Improving the prediction of biochemical recurrence after radical prostatectomy with the addition of detailed pathology of the positive surgical margin and cribriform growth

Sebastiaan Remmers\textsuperscript{a},\textsuperscript{*,} Eva Hollemans\textsuperscript{b}, Daan Nieboer\textsuperscript{a,c}, Henk B. Luiting\textsuperscript{a}, Geert J.L. H. van Leenders\textsuperscript{b}, Jozien Helleman\textsuperscript{a}, Monique J. Roobol\textsuperscript{a}

\textsuperscript{a} Department of Urology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, the Netherlands
\textsuperscript{b} Department of Pathology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, the Netherlands
\textsuperscript{c} Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands

ARTICLE INFO

Keywords: Clinical Decision Making; Nomograms; Probability; Prostatectomy; Prostatic Neoplasms

ABSTRACT

The risk on biochemical recurrence (BCR) after radical prostatectomy (RP) is usually estimated using PSA and pathological stage and grading including the presence of positive surgical margins (PSM). Objective was to investigate whether the presence of cribriform growth in the primary tumor, Grade Group (GG) at the PSM, and length of the PSM have added value in the prognostication. We analyzed data of 835 patients initially treated with RP between 2000 and 2017. Cox regression models were developed to compare the baseline model (PSA, pT-stage, pN-stage, GG at RP, and presence of PSM) with an extended model (adding the presence of cribriform growth, length and GG at the PSM) using the likelihood ratio test. Discrimination was assessed at internal validation by the time-dependent area under the receiver operating characteristic curve (AUC) at 3- and 5-year. A total of 224 men experienced BCR. Median follow-up for men without BCR was 50.4 months (interquartile range, IQR 11.9–95.5). The extended model had a significant better fit, \( \chi^2(4) = 31.0, p < 0.001 \) than the baseline model. The AUC of the 3- and 5-year extended model was 0.85 (95% CI 0.81–0.88) compared to 0.83 (95% CI 0.79–0.87) for the baseline model. Importantly, the presence of cribriform growth in the primary tumor, and GG \( \geq 2 \) at PSM were associated with a higher risk on BCR. In conclusion, the addition of pathological variables improved the prediction of the risk on BCR after RP slightly. However, the clinical implications of this model are important.

1. Introduction

Several multivariable prediction models have been developed to quantify the risk of biochemical recurrence (BCR) after radical prostatectomy (RP) after the diagnosis of localized prostate cancer (PCa) which subsequently can be used in patient communication. We recently performed an external validation and head-to-head comparison of three well-known models and observed that the risk on BCR is estimated on the value of the preoperative PSA level, pathological (p) Gleason Score (or Grade Group [GG]), pN-stage, and the presence of extraprostatic extension, seminal vesicle invasion, and positive surgical margins (PSM) at RP \([1]\). We also observed good discrimination for the prediction of BCR at 2 or 5-years with an area under the curve (AUC) between 0.75 and 0.84 \([1]\).

However, recent studies investigated the relation between detailed pathological information in PCa patients with PSM experiencing BCR, and found that the cumulative length of the PSM was related to a higher risk on BCR \([2-8]\). As an example, in the most recent study we performed having a median follow-up of 54 months included besides the known risk factors mentioned above also the presence of cribriform growth in the primary tumor, the cumulative length of the PSM, the GG at the PSM, and the presence of cribriform growth in the PSM \([4]\). We found in a cohort of 284 PCa patients with PSM that significant predictors for BCR included besides PSA at diagnosis and pN-stage, also the cumulative length of the PSM, and the GG at the PSM. Up to now, all available analyses on the prediction of BCR after RP including detailed

* Corresponding author at: Department of Urology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, P.O. Box 2040, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.

