Title

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Addition of cribriform pattern 4 and intraductal prostatic carcinoma into the CAPRA-S tool improves post-radical prostatectomy patient stratification in a multi-institutional cohort

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ABSTRACT

Aims Pre-surgical risk classification tools for prostate cancer have shown better patient stratification with the addition of cribriform pattern 4 (CC) and intraductal prostatic carcinoma (IDC) identified in biopsies. Here, we analyse the additional prognostic impact of CC/IDC observed in prostatectomies using Cancer of Prostate Risk Assessment post-surgical (CAPRA-S) stratification.

Methods A retrospective cohort of treatment-naïve radical prostatectomy specimens from three North American academic institutions (2010–2018) was assessed for the presence of CC/IDC. Patients were classified, after calculating the CAPRA-S scores, into low-risk (0–2), intermediate-risk (3–5) and high-risk (6–12) groups. Kaplan-Meier curves were created to estimate biochemical recurrence (BCR)-free survival. Prognostic performance was examined using Harrell's concordance index, and the effects of CC/IDC within each risk group were evaluated using the Cox proportional hazards models.

Results Our cohort included 825 prostatectomies (grade group (GG)1, n=94; GG2, n=475; GG3, n=185; GG4, n=13; GG5, n=58). CC/IDC was present in 341 (41%) prostatectomies. With a median follow-up of 4.2 years (range 2.9–6.4), 166 (20%) patients experienced BCR. The CAPRA-S low-risk, intermediate-risk and high-risk groups comprised 357 (43%), 328 (40%) and 140 (17%) patients, and discriminated for BCR-free survival (p<0.0001). For CAPRA-S scores 3–5, the addition of CC/IDC status improved stratification for BCR (HR 2.27, 95% CI 1.41 to 3.66, p<0.001) and improved the overall c-index (0.689 vs 0.667, analysis of variance p<0.001).

Conclusion The addition of CC/IDC into the CAPRA-S classification significantly improved post-radical prostatectomy patient stratification for BCR among the intermediate-risk group (CAPRA-S scores 3–5). The reporting of CC and IDC should be included in future prostate cancer stratification tools for improved outcome prediction.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is growing and robust evidence that cribriform pattern 4 (CC) and intraductal carcinoma (IDC) in prostate cancer are associated with adverse clinical outcomes.

WHAT THIS STUDY ADDS

⇒ This is the second multi-institutional study demonstrating that the addition of CC/IDC into contemporary post-radical prostatectomy risk stratification tools can improve outcome predictions in prostate cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study reinforces the importance of reporting CC and IDC in prostate cancer. Future studies will aim to develop and validate modified prognostic models that integrate the presence or absence of CC/IDC.

INTRODUCTION

In North America and Europe, prostate cancer is the most common non-skin malignancy in men, and despite advances in identification through multiparametric MRI and expansion of treatment options, it consistently ranks among the top leading causes of male cancer-related mortality.[1–3] Multiple treatment modalities are available, including active surveillance, focal therapy, radical prostatectomy, radiation therapy and hormone therapy. Several pre-surgical risk stratification tools based on clinical and biopsy parameters exist to aid clinicians in treatment decision-making, such as the National Comprehensive Cancer Network (NCCN) risk grouping system, the Cancer of Prostate Risk Assessment (CAPRA) score and the Memorial Sloan Kettering Cancer nomogram.[4]

Among patients who undergo radical prostatectomy, adjuvant therapy can be offered in high-risk subsets to decrease the likelihood of disease recurrence. To identify low-risk, intermediate-risk and high-risk patients, the CAPRA post-surgical (CAPRA-S) score, developed at the University of California San Francisco, is employed by clinicians.[5] It is similar to the biopsy CAPRA score concept, but incorporates pathological features assessed on the radical prostatectomy in place of the biopsy specimen, which improves the accuracy of postoperative prognostication.

The presence of cribriform pattern 4 (CC) and intraductal carcinoma (IDC) in biopsy and radical prostatectomy specimens are adverse pathological features associated with extraprostatic extension, seminal vesicle invasion, positive surgical margins,

biochemical recurrence (BCR), lymph node metastasis, distant metastasis and cancer-specific death.[6–38] These associations were further confirmed by recent meta-analyses.[39–41] Nonetheless, CC/IDC presence had not been recommended to be specified in addition to grade in pathological diagnoses until recently,[42 43] and there is a lack of studies demonstrating how their incorporation in contemporary risk stratification tools could impact predictions for adverse outcomes.

Previously, we conducted the first comprehensive studies demonstrating the prognostic effects of CC and IDC identified in biopsies when added to the CAPRA and NCCN pretreatment risk classification tools.[44 45] We showed that the addition of CC/IDC improved stratification for BCR and event-free survival (EFS). The impact of CC and IDC in prostatectomies on post-surgical patient stratification tools remains however underexplored.

In this study, our main aim was to analyse the impact of CC and/or IDC observed in prostatectomies on BCR and on EFS using CAPRA-S stratification, based on a multi-institutional North American cohort. Our secondary aim was to determine the prognostic impact of each combination of these binary variables on BCR and on EFS in a subgroup of patients where CC and IDC were assessed separately for their presence or absence with the aid of basal immunohistochemical markers.

