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Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy

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Invasive cribriform and intraductal carcinoma in radical prostatectomy specimens have been associated with an adverse clinical outcome. Our objective was to determine the prognostic value of invasive cribriform and intraductal carcinoma in pre-treatment biopsies on time to disease-specific death. We pathologically revised the diagnostic biopsies of 1031 patients from the first screening round of the European Randomized Study of Screening for Prostate Cancer (1993–2000). Ninety percent of all patients ($n = 923$) had received active treatment, whereas 10% ($n = 108$) had been followed by watchful waiting. The median follow-up was 13 years. Patients who either had invasive cribriform growth pattern or intraductal carcinoma were categorized as CR/IDC+. The outcome was disease-specific survival. Relationships with outcome were analyzed using multivariable Cox regression and log-rank analysis. In total, 486 patients had Gleason score 6 (47%) and 545 had ≥7 (53%). The 15-year disease-specific-survival probabilities were 99% in Gleason score 6 ($n = 486$), 94% in CR/IDC− Gleason score ≥7 ($n = 356$) and 67% in CR/IDC+ Gleason score ≥7 ($n = 189$). CR/IDC− Gleason score 3+4 = 7 patients did not have statistically different survival probabilities from those with Gleason score 6 ($P = 0.30$), while CR/IDC+ Gleason score 3+4 = 7 patients did ($P < 0.001$). In multivariable analysis, CR/IDC+ status was independently associated with a poorer disease-specific survival (HR 2.6, 95% CI 1.4–4.8, $P = 0.002$). We conclude that CR/IDC+ status in prostate cancer biopsies is associated with a worse disease-specific survival. Our findings indicate that men with biopsy CR/IDC− Gleason score 3+4 = 7 prostate cancer could be candidates for active surveillance, as these patients have similar survival probabilities to those with Gleason score 6.
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The management of newly diagnosed prostate cancer is challenging because of its heterogeneity in histology, genetics, and clinical outcome. Today, clinical decision-making mostly depends upon serum prostate-specific antigen (PSA) level, clinical tumor stage, and pathologic biopsy Gleason score—a grading system based on architectural tumor patterns. Although patients with the lowest Gleason scores ≤6 have an excellent outcome, those with the highest Gleason scores (9–10) have the worst.[1]

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The clinical outcome of Gleason score 7 prostate cancer patients is highly variable. Improving risk assessment is of particular interest, as Gleason score 7 prostate cancer on biopsy is an important clinical threshold for active treatment. Recent studies have suggested that the broad contemporary definition of the Gleason grade 4 pattern may be one of the explanations for the variable outcomes of patients with Gleason score 7 prostate cancer.[2–5] Architecturally, four Gleason grade 4 growth patterns are recognized: ill-formed, fused, glomeruloid, and cribriform.[1,6] Recently, cribriform pattern has been associated with adverse outcome after radical prostatectomy in Gleason score 7 prostate cancer.[2–5]

In recent years, the clinical relevance of intraductal carcinoma of the prostate—a high-risk lesion defined as malignant epithelium filling large acini or

ducts with preservation of basal cells—has been acknowledged. Although not included in the Gleason score, intraductal carcinoma has been associated with high Gleason scores, advanced tumor stage, biochemical relapse, and distant metastasis.[7–12] Intraductal carcinoma can, however, microscopically mimic invasive cribriform carcinoma requiring additional immunohistochemistry for their distinction. Studies on the prognostic value of invasive cribriform and intraductal carcinoma have mostly been based on radical prostatectomy specimens.[2–5,11,13] The aim of this study was to determine the prognostic value of invasive cribriform and intraductal carcinoma in diagnostic biopsies on time to disease-specific death.

Materials and methods

Patient Selection

We included all 1078 men from the first screening round of the Dutch part of the European Randomized Study of Screening for Prostate Cancer (ERSPC), who had been diagnosed with prostate cancer between November 1993 and March 2000 in Erasmus Medical Centre, Rotterdam, The Netherlands. The trial protocol has been published previously.[14,15] The ERSPC is an ongoing multicenter randomized screening trial that was initiated in the early 1990s to evaluate the effect of screening with PSA testing on disease-specific mortality rates. Exclusion criteria of the present study were unavailability of slides or paraffin blocks for review ($n=24$) and presence of lymph node or distant metastasis at the time of diagnosis ($n=23$), leaving 1031 patients for analysis.