E-mail address: s.remmers@erasmusmc.nl (S. Remmers).

https://doi.org/10.1016/j.anndiagpath.2021.151842
 information of the PSM are performed in men with PSM. This limits the clinical use of a particular model. In addition to the importance of detailed pathological information of the PSM, it has also been demonstrated that cribriform growth in the RP specimen is related to worse prognosis [9,10]. These findings suggest that prediction models on BCR after RP for men with and without PSM can be improved by adding detailed pathological information.

The aim of the former study of Hollemans et al. [4] was to assess clinicopathological characteristics and risk factors for BCR in men with PSM stressing the importance of detailed pathological report. However as mentioned above, this limits the clinical applicability of a model. The aim of the present study was to assess whether more detailed pathological information of the PSM and the presence of cribriform growth in the primary tumor have added value in the prognostication of BCR after RP including also those men with a negative surgical margin to develop clinically applicable model.

2. Material and methods

2.1. Study population

Our study population, previously reported in Hollemans et al. [4], consist of 835 PCa patients initially treated with RP without neo-adjuvant treatment between 2000 and 2017 at the Erasmus University Medical Center, Rotterdam, The Netherlands. All RP specimens had been reviewed by two investigators (E.H. and G.v.L) in common sessions. At review the following parameters were recorded: GG according to the International Society of Urological Pathological 2014 guidelines [11], presence of cribriform carcinoma defined as a field of contiguous tumor cells without intervening stroma and with visible intercellular lumina [12,13], pt-stage according to the American Joint Committee on Cancer TNM 8th edition [14], and PSM including the cumulative length of the positive margins and the highest GG found in the margin. No distinction between invasive cribriform growth and intraductal carcinoma was made. BCR was defined as two consecutive postoperative PSA ≥0.2 ng/ml after being undetectable [15], a postoperative PSA of at least 2.0 ng/ml after being undetectable [16,17], or PSA persistence since this is related to worse outcome than men with an undetectable PSA after RP [18]. Men who received adjuvant treatment or salvage treatment without the previous definition of BCR were censored at the moment they received adjuvant treatment.

2.2. Statistical analyses

A Cox Proportional Hazard regression was used to evaluate two models predicting the probability of experiencing BCR after RP. In the first model (i.e., the baseline model), predictors for BCR included PSA at diagnosis, GG at RP, pN-stage, pT-stage, and the presence of PSM. In the second model, we extended the first model by replacing the dichotomous predictor PSM with the GG at the surgical margins, and added the presence of cribriform growth in the GG at the primary tumor and the cumulative length of the surgical margin as additional variables. We did not perform stepwise selection of the additional predictors to limit overfitting. We compared the improvement in model fit using the likelihood ratio test. To limit the risk of overfitting, we applied a heuristic method with 2000 bootstrap samples. We multiplied the parameters of the original model by this shrinkage factor to obtain shrinkage corrected parameters. The discrimination of the baseline model and the extended model was assessed by the time-dependent area under the receiver operating characteristic curve (AUC) at 3- and 5-year follow-up (till BCR, death or last follow-up) of 36.5 months (interquartile range, IQR 9.2–80.9). The use of competing risk regression was waived because only 39 (4.7%) of men died (all not PCa related) before experiencing BCR. Median follow-up for men without BCR was 50.4 months (IQR 11.9–95.5). A total of 298 patients were followed for at least 60 months, and 153 patients for at least 100 months. In Table 1 the relevant patient characteristics are described. Men with pT4 (n = 3) and pT3b were merged into a category pT3b/pT4 and men with GG3 (n = 23), GG4 (n = 32), and GG5 (n = 33) at PSM were grouped into a category ≥GG3. All men with cribriform growth in surgical margin also had cribriform growth in the GG, so we excluded this variable in the analysis. Seventy-four percent of patients without BCR had a negative surgical margin as compared to 43% of the men with BCR.