METHODS

Patient cohort

Retrospective searches of the laboratory information systems (LIS) were performed to identify radical prostatectomy specimens diagnosed with prostatic acinar adenocarcinoma in the following three North American academic institutions: Sunnybrook Health Sciences Centre (time period 2010–2018), University Health Network (time period 2010–2017) and Medical College of Wisconsin (time period 2014–2018). The vast majority of patients included in this study were part of previous publications.[44 45] The present study included radical prostatectomy specimens that had matched in-house prostate biopsy and for which we were able to collect, from the electronic patient record and LIS, the following clinicopathological parameters: preoperative serum prostate-specific antigen (PSA) level, ISUP (International Society of Urological Pathologists) grade group (GG),[42] surgical margin and pathological tumour (pT) stage. Patients who received radiotherapy, hormone therapy or chemotherapy preoperatively were excluded. For our secondary aim, we included radical prostatectomy specimens from our full cohort for which basal immunohistochemical markers were previously performed to distinguish CC and IDC.

Specimen processing

All radical prostatectomy specimens from Sunnybrook Health Sciences Centre were submitted in toto for histological examination. Radical prostatectomies from University Health Network were submitted in toto if 45 g or less; for specimens more than 45 g, the posterior prostate was submitted in toto with two transverse sections of the anterior portion of the mid-gland, and the remainder of the anterior prostate would only be submitted when carcinoma was identified in the initial blocks.[29] At Medical College of Wisconsin, up until late 2014, specimens were submitted in toto if the weight was 50 g or less, and representatively submitted including the dominant nodule if the weight was more than 50 g; starting late 2014 through 2018, approximately 60% of the specimens followed the same protocol while the remainder ~40% were entirely submitted as whole mount sections as part of a research protocol.

Data interpretation

Genitourinary pathologists (MRD, THvdK and KAI) assessed for the presence and absence of CC and IDC for each radical prostatectomy specimen included in our cohort. Identification of CC was done using the ISUP definition (confluent sheet of malignant epithelial cells with multiple glandular lumina, prominent at 10× magnification, with no intervening stroma or mucin separating individual or fused glandular structures; this includes small and large cribriform patterns).[46] IDC was defined as an expansile, neoplastic, epithelial proliferation within pre-existing ducts or acini, surrounded by residual basal cells; it is characterised by a lumen-spanning solid, cribriform or comedo pattern, or otherwise loose cribriform or micropapillary pattern with large pleomorphic nuclei.[6]

For the radical prostatectomy specimens from Sunnybrook Health Sciences Centre and University Health Network, the assessment for CC/IDC was retrospective for specimens from 2010 until 2014 by retrieving and reviewing all H&E slides and available immunostained slides—this retrospective review was completed as part of prior studies.[44 45] The presence or absence of CC/IDC was reported and prospectively documented for the specimens from 2015 until 2018. IDC was not incorporated into the final Gleason score.

Regarding the prostatectomies from Medical College of Wisconsin, data from the original report were used to determine the presence or absence of CC/IDC, except for prostatectomies signed out by another pathologist, which were retrospectively assessed for CC/IDC by pulling the H&E and pertinent immunostained slides. IDC admixed with invasive cancer was included in Gleason scoring.

We combined CC and IDC for our main aim, classifying prostatectomy specimens as either with or without CC/IDC. For our secondary aim, these two binary variables were individually assessed for their presence or absence, with the aid of basal immunohistochemical markers, such that patients were classified into one of these four combinations: CC−/IDC−, CC−/IDC+, CC+/IDC−, CC+/IDC+. The CAPRA-S score was calculated for each patient by assigning and summing up points for PSA level (ng/mL), Gleason score, positive surgical margin, seminal vesicle invasion, extracapsular extension and lymph node invasion.[5] Of note, prostatectomies staged as pT3b were given 2 points for seminal vesicle invasion and 0 point for extraprostatic extension; patients for which pathological nodal stage was not assigned (no nodes submitted or found) were considered to have no lymph node invasion (0 points). Patients were then categorised into low-risk (0–2), intermediate-risk (3–5) and high-risk (6–12) CAPRA-S groups.

Outcome variables

Endpoints were BCR and EFS based on chart review. BCR was defined as two consecutive PSA levels ≥0.2 ng/mL after radical prostatectomy, as endorsed by the Prostate Cancer Guidelines Update Panel.[47] Events refer to nodal and distant metastases, and cancer-specific death. Time to endpoint is the time lapse from the radical prostatectomy date. Patients with nodal metastasis detected at the time of radical prostatectomy were excluded from the analysis for EFS probabilities. Patients with no report of BCR or event were censored at the date of last follow-up.

Statistical methods

The cohort's clinicopathological characteristics were summarised using descriptive statistics. BCR and EFS were estimated using the Kaplan-Meier method. The 5-year survival probabilities were

Table 1 Clinicopathological characteristics of the full cohort and by institution

