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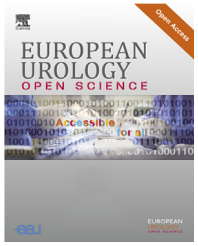

European Association of Urology

Brief Correspondence

Updating the Rotterdam Prostate Cancer Risk Calculator with Invasive Cribriform and/or Intraductal Carcinoma for Men with a Prior Negative Biopsy

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Abstract

The Rotterdam Prostate Cancer Risk Calculator (RPCRC) is a well-validated tool for upfront risk stratification to reduce the number of prostate biopsies and magnetic resonance imaging scans among both biopsy-naïve and previously biopsied men. The presence of invasive cribriform and/or intraductal carcinoma (CR/IDC) identifies men with aggressive grade group (GG) 2 tumors. This finding was recently incorporated in the RPCRC for biopsy-naïve men to predict the probability of no PCa, indolent PCa (GG 1 disease and GG 2 disease without CR/IDC), and clinically significant PCa (csPCa: GG 2 disease with CR/IDC and higher). The aim of the current study was to update the RPCRC for men with a previous negative biopsy with the presence of CR/IDC. A total of 2215 men were eligible for analyses, of whom 1776 (80%) were not diagnosed with PCa, 358 (16%) were diagnosed with indolent PCa, and 81 (4%) were diagnosed with csPCa according to the original 2014 Gleason grading. The optimism-corrected area under the curve was 0.69 for any PCa and 0.77 for csPCa. With a threshold of 10% for indolent PCa or 1% for csPCa, 20% of all prostate biopsies could be avoided and 2% of all csPCa cases would be missed. Our results support upfront risk stratification with the updated RPCRC.

Patient summary: Risk stratification for men without a prior diagnosis of prostate cancer can reduce the number of prostate biopsies and magnetic resonance imaging scans carried out in this patient population. Our study shows that it is possible to update the Rotterdam Prostate Cancer Risk Calculator for men with a previous negative biopsy with the presence of invasive cribriform and/or intraductal carcinoma.

Upfront risk stratification before magnetic resonance imaging (MRI) and/or prostate biopsy can be used to identify men at higher risk of having clinically significant (cs) prostate cancer (PCa) who would benefit from early detection and subsequent treatment. Implementation of such a risk stratification leads to a reduction in unnecessary (potentially harmful) tests while maintaining patient safety. Hence, risk stratification after prostate-specific antigen

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(PSA) measurement is recommended in the European Association of Urology (EAU) guidelines and is part of a recently developed, contemporary, organized, risk-stratified program for early detection of PCa [1–3]. One well-known and externally validated risk stratification tool is the Rotterdam Prostate Cancer Risk Calculator (RPCRC), which estimates the probability of finding any PCa or csPCa (grade group [GG] ≥2) on prostate biopsy on the basis of several patient characteristics such as PSA level and prostate volume. The set of risk prediction tools collected on the website and as a mobile application aims to provide information and individual risk assessment throughout a patient's journey, starting from considering PCa screening through to treatment choice after diagnosis [4].

A recent finding relating to disease aggressiveness should be taken into account when assessing individual risk. It was demonstrated that information about the presence of invasive cribriform and/or intraductal carcinoma (CR/IDC) alongside GG at prostate biopsy results in better prediction of metastasis-free survival and disease-specific survival in comparison to GG alone [5,6]. To elaborate, men with GG 2 PCa at biopsy without the presence of CR/IDC showed similar disease-specific survival to men with GG 1 PCa at biopsy. Hence, the presence (or absence) of CR/IDC can lead to a stage shift in the prognostication for newly diagnosed patients. Documenting the presence of CR/IDC is part of the standard reporting for prostate biopsies [7].

This finding is already incorporated in the RPCRC for biopsy-naïve men. This contemporary risk calculator predicts the probability of not finding PCa, indolent PCa (GG 1 or GG 2 without CR/IDC), and csPCa (GG ≥2 with CR/IDC) at prostate biopsy [8] and can thus be used to avoid MRI and/or prostate biopsy and decrease overdiagnosis.

Since the risk of having (cs)PCa is lower for men who have had at least one previous negative prostate biopsy, the RPCRC offers different risk calculators for biopsy-naïve and previously biopsied men [4]. An RPCRC version including the presence or absence of CR/IDC was not yet available for men with a previous negative prostate biopsy. Here we report on the development of this important risk calculator, which is, like the original version, based on men with a prior negative biopsy who attended screening for the second time in the Dutch arm of the ERSPC trial between 1997 and 2004 [9].