Pathological Evaluation

Three investigators (CFK, IPK, and GJvL), who were blinded to patient information and outcome, revised all histopathological slides. For each biopsy core, we recorded tumor percentage, tumor length (mm), Gleason score, presence of intraductal carcinoma, and presence of Gleason grade 4 and 5 growth patterns.[1] The overall tumor percentage per patient was defined as the sum of total tumor length (mm) divided by the sum of total biopsy length (mm). The label CR/IDC+ was given to patients who either had invasive cribriform carcinoma, intraductal carcinoma or both, CR/IDC− to those who had neither. CR/IDC-specific tumor percentage per patient was defined as the sum of total length CR/IDC glands (mm) divided by the sum of total biopsy length (mm). Gleason grading was performed according to the 2014 ISUP recommendations.[1] To distinguish invasive cribriform carcinoma from intraductal carcinoma and high-grade prostatic epithelial neoplasia (HGPIN) from intraductal carcinoma, we used morphological criteria as described by Guo *et al*.[7] In case morphological distinction between invasive cribriform carcinoma and intraductal carcinoma was not certain (105/193, 54%), we applied high-molecular-weight-keratin immunohistochemistry to detect the presence of basal cells.

Clinical Follow-up

After diagnosis and initial treatment, patients were semi-annually monitored by chart review to assess potential progression and secondary treatments. The cause of death was evaluated by an independent cause-of-death committee, where deaths due to causes related to screening were also counted as prostate cancer deaths.[16] Although data on the occurrence of distant metastases were available, we did not include this end point in our study, as these events largely overlapped with the number of disease-specific deaths.

Statistical Analysis

Continuous parameters were analyzed by the Mann-Whitney *U*-test or Kruskal-Wallis test, categorical parameters by the Pearson's chi-square (χ^2) test. Non-normally distributed continuous variables underwent log base 2 transformation such that effects related to a doubling in unit. We estimated survival probabilities using the Kaplan-Meier method. Unadjusted comparisons for survival time were made using log-rank tests with censoring of men lost to follow-up or dying of other causes. Crude and adjusted hazard ratios (HRs) for survival time were calculated using Cox proportional hazards regression. The concordance index (c-index) was used to quantify the ability of single variables and combinations of variables in multivariable models to discriminate between patients with and without the event of interest.[17] The c-index takes values between 0.5 and 1, where 0.5 indicates that the model is not better than chance classification and 1 means perfect discrimination.[18] Regression models were compared using the likelihood-ratio test. All statistical analyses were performed in R version 3.1.2 (R, Vienna, Austria). Two-sided *P*-values of <0.05 were considered statistically significant.

Results

Patient Characteristics

The median age of the entire cohort ($N=1031$) was 66 years (IQR 62–71) and the median follow-up was 13 years (IQR 9.4–16; Table 1). In total, 90% of all patients ($n=923$) had received active treatment, whereas 10% ($n=108$) had been followed by watchful waiting. A total of 496 patients died during follow-up, 72 of whom from prostate cancer. The majority (53%) of patients had Gleason score 3+4 = 7 or higher. Gleason score was positively associated with age, PSA level, tumor percentage, and

Table 1 Patient and tumor characteristics ($N = 1031$)