Patient characteristics	Full cohort (n=825)	Sunnybrook Health Sciences Centre (n=211)	University Health Network (n=230)	Medical College of Wisconsin (n=384)	P value
Age (years)					**<0.001**
Mean (SD)	62.8 (6.8)	64.4 (7.1)	62.5 (6.6)	62.2 (6.6)	
Median (range)	63 (40–83)	65.0 (44–79)	63 (41–75)	63 (40–83)	
PSA (ng/mL)					0.67
Mean (SD)	9.1 (11.2)	8.6 (6.5)	9.0 (10.0)	9.4 (13.7)	
Median (range)	6.6 (0.5–154.0)	7.0 (0.5–50.9)	7.0 (0.8–97.0)	6.3 (0.7–154.0)	
Prostatectomy ISUP grade group					**<0.001**
1	94 (11.4)	22 (10.4)	24 (10.4)	48 (12.5)	
2	475 (57.6)	100 (47.4)	127 (55.2)	248 (64.6)	
3	185 (22.4)	61 (28.9)	60 (26.1)	64 (16.7)	
4	13 (1.6)	5 (2.4)	6 (2.6)	2 (0.5)	
5	58 (7.0)	23 (10.9)	13 (5.7)	22 (5.7)	
Surgical margin					0.84
Negative	576 (69.8)	144 (68.2)	161 (70.0)	271 (70.6)	
Positive	249 (30.2)	67 (31.8)	69 (30.0)	113 (29.4)	
Pathological stage					**<0.001**
pT2	543 (65.8)	130 (61.6)	121 (52.6)	292 (76.0)	
pT3a	178 (21.6)	41 (19.4)	76 (33.0)	61 (15.9)	
pT3b	104 (12.6)	40 (19.0)	33 (14.3)	31 (8.1)	
CAPRA-S score					**0.004**
0	39 (4.7)	11 (5.2)	7 (3.0)	21 (5.5)	
1	171 (20.7)	39 (18.5)	41 (17.8)	91 (23.7)	
2	147 (17.8)	36 (17.1)	42 (18.3)	69 (18.0)	
3	140 (17.0)	28 (13.3)	36 (15.7)	76 (19.8)	
4	102 (12.4)	21 (10.0)	37 (16.1)	44 (11.5)	
5	86 (10.4)	22 (10.4)	25 (10.9)	39 (10.2)	
6	61 (7.4)	27 (12.8)	19 (8.3)	15 (3.9)	
7	41 (5.0)	15 (7.1)	8 (3.5)	18 (4.7)	
8	20 (2.4)	4 (1.9)	10 (4.3)	6 (1.6)	
9	11 (1.3)	4 (1.9)	4 (1.7)	3 (0.8)	
10	6 (0.7)	3 (1.4)	1 (0.4)	2 (0.5)	
11	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)	
12	0 (0)	0 (0)	0 (0)	0 (0)	
CAPRA-S risk group					**<0.001**
Low risk (0–2)	357 (43.3)	86 (40.8)	90 (39.1)	181 (47.1)	
Intermediate risk (3–5)	328 (39.8)	71 (33.6)	98 (42.6)	159 (41.4)	
High risk (6–12)	140 (17.0)	54 (25.6)	42 (18.3)	44 (11.5)	
CC/IDC					**<0.001**
No	484 (58.7)	113 (53.6)	102 (44.3)	269 (70.1)	
Yes	341 (41.3)	98 (46.4)	128 (55.7)	115 (29.9)	
BCR					0.26
No BCR	659 (79.9)	167 (79.1)	192 (83.5)	300 (78.1)	
BCR	166 (20.1)	44 (20.9)	38 (16.5)	84 (21.9)	
Metastasis or cancer-specific death					0.16
No	743 (96.1)	185 (94.9)	204 (94.9)	354 (97.5)	
Yes	30 (3.9)	10 (5.1)	11 (5.1)	9 (2.5)	
Excluded (nodal metastasis at RP)	52	16	15	21	
CAPRA-S risk group, CC/IDC					**<0.001**
Low risk, CC/IDC=no	274 (33.2)	66 (31.3)	55 (23.9)	153 (39.8)	
Low risk, CC/IDC=yes	83 (10.1)	20 (9.5)	35 (15.2)	28 (7.3)	
Intermediate risk, CC/IDC=no	176 (21.3)	36 (17.1)	41 (17.8)	99 (25.8)	
Intermediate risk, CC/IDC=yes	152 (18.4)	35 (16.6)	57 (24.8)	60 (15.6)	
High risk, CC/IDC=no	34 (4.1)	11 (5.2)	6 (2.6)	17 (4.4)	
High risk, CC/IDC=yes	106 (12.8)	43 (20.4)	36 (15.7)	27 (7.0)	

Statistically significant p values are in bold.
BCR, biochemical recurrence; CAPRA-S, Cancer of the Prostate Risk Assessment post-surgical; CC, cribriform pattern 4; IDC, intraductal carcinoma; ISUP, International Society of Urological Pathologists; PSA, prostate-specific antigen; pT, pathological tumour; RP, radical prostatectomy.

reported for each stratification group of interest, and differences across groups were assessed using the log-rank test.

Kaplan-Meier curves stratified by CAPRA-S and CAPRA-S plus CC/IDC status were visualised. Cox proportional hazards models to quantify the prognostic impact of CC/IDC within each CAPRA-S subgroup were fit. To assess the addition of CC/IDC status to CAPRA-S on prognostication, Cox models incorporating CAPRA-S as the sole predictor and CAPRA-S±IDC/CC as the sole predictor were fit. Harrell's c-index was estimated from each model, and differences in c-indices were assessed using analysis of variance (ANOVA) tests.

To assess the prognostic impact of CC and IDC separately, Kaplan-Meier curves stratified by the four combination groups were visualised, based on the subgroup of patients for which slides stained for basal markers were available to distinguish between IDC and CC. Cox proportional hazards models incorporating the group as the predictor were fit. To explore any potential interaction between CC and IDC, separate models incorporating an interaction term between CC and IDC were fit for each outcome.

The proportional hazards assumption for all Cox models was verified by assessing the Schoenfeld residuals from each fitted model. Statistical analyses were conducted using R V.4.2.2 (R Core Team), all statistical tests were two sided and p values less than 0.05 were considered significant.