In general the indication for biopsy was PSA ≥3.0 ng/ml. The development cohort consisted of 2217 men. Similar to the original RPCRC for men with a previous negative biopsy, variables in the model included PSA level, prostate volume, and digital rectal examination and transrectal ultrasound results (abnormal/normal). In addition, for the RPCRC updated with CR/IDC, we also included age at biopsy [8,10]. The updated model was internally validated using bootstrapping to correct for optimism.

Two patients with GG 2 tumors were excluded because the biopsy specimen was of insufficient quality for re-review for the presence of CR/IDC. A total of 2215 men were included in the analyses, of whom 1776 (80%) were not diagnosed with PCa, 358 (16%) were diagnosed with indolent PCa, and 81 (4%) were diagnosed with csPCa according to the original 2014 Gleason grading (Table 1). After pathology review, the absence of CR/IDC led to a stage shift for 50 men (72% of all 69 men with GG 2 disease) to indolent PCa. Ordinal regression was not appropriate because of violation of the proportional odds assumption, so we performed multinominal regression. The optimism-corrected area under the curve was 0.69 for any PCa and 0.77 for csPCa. The calibration-slope was 0.95 for any PCa and 0.94 for csPCa.

Table 1 – Patient characteristics.

Parameter	No PCa (n = 1776)	Indolent PCa[a] (n = 358)	csPCa[b] (n = 81)
Median PSA, ng/ml (IQR)	4.5 (3.5–6.2)	4.2 (3.4–5.7)	4.8 (3.8–6.4)
Median prostate volume, cm^3 (IQR)	50.2 (39.9–64.0)	41.5 (32.3–51.9)	35.9 (30.4–47.5)
Median age, yr (IQR)	67.3 (63.4–70.8)	66.8 (62.8–70.8)	67.8 (64.8–71.6)
Abnormal DRE, n (%)	336 (19)	98 (27)	44 (54)
Abnormal TRUS, n (%)	278 (16)	78 (22)	29 (36)
Previous Bx in screening round 1, n (%)	837 (47)	97 (27)	19 (23)

Bx = biopsy; csPCa = clinically significant PCa; DRE = digital rectal examination; IQR = interquartile range; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.
[a] Indolent PCa was defined as grade group 1 disease or grade group 2 disease without invasive cribriform and/or intraductal carcinoma.
[b] csPCa was defined as grade group 2 disease with invasive cribriform and/or intraductal carcinoma and higher.

A net benefit of the updated model was observed at a threshold from 10% for indolent PCa and 1% for csPCa (Fig. 1). If biopsies were offered to men with a risk ≥10% for indolent PCa or ≥1% for csPCa, 20% (95% confidence interval [CI] 18–21%; 433 cases) of all prostate biopsies could be avoided and 10% (95% CI 7–13%; 35 cases) of all indolent PCa and 2% (95% CI 1–9%; 2 cases) of all csPCa cases would be missed. At a threshold of 10% for indolent PCa or 5% for csPCa, 26% (95% CI 24–27%; 567 cases) of all prostate biopsies could be avoided and 13% (95% CI 10–17%; 47 cases) of all indolent PCa and 6% (95% CI 3–14%; 5 cases) of all csPCa cases would be missed. The RPCRC update for men with a prior negative biopsy shows a favorable trade-off between the number of biopsies avoided and the number of csPCa cases missed (Supplementary Table 1). A 20% reduction in biopsies would imply 225 000 fewer biopsies in Europe on the basis of incidence of 450 000 cases per year and a positive predictive value of 40% (1.12 million biopsies).

To stimulate the use of risk stratification before prostate biopsies, the current results alongside the already published calculator for biopsy-naïve men [8] are available as an online risk calculator (www.prostatecancer-riskcalculator.com) and as a mobile application.

Currently, these two risk calculators that incorporate contemporary pathological grading in their outcome are meant to be used before MRI and/or biopsy. Future developments are aimed at incorporating MRI findings (for both biopsy-naïve men and men with a prior negative biopsy)

