten van een biopsie alleen geïndiceerd bij een blijvende verdenking op prostaatkanker, meestal gebaseerd op PSA(-kinetiek), na een negatieve TRUS-biopsie. Echter, niet alle mannen met een blijvende verdenking op prostaatkanker na een negatieve TRUS-biopsie hebben (hooggradig) prostaatkanker. Selectie van patiënten voor multi-parametrische MRI op basis van multivariabele risico-stratificatie kan het verrichten van onnodige, dure MRI-scans voorkomen. In **Hoofdstuk 4** wordt aangetoond dat risico-stratificatie met behulp van de ERSPC-risico calculator(4) het verrichten van 50% van de MRI-scans zou voorkomen in een klinisch cohort van 122 mannen, waarbij 10% van de hooggradige prostaatkankers zou worden gemist. Er wordt geconcludeerd dat verdere verbetering kan worden bewerkstelligd door de ERSPC-risico calculator(4), die geconstrueerd is op basis van sextant TRUS-biopsie gegevens in een screening cohort, aan te passen aan de klinische setting met 10 – 12 TRUS-biopten en MRI (+/- gerichte biopsie).

Multivariabele risico-stratificatie is te prefereren vóór het verrichten van een multi-parametrische MRI om zo onnodige MRI-scans te voorkomen. Echter, het onderscheidend vermogen van predictiemodellen met alleen klinische parameters kan worden verbeterd door MRI parameters zoals de PI-RADS score te incorporeren, om zo onnodige bioptprocedures te voorkomen na het verrichten van een MRI-scan. In **Hoofdstuk 5** worden de ERSPC-risico calculator 3 en 4 aangepast voor het voorspellen van prostaatkanker en hooggradig prostaatkanker in 12 TRUS-biopten +/- MRI-gerichte biopten, gebruikmakende van gegevens van een multi-institutioneel cohort van 961 mannen. Gebruik van deze verbeterde MRI-ERSPC risico calculators zou 25% van de bioptprocedures hebben voorkomen, waarbij 4% van de hooggradige prostaatkankers zou zijn gemist.

Deel II Active surveillance

Mannen met gelokaliseerd hooggradig (Gleason score ≥3+4) prostaatkanker worden meestal behandeld met als doel te genezen (i.e. radicale prostatectomie of radiotherapie), gezien de tumor in potentie kan metastaseren en ziekte-specifieke morbiditeit en mortaliteit kan veroorzaken. Daarentegen worden mannen met gelokaliseerd laaggradig (Gleason score 3+3) prostaatkanker vaak actief opgevolgd (active surveillance) gezien er geen metastasering optreedt indien er daadwerkelijk alleen sprake is van Gleason 3+3 prostaatkanker. Desalniettemin zijn in totaal 15 mannen die in de eerste screening ronde van de ERSPC Rotterdam gediagnosticeerd werden met cT1/2 Gleason score 3+3 prostaatkanker uiteindelijk aan de ziekte overleden. In **Hoofdstuk 6** toonde pathologische revisie van de biopten bij de helft van deze mannen een hooggradige tumor component volgens de hedendaagse Gleason score. Bovendien werd aangetoond dat het cribriforme Gleason graad 4 groeipatroon en intraductaal carcinoom geassocieerd zijn met prostaatkanker dood en daarom gebruikt zouden kunnen worden bij de patiënten selectie voor active surveillance.

Mannen op active surveillance worden meestal opgevolgd volgens een strikt protocol met herhaalde metingen van de PSA-waarde en biopsieën. Een strikt opvolgschema en met name herhaalde biopsieën zouden belastend kunnen zijn voor patiënten op active surveillance. In **Hoofdstuk 7** wordt de naleving van de PSA metingen en opvolg biopsieën geëvalueerd binnen de grootste active surveillance studie wereldwijd: de 'Prostate cancer Research: International Active Surveillance (PRIAS)' studie. Alhoewel de naleving van PSA metingen persisterend hoog (>90%) was gedurende opvolging, werd er een drastische vermindering van de naleving van opvolg biopsieën geobserveerd, van 81% bij het confirmatie biopt 1 jaar na diagnose tot slechts 33% bij de biopsie 10 jaar na diagnose. Dit lijkt erop te wijzen dat herhaalbiopsieën als belastend worden ervaren door patiënten en dat er behoefte is aan strategieën om het aantal herhaalbiopsieën veilig te reduceren en zo de naleving van het opvolgprotocol te verbeteren.