	Mean (median, IQR) or n (%)					
	Gleason score 6 (n = 486)	*Gleason score 3+4 = 7 (n = 310)*	*Gleason score 4+3 = 7 (n = 104)*	*Gleason score 8 (n = 64)*	*Gleason score 9–10 (n = 67)*	P-*value*
Age at diagnosis (years)	66 (66, 61–70)	66 (67, 62–71)	68 (69, 65–71)	68 (69, 66–72)	67 (67, 64–71)	< 0.001[a]
PSA level at diagnosis (ng/ml)	5.8 (4.7, 3.5–6.9)	8.8 (5.8, 4.0–9.0)	15 (8.6, 4.7–18)	19 (11, 6.2–17)	16 (9.4, 5.4–16)	< 0.001[a]
Percentage of positive cores (%)	31 (29, 17–43)	2.9 (3.0, 2.0–4.0)	50 (43, 29–71)	55 (50, 40–71)	62 (57, 43–86)	< 0.001[a]
Tumor percentage (%)	24 (17, 9.5–33)	43 (44, 27–57)	51 (51, 33–68)	51 (52, 33–66)	56 (56, 41–74)	< 0.001[a]
Gleason grade 4 patterns						
Ill-formed		227 (73)	63 (85)	51 (80)	64 (96)	< 0.001[b]
Fused		153 (49)	46 (62)	32 (50)	39 (58)	0.07[b]
Cribriform		24 (7.7)	38 (37)	23 (36)	26 (39)	< 0.001[b]
Glomeruloid		33 (11)	14 (19)	13 (20)	11 (16)	0.02[b]
Gleason grade 5 patterns						
Single cells and strands				35 (55)	61 (91)	< 0.001[b]
Solid				3 (4.7)	16 (24)	0.002[b]
Intraductal carcinoma	4 (0.82)	41 (13)	44 (42)	18 (28)	32 (48)	< 0.001[b]
CR/IDC+ status	4 (0.82)	54 (17)	60 (58)	33 (52)	42 (63)	< 0.001[b]
Primary treatment						
Radical prostatectomy	216 (44)	129 (42)	33 (32)	14 (22)	14 (21)	< 0.001[b]
Radiotherapy	188 (39)	154 (59)	66 (63)	48 (75)	52 (78)	< 0.001[b]
Endocrine treatment	2 (0.41)	3 (0.97)	1 (0.96)	1 (1.6)		
Watchful waiting	80 (17)	23 (7.4)	3 (2.8)	1 (1.6)	1 (1.5)	< 0.001[b]
Radiotherapy and endocrine treatment			1 (0.96)			
Unknown		1 (0.27)				
Prostate-cancer-specific deaths	8 (1.6)	14 (4.5)	17 (16)	14 (22)	19 (28)	

[a]Kruskal-Wallis test. [b]Pearson's chi-square (χ^2) test.

percentage of positive cores. The most frequently observed Gleason grade 4 pattern in Gleason score 3+4 = 7 or higher was ill-formed (80%), followed by fused (53%), cribriform (20%), and glomeruloid (15%). Presence of cribriform growth was the most discriminative Gleason grade 4 pattern between Gleason score 3+4 = 7 and 4+3 = 7 (7.7 *vs* 37%, χ^2 $P < 0.001$). We found a similar association for intraductal carcinoma (13 *vs* 42%, χ^2 $P < 0.001$). Intraductal carcinoma co-existed with invasive cribriform carcinoma in 57 of 111 patients (51%). Invasive cribriform and intraductal carcinoma were predominantly seen in Gleason score 4+3 = 7 and higher prostate cancer. In total, 193 patients had CR/IDC+ status; the distribution among Gleason score is shown in Table 1. Most low-risk patients had undergone radical prostatectomy whereas high-risk patients had received radiotherapy.

Prognostic Value of CR/IDC Status

Presence of intraductal carcinoma (crude HR 7.6, 95% CI 4.8–12; $P < 0.001$, c-index = 0.697) and invasive cribriform carcinoma (crude HR 6.3, 95% CI 3.9–10; $P < 0.001$, c-index = 0.639) were both significantly associated with worse disease-specific survival in univariate analyses. The combined CR/IDC+ status was also strongly associated with worse disease-specific survival (crude HR 11, 95% CI 6.6–18; $P < 0.001$, c-index = 0.758) and was similar if intraductal carcinoma and invasive cribriform carcinoma were analyzed as separate predictors in a model (c-index = 0.761). When separating each Gleason score group for CR/IDC status the disease-specific-survival probabilities were significantly lower in CR/IDC+ patients with Gleason score 3 +4 = 7, 8, and 9–10 (Figure 1). Although we saw some evidence of lower survival probabilities in CR/IDC+ Gleason score 4+3 = 7, differences between groups did not meet conventional levels of statistical significance (log rank $P = 0.054$). The Gleason score 6 group contained only four CR/IDC+ patients (all intraductal carcinoma). CR/IDC – Gleason score 3+4 = 7 patients did not have significantly different survival probabilities from those with Gleason score 6 (log rank $P = 0.30$), while CR/IDC+ Gleason score 3 +4 = 7 patients had significantly worse survival probabilities than those with Gleason score 6 (log rank $P < 0.001$) and CR/IDC – Gleason score 3+4 = 7 (log rank $P = 0.001$). The survival probabilities of CR/IDC – patients with 4+3 = 7 or higher were significantly lower than of those with Gleason score 6 (log rank $P < 0.001$, $P = 0.03$, and $P < 0.001$, respectively). CR/IDC – Gleason score 4+3 = 7 patients also had worse survival probabilities than those with CR/IDC – 3+4 = 7 ($P = 0.03$). Although patients with CR/IDC – Gleason score 9–10 had poorer survival probabilities than those with CR/IDC – Gleason score 3+4 = 7 prostate cancer (log rank $P = 0.001$),

