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

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

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?

Arnout R. Alberts [a,*], *Ivo G. Schoots* [b], *Leonard P. Bokhorst* [a], *Frank-Jan H. Drost* [a,b], *Geert J. van Leenders* [c], *Gabriel P. Krestin* [b], *Roy S. Dwarkasing* [b], *Jelle O. Barentsz* [d], *Fritz H. Schröder* [a], *Chris H. Bangma* [a], *Monique J. Roobol* [a]

[a] *Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [b] *Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands;* [c] *Department of Pathology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [d] *Department of Radiology, Radboud University Medical Center, Nijmegen, The Netherlands*

Article info

Article history:
Accepted June 7, 2017

Associate Editor:
Giacomo Novara

Statistical Editor:
Andrew Vickers

Keywords:
Biopsy
MRI
Multivariable risk stratification
Prostate cancer
Risk calculator
Screening

Abstract

Background: The harm of screening (unnecessary biopsies and overdiagnosis) generally outweighs the benefit of reducing prostate cancer (PCa) mortality in men aged ≥70 yr. Patient selection for biopsy using risk stratification and magnetic resonance imaging (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 yr with high-grade PCa.
Design, setting, and participants: Three hundred and thirty-seven men with prostate-specific antigen ≥3.0 ng/ml at a fifth screening (71–75 yr) in the European Randomized study of Screening for Prostate Cancer Rotterdam were biopsied. One hundred and seventy-nine men received six-core transrectal ultrasound biopsy (TRUS-Bx), while 158 men received MRI, 12-core TRUS-Bx, and fusion TBx in case of Prostate Imaging Reporting and Data System ≥3 lesions.
Outcome measurements and statistical analysis: The 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 six-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.
Results and limitations: Fifty-five percent of men were previously biopsied. The overall, low-grade, and high-grade PCa rates in biopsy naïve men were 48%, 27%, and 22%, respectively. 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%). Rotterdam Prostate Cancer Risk Calculator 4-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%).

* Corresponding author. Erasmus University Medical Center, Urology, Room Na-1710, Wytemaweg 80, Rotterdam 3015CN, The Netherlands. Tel. +31-65-1257053; Fax: +31-10-7035315.
E-mail address: a.r.alberts@erasmusmc.nl (A.R. Alberts).

http://dx.doi.org/10.1016/j.eururo.2017.06.019

Conclusions: After four repeated screens and ≥1 previous biopsies in half of men, a significant proportion of men aged ≥70 yr still 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 nonaggressive tumors, especially in repeatedly screened elderly men. To tackle these drawbacks screening should consist of an upfront risk-assessment followed by magnetic resonance imaging and transrectal ultrasound-guided biopsy.

1. Introduction

The European Randomized study of Screening for Prostate Cancer (ERSPC) showed a 21% prostate cancer (PCa) mortality reduction at 13-yr 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 prostate-specific antigen (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 cases 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 in men aged ≥70 yr 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 a higher age could be tackled by improved patient selection for biopsy using risk stratification and magnetic resonance imaging (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 fifth screening round (71–75 yr) 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.

2. Material and methods

2.1. Study population

All participants of the ERSPC Rotterdam fifth screening round (October 2010 to 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 yr were randomized to a screening or control arm. In the screening arm men were offered PSA testing with a 4-yr interval until the age of 75 yr. At each screening visit sextant TRUS-Bx was offered in cases of PSA ≥3.0 ng/ml. Within the fifth (last) screening round an MRI side study (Medical Ethics Committee 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).

2.2. Multi-parametric MRI

According to the Prostate Imaging Reporting and Data System (PI-RADS) guidelines [21] the protocol consisted of T2-weighted imaging, diffusion-weighted imaging with apparent diffusion coefficient (ADC) reconstructions, and dynamic contrast enhanced imaging, as described previously [22]. Imaging was performed on a 3-Tesla MRI-scanner (Discovery MR750, General Electric Healthcare, Little Chalfront, UK) using a 32-channel pelvic phased-array coil. The images were independently analyzed by three urogenital radiologists (IS, RD, and 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). MRIs were classified as positive in the presence of ≥1 PI-RADS ≥3 lesions.

2.3. 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 two cores per lesion using the UroStation (Koelis, Meylan, France) for MRI-TRUS fusion. All biopsy procedures were performed by three experienced operators (AA, LB, and F-JD). The biopsy specimens were graded by one expert uropathologist (GL) according to the International Society of Urological Pathology 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.

2.4. 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).

Please cite this article in press as: Alberts AR, et al. 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