Based on the likelihood ratio test, the extended model had a significantly better fit on the data compared to the baseline model, for both the baseline and the extended model. The 3- and 5-year AUC for the baseline model was 0.83 (95% CI 0.79–0.87) and for the extended model 0.85 (95% CI 0.81–0.88). The calibration slope of the extended model after internal validation was 1.10 (95% CI 0.98–1.22). Our extended model showed an overall higher net-benefit compared to the baseline model for both the prediction of 3- and 5 year BCR although at certain probabilities the increase in net-benefit is limited, see Fig. 1. In the extended model, significant predictors for BCR were the PSA at diagnosis, GG at the primary tumor at RP, pt-stage, pN-stage, the presence of cribriform growth pattern in the primary tumor, and GG at the PSM, see Table 2. Most interestingly, men with GG2 at primary tumor without cribriform growth did not show a significant higher risk on BCR than men with GG1 at primary tumor. In addition, men with GG1 at PSM do not show a higher risk on BCR than men with negative margins. We observed multicollinearity between the cumulative length of the PSM and the GG at the PSM in which a higher cumulative length of the PSM was related to a higher GG at the PSM (data not shown).

4. Discussion

In this study we investigated if additional pathological information could improve the prediction of BCR after RP. The addition of cribriform growth in the primary tumor, the GG at the PSM (instead of the dichotomous PSM), and the cumulative length of the PSM significantly improved the baseline model consisting of PSA at diagnosis, GG at the primary tumor, pt-stage, pN-stage, and PSM. Overall, the net-benefit of the extended model was higher than the baseline model for both the prediction of BCR at 3- and 5-year after RP. We acknowledge that the increase in discriminative ability between the baseline model and the extended model is limited (0.83 for the baseline model and 0.85 for the extended model). However, our results stress the importance of including additional pathological information in the prognostication for the clinician. First, the addition of cribriform growth pattern to the model enabled the identification of a subgroup of men with GG2 disease at primary tumor (without cribriform growth) having a comparable risk on BCR as men with GG1 disease at primary tumor. Second, the addition of the GG at the PSM showed that men with GG1 at the PSM did not have a higher risk on BCR than patients without PSM.

All statistical analyses were performed using R version 3.5.1, survival analyses were done with R-package survival, missing values were imputed once with R-package mice using predictive mean matching, and time dependent ROC curves were calculated by R-package survivalROC.
cumulative length of the PSM and the GG at the PSM in which the in
growth in primary tumor had a higher risk on BCR. An explanation for
logical parameters (even not significant) improved the fit of the data.
model including this measurement and found that additional patho
length of the PSM should not be ignored because we created a prognostic
which we developed a prognostic model. However, the cumulative
study since in the current study also men without PSM were included for
formation of the cumulative length of the PSM is already presented in
the PSM and BCR. This results from the multicollinearity between the
dictors for men with PSM [4]. The most important difference is that we
Another difference in results between the current study and our previous
cribriform growth was related to worse BCR-free survival [10,24]. In addition, two previous studies found that the presence of
crribiform growth in primary tumor had a higher risk on BCR in men with Gleason
6 PCa [23]. In addition, the presence of cribriform growth related to worse BCR-free survival [16]. In addition,
management and to communicate the risk of recurrence with the patient.
Future studies can be aimed at investigating the role between the GG
at the PSM and the location of the recurrence (i.e., localized PCa
recurrence in the pelvic or distant metastasis) since this will result in a

tiotic growth pattern in primary tumor at RP
No Yes
808 (97%) 603 (99%) 205 (92%)
27 (3%) 8 (1%) 19 (8%)
Cumulative length of the surgical margin (mm)
Median (IQR) 0.0 (0.0–2.0) 0.0 (0.0–0.2) 1.9 (0.0–6.8)
Follow-up (months)
Median (IQR) 36.5 50.4 18.0
(9.2–80.9) (11.9–95.5) (7.5–41.9)