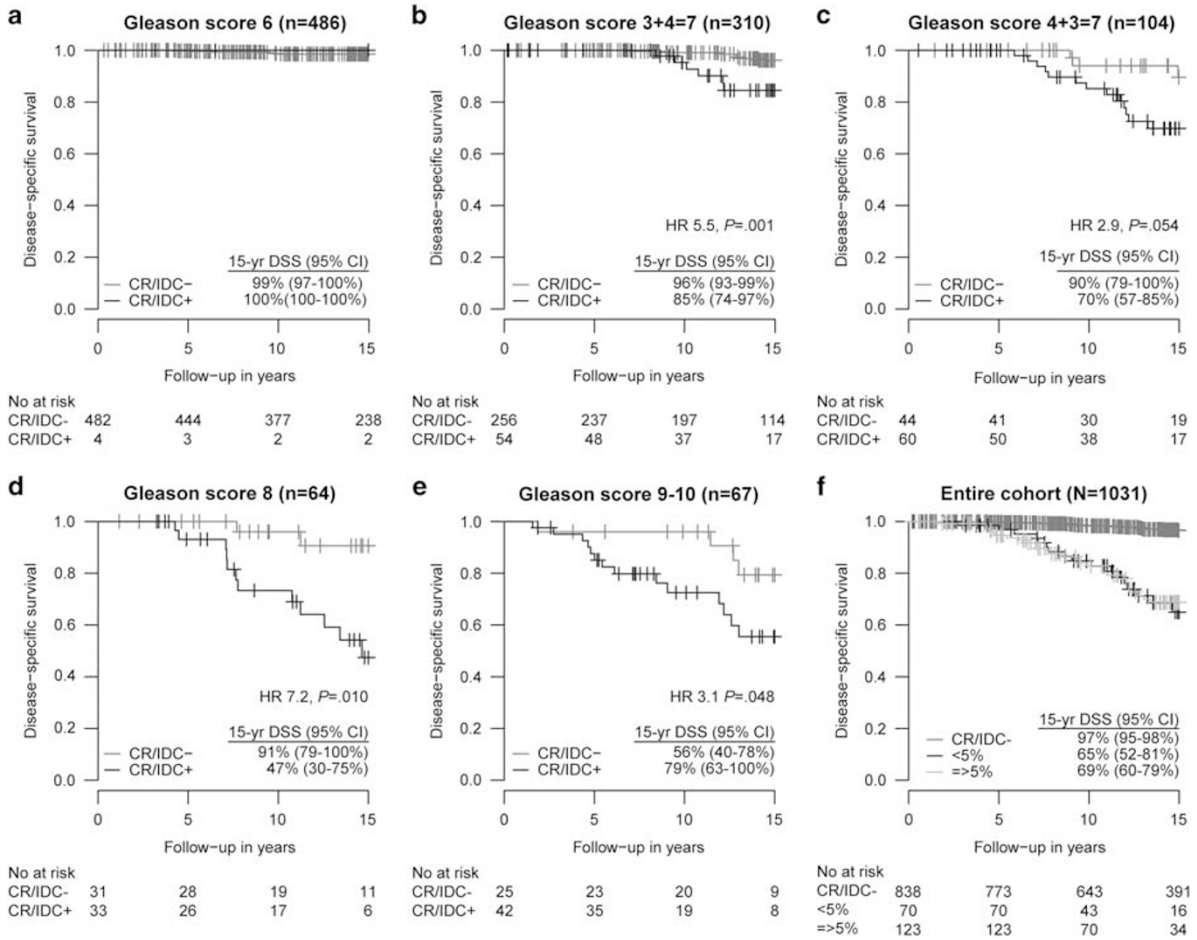

Figure 1 Kaplan-Meier disease-specific survival (DSS) according to Gleason score and CR/IDC status. (**a**) Gleason score 6. (**b**) Gleason score 3+4 = 7. (**c**) Gleason score 4+3 = 7. (**d**) Gleason score 8. (**e**) Gleason score 9–10. (**f**) DSS probabilities according to percentage of CR/IDC glands.

there was no statistical difference in disease-specific-survival probabilities comparing CR/IDC − Gleason score 9–10 with CR/IDC − Gleason score 4+3 = 7 and CR/IDC − Gleason score 8 patients (log rank $P = 0.41$ and $P = 0.40$, respectively). In general, the 15-year disease-specific-survival probabilities were 94% (95% CI 91–97%) in CR/IDC − Gleason score 3+4 = 7 or higher ($n = 356$) and 67% (95% CI 59–76%) in CR/IDC+ Gleason score 3+4 = 7 or higher ($n = 189$). The presence of CR/IDC growth affected disease-specific survival regardless of its extent (Figure 1f).