RESULTS

Clinicopathological characteristics

Our main analysis included 825 patients. Table 1 displays the clinicopathological characteristics of the full cohort and by institution. In the full cohort, the median age was 63 years (range 40–83) and the median PSA was 6.6 ng/mL (range 0.5–154.0) at diagnosis. Most prostatectomies were GG2 (58%), and the pT stage was predominantly pT2 (66%). The surgical margin was positive in 249 (30%) prostatectomies. Calculation of the CAPRA-S scores resulted in the classification of 357 (43%) patients into the low-risk group (0–2), 328 (40%) into the intermediate-risk group (3–5) and 140 (17%) into the high-risk group (6–12). CC/IDC was identified in 341 (41%) prostatectomies. Among the low-risk, intermediate-risk and high-risk groups, 23%, 46% and 76% of patients, respectively, had CC/IDC in the prostatectomy specimen. With a median follow-up of 4.2 years (range 2.9–6.4), BCR occurred in 166 (20%) patients. Metastatic disease/cancer-specified death following radical prostatectomy was noted for 30 (4%) patients. Out of the 191 patients whose prostatectomy included lymph node dissection, 52 patients had nodal metastasis.

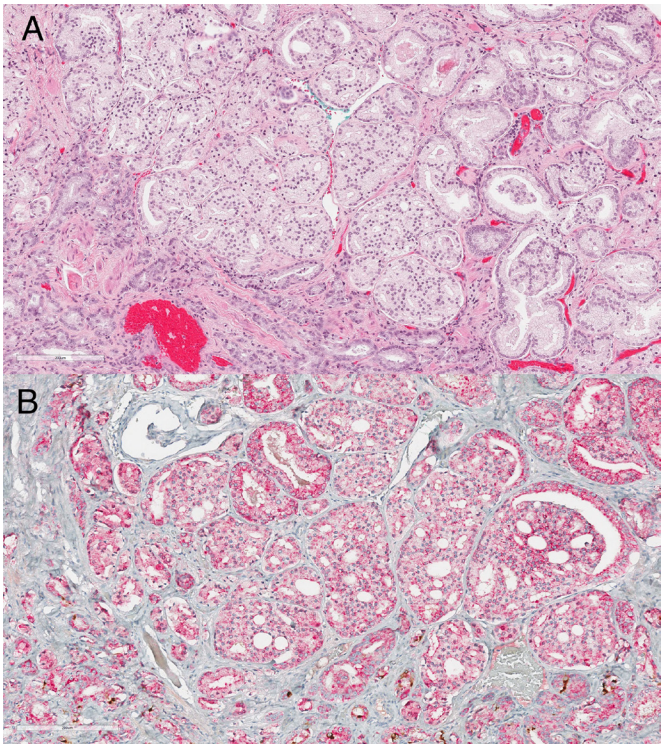

Figure 1 Cribriform pattern 4 (CC) in a radical prostatectomy specimen. (A) H&E and (B) prostate cocktail (p63, 34ßE12, AMACR) immunostain showing a lack of basal cells, supporting the diagnosis of CC.

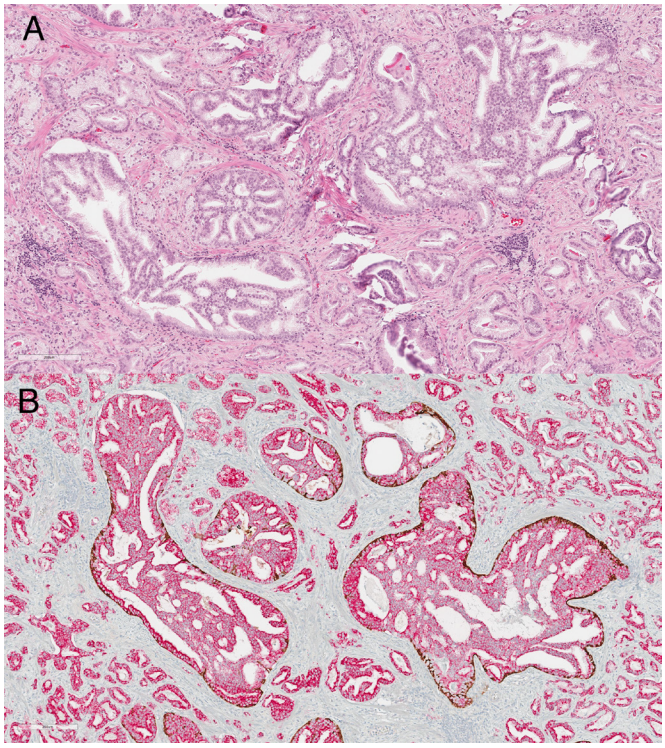

Figure 2 Intraductal carcinoma (IDC) in a radical prostatectomy specimen. (A) H&E and (B) prostate cocktail (p63, 34ßE12, AMACR) immunostain showing retained basal cells, supporting the diagnosis of IDC.

Our subanalysis, which aims to study the impact of CC and IDC assessed separately on outcome probabilities, included all prostatectomy specimens for which basal marker slides were available for retrospective review (n=426). Figure 1 illustrates an example of a case with CC, and figure 2 shows an example of a case with IDC. We identified 215 prostatectomies with CC−/IDC−, 42 prostatectomies with CC−/IDC+, 123 prostatectomies with CC+/IDC− and 46 prostatectomies with CC+/IDC+. Out of these 426 prostatectomies, 28 (7%) had nodal metastasis at radical prostatectomy.