GG3 at the PSM was related to a higher risk on BCR in men with Gleason
7 PCa [23]. In addition, two previous studies found that the presence of
crribiform growth was related to worse BCR-free survival [10,24]. However, there are some discrepancies between the findings from the
current study and those we previously performed investigating pre
ceeding. However, there are some discrepancies between the findings from the
current study and those we previously performed investigating pre
ceeding. However, there are some discrepancies between the findings from the
current study and those we previously performed investigating pre
ceeding. However, there are some discrepancies between the findings from the
current study and those we previously performed investigating pre
ceeding. However, there are some discrepancies between the findings from the

to the PSM in which the in
growth in primary tumor had a higher risk on BCR. An explanation for
logical parameters (even not significant) improved the fit of the data.
model including this measurement and found that additional patho
length of the PSM should not be ignored because we created a prognostic
which we developed a prognostic model. However, the cumulative
study since in the current study also men without PSM were included for
formation of the cumulative length of the PSM is already presented in
the PSM and BCR. This results from the multicollinearity between the
dictors for men with PSM [4]. The most important difference is that we
Another difference in results between the current study and our previous
cribriform growth was related to worse BCR-free survival [10,24]. In addition, two previous studies found that the presence of
crribiform growth in primary tumor had a higher risk on BCR in men with Gleason
6 PCa [23]. In addition, the presence of cribriform growth related to worse BCR-free survival [16]. In addition,
management and to communicate the risk of recurrence with the patient.
Future studies can be aimed at investigating the role between the GG
at the PSM and the location of the recurrence (i.e., localized PCa
recurrence in the pelvic or distant metastasis) since this will result in a
different management strategy. Up until now, the relation between the
GG at the PSM and salvage radiotherapy is unclear. There are several
tials showing that in patients with PSM, adjuvant radiotherapy
improved BCR-free survival, but not PCa specific survival [25-27]. However, the RADICALS-RT (timing of radiotherapy after prostate-
tomy) trial and the ARTISTIC meta-analysis [17] did not find that
adjuvant radiotherapy improved BCR-free survival [16]. In addition,
Fig. 1. Decision curve analysis for the baseline model and the extended model predicting the risk on BCR at 3- and 5 year after RP.
other research has shown that salvage radiotherapy will lead to less disease progression in men with PSM compared to men with negative surgical margins [28–30]. It is interesting to investigate whether this effect is observed for any GG at the PSM or whether this effect is limited for men with GG2 or higher at the PSM, because our result suggest that GG1 at the PSM is indolent.

The present study is not without limitations. Before a newly developed prediction model can be implemented in clinical practice, external validation is required. However, we did perform an internal validation in which we introduced some bias in our model to allow better generalizability. Another limitation is that there was no data on preoperative prostate specific membrane antigen (PSMA) PET-CT scan, a procedure becoming more and more common nowadays [31], which could improve our model even further since a recent trial randomised men pre-treatment to either conventional imaging or PSMA PET-CT and found that the latter was superior in detecting metastatic disease [32].

The strength of this study is the relatively large sample size reflecting current contemporary clinical practice which allowed us to investigate the effect of multiple additional parameters. In addition, the clinical treatment to either conventional imaging or PSMA PET-CT and found becoming more and more common nowadays [31], which could be validated studies as surgeries in the current study were performed more recently. To elaborate, the current study includes data between 2000 and 2017, while this was between 1992 and 2005 in the study of Walz et al. [33] and between 1992 and 2010/2011 (exact year not specified) in the study of Cooperberg et al. [34] respectively.

In conclusion, we investigated whether a model predicting the risk on BCR after RP could be improved with the addition of more detailed pathological variables and found that the addition of the presence of cribriform growth in the primary tumor, GG at the PSM, and the length of the PSM have added value in the prognostication of BCR. The increase in discrimination of the extended model is limited compared to the baseline model. Overall, the net-benefit of the extended model was higher than the baseline model for both the prediction of BCR at 3- and 5-year after RP. Given the fact that the pathological information included in the extended model can be part of the reporting, this model should be used for a more accurate prediction of the risk on BCR after RP after external validation. In addition, clinicians should be aware of the role of the GG at the PSM and the presence of cribriform growth to quantify the risk of BCR.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

Acknowledgements

None.

References