Multiparametrische MRI wordt in toenemende mate gebruikt bij mannen op active surveillance. Een MRI-scan bij diagnose zou de selectie van mannen met laag-risico prostaatkanker die geschikt zijn voor active surveillance kunnen verbeteren. Bovendien zou MRI gebruikt kunnen worden om het aantal opvolg biopsieën veilig te reduceren. In **Hoofdstuk 8** wordt een vergelijkbaar percentage (ongeveer 25%) geobserveerd van mannen die reclassificeren (Gleason score ≥3+4) bij diagnose, bij het eerste herhaalbiopt (1 jaar na diagnose) en bij surveillance biopsie (4 jaar na diagnose) in een cohort van 210 mannen op active surveillance die een eerste MRI +/- gerichte biopsie krijgen. Ziekte reclassificatie werd niet geobserveerd bij mannen met een PI-RADS score 1 – 3 en een lage PSA-densiteit (<0.15 ng/mL^2). Risico-stratificatie op basis van de PI-RADS score en PSA-densiteit zou dus kunnen helpen om het aantal herhaal biopsieën bij mannen op active surveillance veilig te reduceren.

ABOUT THE AUTHOR

Arnout Roderick Alberts was born in Nijmegen on the 16th of August, 1988. He completed his secondary school in 2006 at the Coornhert Gymnasium in Gouda. From 2006 until 2013 he studied medicine at the Catholic University of Leuven. The final year of his medical studies consisted of a dedicated year at the Urology department of the University Hospital of Leuven under the supervision of prof. H. van Poppel, prof. D. de Ridder and prof. S. Joniau. After obtaining his medical degree he worked as a resident at the Urology department of the Erasmus University Medical Center in Rotterdam under the supervision of dr. P.C.M.S. Verhagen. From July 2014 until June 2017 he worked on his PhD project at the departments of Urology and Radiology of the Erasmus University Medical Center under the supervision of prof. M.J. Roobol, prof. C.H. Bangma, dr. I.G. Schoots and prof. G.P. Krestin. As part of his Urology traineeship, he is currently working as a resident at the General Surgery department of the Amphia Hospital in Breda under the supervision of dr. L. van der Laan.

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Alberts AR, Joniau S, van Raemdonck D, Verbeken E, van Poppel H.
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2. Prostate-specific antigen-based prostate cancer screening: past and future.

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3. Guidelines on the early detection of prostate cancer.

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6. Risk-based patient selection for magnetic resonance imaging-targeted prostate biopsy after negative transrectal ultrasound-guided random biopsy avoids unnecessary magnetic resonance imaging scans.

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7. Complications after prostate biopsies in men on active surveillance and its effects on receiving further biopsies in the Prostate cancer Research International: Active Surveillance (PRIAS) study.

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8. Biopsy undergrading in men with Gleason score 6 and fatal prostate cancer in the European Randomized study of Screening for Prostate Cancer Rotterdam.

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9. Risk-stratification based on magnetic resonance imaging and prostate-specific antigen density may reduce unnecessary follow-up biopsy procedures in men on active surveillance for low-risk prostate cancer.

Alberts AR, Roobol MJ, Drost FH, van Leenders GJ, Bokhorst LP, Bangma CH, Schoots IG.

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10. Additional benefit of using a risk-based selection for prostate biopsy: an analysis of biopsy complications in the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC)

Chiu PK, Alberts AR, Venderbos LDF, Bangma CH, Roobol MJ.