Prognostic impact of CC/IDC on CAPRA-S risk stratification

Kaplan-Meier survival curves for BCR-free survival demonstrated that the three CAPRA-S risk groups discriminated for BCR (p<0.0001), as shown in figure 3A and table 2. The addition of CC/IDC into the CAPRA-S classification (figure 3B and table 2) provided further stratification for BCR in the

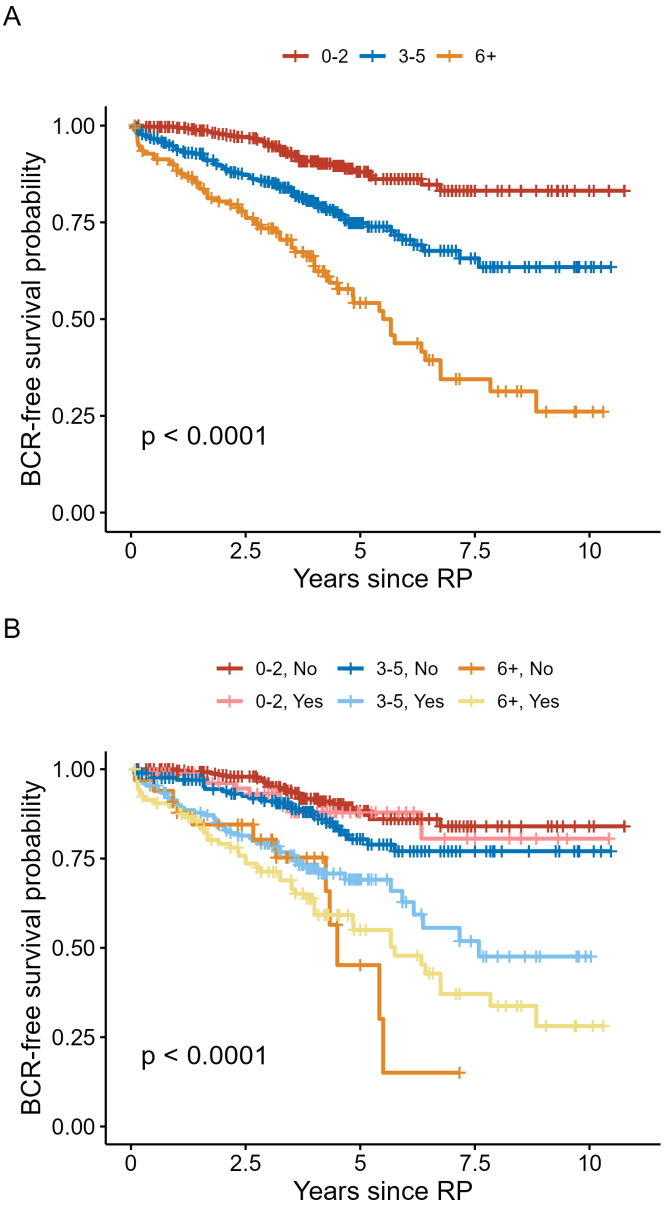

Figure 3 Impact of CC/IDC on biochemical recurrence (BCR)-free survival probabilities of the full cohort using CAPRA-S risk stratification. (A) Full cohort stratified by CAPRA-S only. (B) Full cohort stratified by CAPRA-S with the addition of CC/IDC. CAPRA-S, Cancer of the Prostate Risk Assessment post-surgical; CC, cribriform pattern 4; IDC, intraductal carcinoma; RP, radical prostatectomy.

intermediate-risk group (p<0.0001), but did not improve the ability to stratify the low-risk group for BCR. For the high-risk group, it seems that patients without CC/IDC did marginally better than their counterparts with CC/IDC between years 4 and 5, but the survival probability dropped substantially following that period, which we interpret as inconclusive. The c-index was 0.667 in the model when CC/IDC was not taken into account, and increased to 0.689 in the model with CC/IDC. Though the increase was small, the ANOVA comparing the two models was statistically significant (ANOVA p<0.001), which demonstrates that addition of CC/IDC elicited a better prediction for postoperative BCR. Among the intermediate-risk group, the HR for BCR was 2.27 times higher in patients with CC/IDC compared with patients without CC/IDC (95% CI 1.41 to 3.66, p<0.001). The differences in hazard rates were not statistically significant

Table 2 Five-year biochemical recurrence (BCR)-free survival of the full cohort, stratified by CAPRA-S without and with the addition of CC/IDC

Stratification	BCR	5-year BCR-free survival (95% CI)	P value
By CAPRA-S only			<0.0001
Low risk (0–2)	33/357	0.88 (0.84, 0.92)	
Intermediate risk (3–5)	73/328	0.75 (0.69, 0.81)	
High risk (6–12)	60/140	0.54 (0.45, 0.66)	
By CAPRA-S with the addition of CC/IDC			<0.0001
Low risk, CC/IDC=no	24/274	0.88 (0.84, 0.93)	
Low risk, CC/IDC=yes	9/83	0.88 (0.80, 0.96)	
Intermediate risk, CC/IDC=no	27/176	0.80 (0.73, 0.88)	
Intermediate risk, CC/IDC=yes	46/152	0.69 (0.61, 0.78)	
High risk, CC/IDC=no	12/34	0.45 (0.24, 0.85)	
High risk, CC/IDC=yes	48/106	0.55 (0.45, 0.67)	

CAPRA-S, Cancer of the Prostate Risk Assessment post-surgical; CC, cribriform pattern 4; IDC, intraductal carcinoma.

within the low-risk (HR 1.35, 95% CI 0.63 to 2.90, p=0.44) and high-risk (HR 0.94, 95% CI 0.49 to 1.79, p=0.85) groups.

