Brief Correspondence

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

Sebastiaan Remmersa,*, Daan Nieboera,b, L. Lucia Rijstenbergc, Tim Hansumc, Geert J.L.H. van Leendersc, Monique J. Roobola

Article info

Article history:
Accepted November 8, 2021

Associate Editor:
Guillaume Ploussard

Keywords:
Clinical decision-making
Nomograms
Probability
Prostatic neoplasms

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-naive 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-naive 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.

© 2021 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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
survival in comparison to GG alone [5,6]. To elaborate, CR/IDC alongside GG at prostate biopsy results in better presence of invasive cribriform and/or intraductal carcinoma should be taken into account when assessing individual association of Urology (EAU) guidelines and is part of a recently group [GG].

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-naive 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-naive 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 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 multinomial 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.

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 PCAs 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 PCAs 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-naive 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-naive men and men with a prior negative biopsy)
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 ≥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.

**Obtaining funding:** None.

**Administrative, technical, or material support:** None.

**Supervision:** None.

**Other:** None.

**Financial disclosures:** Sebastiaan Remmers certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** None.

**Appendix A. Supplementary data**

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

**References**

[1] Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. A European model for an organised risk-stratified early detection programme for prostate cancer. Eur Urol Oncol 2021;4:731–9.

[2] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.

[3] Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. Early detection of prostate cancer in 2020 and beyond: facts and recommendations for the European Union and the European Commission. Eur Urol 2021;79:327–9.

[4] Roobol MJ, Steyger EW, Kransie R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. Eur Urol 2010;57:79–85.

[5] van Leenders G, Kweldam CF, Hollemans E, et al. Improved prostate cancer biopsy grading by incorporation of invasive cribriform and intraductal carcinoma in the 2014 grade groups. Eur Urol 2020;77:191–8.

[6] Kweldam CF, Kümmerlin IP, Nieboer D, et al. Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma. Eur J Cancer 2016;66:26–33.

[7] van Leenders G, van der Kwast TH, Grignon DJ, et al. The 2019 International Society of Urological Pathology (ISUP) consensus conference on grading of prostatic carcinoma. Am J Surg Pathol 2020;44:e87–99.

[8] Roobol MJ, Verbeek JFM, van der Kwast T, Kümmerlin IP, Kweldam CF, van Leenders GJLH. Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculator for initial prostate biopsy by incorporating the 2014 International Society of Urological Pathology Gleason grading and cribriform growth. Eur Urol 2017;72:45–51.

[9] Postma R, Schröder FH, van Leenders GJLH, et al. Cancer detection and cancer characteristics in the European Randomized Study of Screening for Prostate Cancer (ERSPC) – Section Rotterdam: a comparison of two rounds of screening. Eur Urol 2007;52:89–97.

[10] Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging: improving the Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculators. Eur Urol 2019;75:310–8.

[11] Van Poppel H, Roobol MJ, Chapelle CR, et al. Prostate-specific antigen testing as part of a risk-adapted early detection strategy for prostate cancer: European Association of Urology position and recommendations for 2021. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2021.07.024.

*Department of Urology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

bDepartment of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

cDepartment of Pathology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

*Corresponding author. Department of Urology, Erasmus University Medical Center, P.O. Box 2040, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Tel. +31 10 7032239; Fax: +31 10 7035315. E-mail address: s.remmers@erasasmusmc.nl (S. Remmers).