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11. Characteristics of prostate cancer found at fifth screening in the European Randomized study of Screening for Prostate Cancer Rotterdam: can we selectively detect high-grade prostate cancer with upfront multivariable risk-stratification and magnetic resonance imaging?

Alberts AR, Schoots IG, Bokhorst LP, Drost F-JH, van Leenders GJ, Krestin GP, Dwarkasing RS, Barentsz JO, Schröder FH, Bangma CH, Roobol MJ.

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12. Multivariable risk-based patient selection for prostate biopsy after magnetic resonance imaging: improving the European Randomized study of Screening for Prostate Cancer Risk Calculators by combining clinical parameters with the Prostate Imaging Reporting and Data System (PI-RADS) score.

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Manuscript in preparation.

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PHD PORTFOLIO

Name: Arnout R. Alberts	PhD period: July 2014 – June 2017
Erasmus MC Departments: Urology & Radiology	Promotors: prof. M.J. Roobol; prof. dr. G.P. Krestin
Research School: MolMed	Co-promotor: dr. I.G. Schoots

1. PhD training

	Year	Workload (ECTS)
General courses		
• Biostatistical Methods I: Basic Principles	2015	5.7
• Biostatistical Methods II: Classical Regression Models	2015	4.3
• Research Integrity	2015	0.3
• Basiscursus Regelgeving Klinisch Onderzoek (BROK)	2014	1.0
Seminars and workshops		
• Department of Urology Journal Club	2014 – 2017	1.0
• Department of Urology Internal Course	2014 – 2017	1.0
• Department of Urology Symposia (Refereeravonden)	2014 – 2017	1.0
Presentations		
• Najaarsvergadering NVU, Nieuwegein	2014	0.5
• Annual meeting BAU, Spa	2014	1.0
• ERSPC meeting, Madrid	2015	0.5
• Annual meeting EAU, Madrid	2015	1.0
• National Medical Interns conference, Egmond aan Zee	2015	1.0
• Annual meeting AUA, New Orleans	2015	1.0
• Najaarsvergadering NVU, Nieuwegein	2015	0.5
• EAU section of Urological Imaging meeting, Barcelona	2015	1.0
• ESO Active Surveillance meeting, Milan	2016	1.0
• ERSPC meeting, Munich	2016	0.5
• Annual meeting EAU, Munich	2016	1.0
• Prostate Partners meeting, Vught	2016	0.5
• Voorjaarsvergadering NVU, Leiden	2016	0.5
• Externe refereeravond Erasmus MC, Rotterdam	2016	0.5
• Annual EMUC meeting, Milan	2016	1.0
• EAU section of Oncological Urology meeting, Barcelona	2017	1.0
• Annual meeting EAU, London	2017	1.0
• Annual meeting AUA, Boston	2017	1.0
International conferences		
• Annual meeting SIU	2014	0.5
• NVU biannual meetings	2014 – 2016	1.0
• Annual meeting BAU	2014	0.5
• Annual ERSPC meetings	2015 – 2016	0.5
• Annual meetings EAU	2015 – 2017	1.5
• Annual meetings AUA	2015, 2017	1.5
• Annual EMUC meetings	2015 – 2016	1.5
• ESO Active Surveillance meeting	2016	1.0
• EAU section of Oncological Urology meeting	2017	1.0
Other		
• Secretary of Prostate Cancer Research Group / Academic Center of Urogenital Tumors Erasmus MC	2014 – 2017	1.0
• Treasurer of Foundation of Urology Residents of Rotterdam (RUAG)	2016 – 2017	1.0

2. Teaching		
	Year	**Workload (ECTS)**
• Urological Anatomy Tutor in the Erasmus Anatomy Research Project (EARP)	2016 – 2017	1.0
• Clinical examination, Anatomy and General Urology for medical students/interns and OR assistants	2016 – 2017	0.5

Totaal **41.3 *ECTS***