Regarding metastasis/cancer-specific death, Kaplan-Meier curves distinguished two risk categories among the CAPRA-S risk groups: the high-risk group versus the low/intermediate-risk group (p<0.0001, figure 4A and table 3). The impact of CC/IDC on EFS is impossible to evaluate due to the very small number of events that occurred during our follow-up within each CAPRA-S risk group (figure 4B and table 3).

Prognostic impact of CC and IDC separately

Figure 5 and table 4 show the BCR-free survival and EFS probabilities for the subgroup of patients for which CC and IDC were assessed separately. The patients with CC−/IDC− had the best BCR-free survival and EFS probabilities. Patients with CC+/IDC+ had the worst BCR-free survival (HR 4.53, 95% CI 2.33 to 8.83, p<0.001); patients with CC−/IDC+ (HR 2.62, 95% CI 1.23 to 5.57, p=0.01) and CC+/IDC− (HR 2.78, 95% CI 1.60 to 4.82, p<0.001) had similar outcomes. There was no interaction observed between CC and IDC for BCR (p=0.34). Due to the small number of events, the impact of CC and IDC on EFS could not be formally assessed.

DISCUSSION

The CAPRA-S tool was designed to predict BCR and adverse clinical outcomes and to identify patients at high risk who could benefit from intensification of adjuvant therapy. While a CAPRA-S high-risk score (6–12) is a strong indication for intensified salvage therapy, patients within the CAPRA-S intermediate group (3–5) are subject to more uncertainty regarding the treatment plans that would benefit them the most. In this study, we hypothesised that CC/IDC can impact the CAPRA-S tool based on the growing and robust evidence that CC/IDC in biopsies and prostatectomies is associated with adverse clinical outcomes in prostate acinar adenocarcinoma. Kweldam *et al* demonstrated that among men diagnosed with GG2 prostate cancer on biopsies, the presence of CC/IDC was associated with a worse disease-specific survival, whereas the absence of CC/IDC rendered survival probabilities similar to GG1 prostate cancer.[16] Moreover, CC/IDC status in GG2 cancer was found to outperform the percentage of Gleason pattern 4 in biopsies

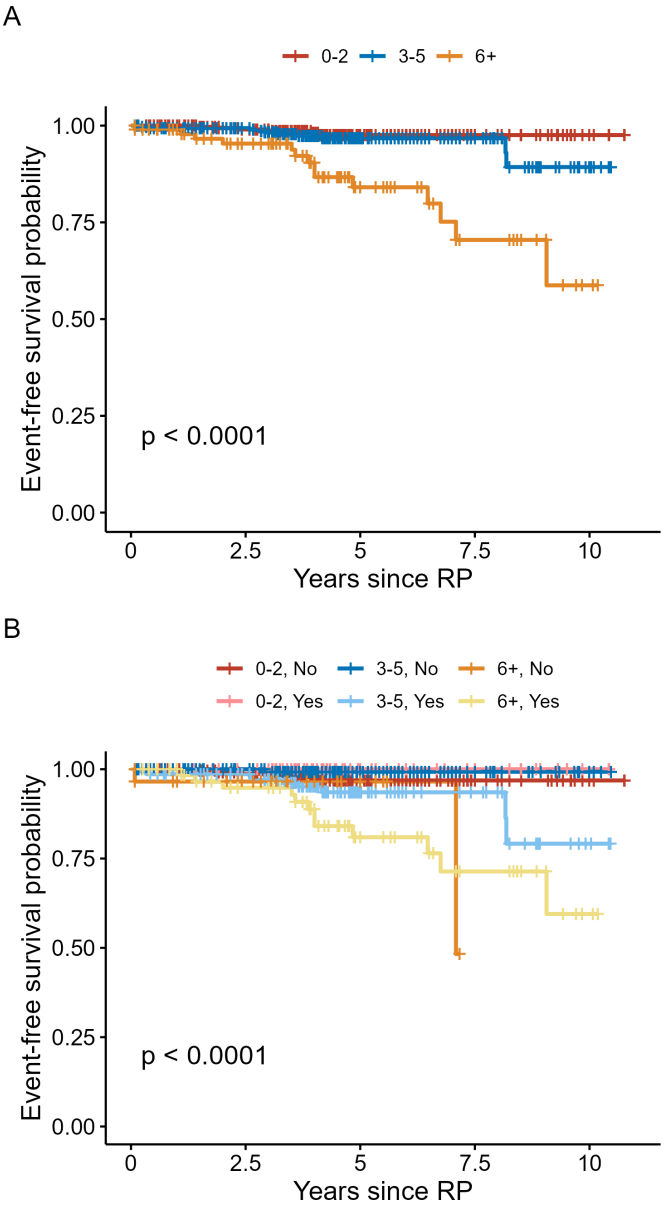

Figure 4 Impact of CC/IDC on event-free survival probabilities of the full cohort using CAPRA-S risk stratification. (A) Full cohort stratified by CAPRA-S only. (B) Full cohort stratified by CAPRA-S with the addition of CC/IDC. CAPRA-S, Cancer of the Prostate Risk Assessment post-surgical; CC, cribriform pattern 4; IDC, intraductal carcinoma; RP, radical prostatectomy.