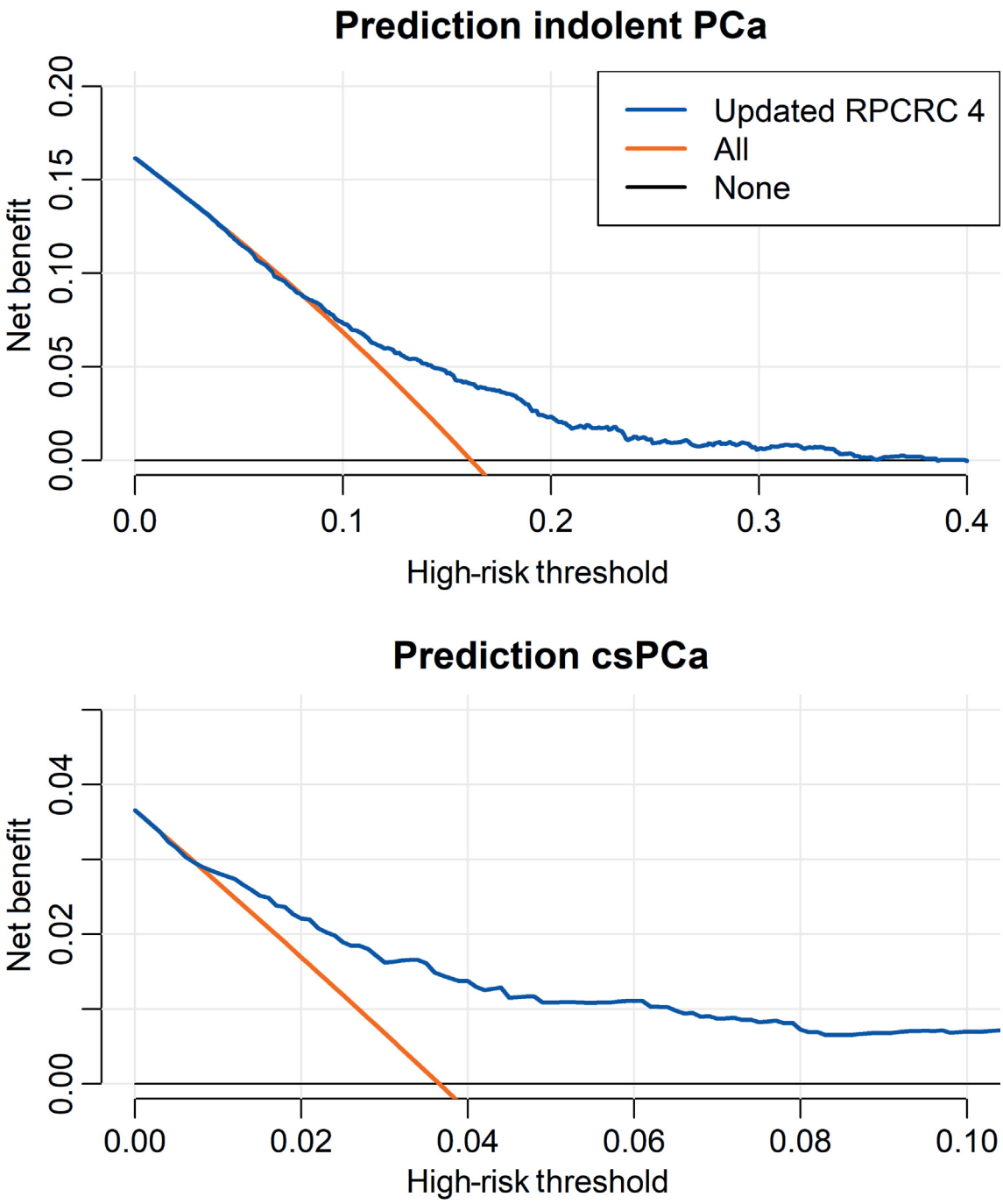

Fig. 1 – Decision curve analysis for the updated Rotterdam Prostate Cancer Risk Calculator (RPCRC). PCa = prostate cancer; csPCa = clinically significant PCa.

to facilitate a state-of-the art risk stratification step after MRI. The current RPCRC version that includes MRI results (but without CR/IDC as an outcome) shows that at a threshold of 5% for csPCa (ie, GG $\geq$2), 27% of all prostate biopsies could be avoided and only 3% of csPCa cases would be missed [10].

There is a general trend to move towards MRI-based screening, which could make the use of a risk calculator less effective and clinically useful. However, the recommendation to not perform MRI as an initial screening tool is rated as strong in the latest EAU guideline [4]. In addition, the EAU recently published a position paper on organized screening that stresses the need for risk stratification before MRI [11].

The strength of the current study is that the basis for our updated RC is the high-quality and well-documented population-based ERSPC data. In addition, the study included PCa biopsies reviewed in detail according to contemporary 2014 International Society of Urological Pathology recommendations.

In summary, we updated the RPCRC for men with a prior negative biopsy by including the presence of CR/IDC in our outcome and found that at a threshold of 10% for indolent PCa or 1% for csPCa, 20% of all prostate biopsies could be avoided and 2% of all csPCa cases would be missed.

Author contributions: Sebastiaan Remmers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Roobol, Remmers.
Acquisition of data: Rijstenberg, Hansum, Van Leenders.
Analysis and interpretation of data: Remmers, Nieboer, Rijstenberg, Hansum, Van Leenders, Roobol.
Drafting of the manuscript: Remmers.
Critical revision of the manuscript for important intellectual content: Remmers, Nieboer, Rijstenberg, Hansum, Van Leenders, Roobol.
Statistical analysis: Remmers, Nieboer.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2021.11.008.

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