Table 3 Five-year event-free survival of the full cohort, stratified by CAPRA-S without and with the addition of CC/IDC

Stratification	Event	5-year event-free survival (95% CI)	P value
By CAPRA-S only			<0.0001
Low risk (0–2)	6/357	0.98 (0.96, 1.00)	
Intermediate risk (3–5)	10/320	0.97 (0.94, 0.99)	
High risk (6–12)	14/96	0.84 (0.75, 0.94)	
By CAPRA-S with the addition of CC/IDC			<0.0001
Low risk, CC/IDC=no	6/274	0.97 (0.94, 0.99)	
Low risk, CC/IDC=yes	0/83	1.00 (1.00, 1.00)	
Intermediate risk, CC/IDC=no	1/175	0.99 (0.98, 1.00)	
Intermediate risk, CC/IDC=yes	9/145	0.94 (0.89, 0.99)	
High risk, CC/IDC=no	2/30	0.97 (0.90, 1.00)	
High risk, CC/IDC=yes	12/66	0.81 (0.70, 0.93)	

CAPRA-S, Cancer of the Prostate Risk Assessment post-surgical; CC, cribriform pattern 4; IDC, intraductal carcinoma.

and radical prostatectomies, and also tertiary pattern 5 in radical prostatectomies for outcome predictions.[18 32] CC/IDC also impacts prognostication in GG4 and GG5 according to other studies.[22 25 28 37 38] Harding-Jackson *et al* found cribriform presence to be more important than the distinction of grades 4+4 vs 3+5 in biopsies.[48]

Here, based on a multi-institutional cohort encompassing all grade groups, the addition of CC/IDC at radical prostatectomy into the CAPRA-S stratification tool yielded better prediction for BCR within the intermediate-risk group. Patients with CC/IDC had more than twice the risk of showing BCR compared with patients without CC/IDC when the CAPRA-S score was 3–5. Interestingly, Jeyapala *et al* also found that stratification by CAPRA-S risk group combined with CC/IDC status improved prognostication for BCR in the CAPRA-S classification, but only in the low-risk group, based on three cohorts from two institutions.[49] Recently, Bogaard *et al* demonstrated that a cribriform pattern and high Ki-67 were independent predictors of adverse clinical outcomes and associated with a higher CAPRA-S risk group.[50] Accumulating evidence has proved that CC/IDC status holds an independent prognostic value and that its addition into the CAPRA-S stratification tool would improve prognostication. Our finding in the present study is particularly relevant since we were able to prove that the addition of CC/IDC has a prognostic impact on the CAPRA-S intermediate-risk group, where treatment decisions can be more challenging since it is neither low risk nor high risk. It was described by Trinh *et al* that the presence of IDC had similar impact as high-risk features such as a GG 4–5, a positive surgical margin and a pT3 stage, with adjuvant radiotherapy reducing BCR rates.[51] In future studies, it would be clinically relevant to determine the net benefit of salvage therapy intensification in patients with both CAPRA-S scores 3–5 and CC/IDC. Even if the presence of CC/IDC in radical prostatectomy specimens has prognostic significance, use of this parameter to guide therapy would have to be balanced with the significant adverse side effects of adjuvant therapy. Forthcoming research should also assess the prognostic impact of CC/IDC in contemporary genome-based risk classification such as the prostatectomy-based Decipher score.[52] In fact, some studies have already shown an association between CC/IDC in prostatectomies and higher Decipher risk scores.[53–55]

The main limitations of the present study were the size of our cohort, the follow-up period and the retrospective design. Statistical results for BCR in the CAPRA-S high-risk group and for EFS in all risk groups when adding CC/IDC were inconclusive due to the relatively small volume of patients comprising each stratification group, and the short follow-up period during which there were too few events. While this study was able to demonstrate the impact of CC/IDC for BCR stratification in the intermediate-risk group, we should keep in mind that BCR has been found to have a limited association with prostate-specific mortality.[56] Demonstration of the impact of CC/IDC on EFS predictions would have added robustness to our study which aims to prove the prognostic significance of CC/IDC. All that being said, in our previous studies, the addition of CC/IDC in risk stratification tools has indeed shown to have an impact on both BCR and EFS probabilities. Our study led by

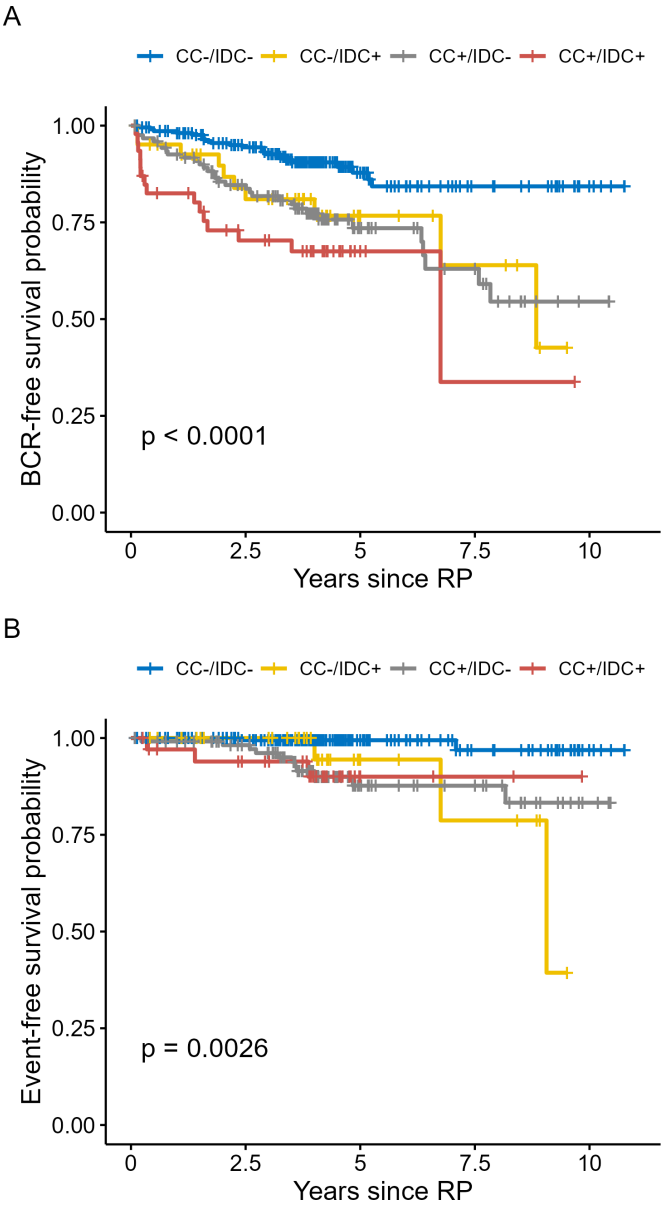

Figure 5 Impact of CC and IDC assessed separately on biochemical recurrence (BCR)-free survival (A) and event-free survival (B). CC, cribriform pattern 4; IDC, intraductal carcinoma; RP, radical prostatectomy.

Yu *et al* demonstrated that the addition of CC/IDC found in biopsies into the pre-surgical CAPRA score had an impact in CAPRA scores 3–5 for BCR, and in CAPRA scores 6–10 for EFS, based on a cohort of 612 patients from two Toronto institutions.[44] Our subsequent study by Downes *et al* showed similar results with improvement of BCR predictions for CAPRA scores 3–5 and of EFS predictions for CAPRA scores 6–10, based on a cohort of 1326 patients from Toronto, Wisconsin and Rotterdam.[45] Thus, we believe that the addition of CC/IDC in prostatectomies into the CAPRA-S score carries the potential to have similar results upon study of a larger, more diverse cohort with a longer follow-up.

Combining CC and IDC as we did for our main aim expands the applicability of their reporting externally since not all institutions systematically perform immunohistochemical studies to distinguish those two entities in equivocal scenarios, especially if the results would not change the Gleason score.[42 43] Nevertheless, it remains relevant to distinguish the impact of CC+/IDC+ vs CC+/IDC− vs CC−/IDC+ to evaluate the pertinency of reporting these two findings separately. Kaplan-Meier curves of a subgroup of our cohort upon breakdown of CC and IDC status depicted that patients with CC−/IDC− had the best prognosis for BCR. CC+/IDC+ was associated with the poorest prognosis for BCR. The presence of either CC or IDC was associated with an intermediate risk for BCR compared with patients with CC−/IDC− or CC+/IDC+. It was however difficult to detect whether there is a significant difference in outcome probabilities for patients with CC only versus patients with IDC only, most likely due to the small number of patients and endpoints that were analysed. The size of the subgroup also restricted our ability to draw conclusions from the Kaplan-Meier curves for EFS. It is reasonable to believe that dichotomisation of these two histological findings could lead to improved outcome predictions; hence, we suggest reporting CC and IDC distinctively for documentation on a research basis. In addition, it would be worthwhile to evaluate if the size and percentage of CC and IDC can factor into prognostication. To date, there is no consensus as to whether the size and extent of CC/IDC have prognostic value.[7 21 36 38 57 58] A caveat for the distinction of CC and IDC is that flattened tumour cells often mimic basal cells on morphology, while basal cells may not be present in the immunostained plane of section because the basal layer is often fragmented in IDC. Molecular profiling of CC and IDC could potentially broaden our knowledge and understanding of CC and IDC specifically their clinical significance.

In conclusion, the addition of CC/IDC in prostatectomies to the CAPRA-S classification allowed significant improvement of BCR stratification for the intermediate-risk group (CAPRA-S scores 3–5) in our multi-institutional North American cohort. This suggests that the CC/IDC status can aid clinicians in evaluating if patients with CAPRA-S scores 3–5 are eligible for intensification or deintensification of salvage therapy after biochemical failure in the post-radical prostatectomy setting. All in all, it remains clear that CC and IDC are strong independent predictors of poorer prognosis in prostate cancer. Our findings reinforce the recommendation to report them in biopsy and prostatectomy

Table 4 Five-year biochemical recurrence (BCR)-free survival and event-free survival of the subgroup for which CC and IDC were assessed separately

Stratification	BCR	5-year BCR-free survival (95% CI)	P value	Event	5-year event-free survival (95% CI)	P value
By CC and IDC status (n=426)			<0.0001			<0.0026
CC−/IDC− (n=215)	21/215	0.88 (0.82, 0.94)		2/215	0.99 (0.98, 1.00)	
CC−/IDC+ (n=42)	10/42	0.77 (0.63, 0.93)		3/33	0.94 (0.84, 1.00)	
CC+/IDC− (n=123)	32/123	0.73 (0.65, 0.83)		11/115	0.88 (0.80, 0.96)	
CC+/IDC+ (n=46)	15/46	0.68 (0.55, 0.83)		3/35	0.90 (0.80, 1.00)	

CC, cribriform pattern 4; IDC, intraductal carcinoma.

specimens,[42 43] and we advocate for their integration in current risk stratification tools for more accurate outcome predictions.

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