In a multivariable model, we analyzed the added prognostic value of CR/IDC status in combination with currently used clinically relevant variables, ie, age, PSA level, treatment modalities, Gleason score, tumor percentage, and percentage of positive cores. In the model without CR/IDC status, the following variables were independently associated with a worse disease-specific survival: PSA level, tumor percentage, percentage of positive cores, and Gleason score 4+3 = 7 or higher (Table 2). After adding CR/IDC status into the model, Gleason score 4+3 = 7 and 8 were not independently associated with a poorer disease-specific survival anymore. We found that the c-index significantly increased from 0.868 to 0.877 after CR/IDC status was added to the model (likelihood-ratio test, $P = 0.001$). There was no statistically significant interaction between CR/IDC status and treatment (likelihood-ratio test, $P = 0.14$) or CR/IDC status and Gleason score (likelihood-ratio test, $P = 0.71$).

Discussion

The current study showed that CR/IDC status in diagnostic biopsies is associated with a worse disease-specific survival. Adding CR/IDC status to a predictive model resulted in a significantly better discriminative ability. The most interesting finding of our study was the overall good outcome of patients whose biopsies lacked CR/IDC growth, particularly in those with CR/IDC − Gleason score 3+4 = 7, whose survival did not differ from patients with Gleason score 6 prostate cancer. We additionally found that presence of a limited CR/IDC tumor component (≤5%) in biopsies was already associated with an unfavorable outcome. This finding is in line with the study of Trudel *et al*,[13] who showed that

Table 2 Adjusted HRs on time to disease-specific death in a clinical setting: the added value of CR/IDC status ($N = 1031$)

	Model without CR/IDC status			*Model with CR/IDC status*		
	Adjusted HR	*95% CI*	P-*value*	*Adjusted HR*	*95% CI*	P-*value*
Age (years)	0.99	0.94–1.0	0.60	0.99	0.94–1.0	0.63
PSA level (log_2)	1.2[a]	1.0–1.5	0.02	1.2[a]	1.0–1.5	0.04
Percentage of positive cores (log_2)	1.8[a]	1.2–2.6	0.006	1.6[a]	1.0–2.4	0.03
Tumor percentage (log_2)	1.5[a]	1.1–2.1	0.02	1.4[a]	1.0–2.0	0.05
Gleason score						
6		Reference			Reference	
3+4 = 7	1.2	0.48–3.1	0.69	0.99	0.38–2.6	0.99
4+3 = 7	3.1	1.2–8.0	0.02	1.9	0.67–5.4	0.23
8	3.7	1.4–10	0.01	2.3	0.78–6.9	0.13
9–10	5.1	2.0–13	< 0.001	3.3	1.2–9.3	0.02
CR/IDC+ status				2.6	1.4–4.8	0.002
Radical prostatectomy	0.23	0.058–0.92	0.04	0.26	0.064–1.0	0.05
Radiotherapy	1.3	0.40–4.5	0.63	1.4	0.42–4.7	0.58

[a]Per doubling unit.

any amount of large cribriform or intraductal carcinoma was associated with shorter time to biochemical recurrence after radical prostatectomy.

In recent radical prostatectomy studies, intraductal carcinoma and invasive cribriform carcinoma have both been identified as independent prognostic factors.[2–5,11,13] To date, only few studies have analyzed the prognostic value of intraductal carcinoma in pre-treatment diagnostic biopsies.[7–9] They showed that intraductal carcinoma is associated with high-grade and non-organ-confined prostate cancer in subsequent radical prostatectomies.[7,8] In addition, Van der Kwast *et al*[9] demonstrated that intraductal carcinoma was associated with shorter time to biochemical recurrence and distant metastasis after radiotherapy in intermediate- to high-risk prostate cancer patients.

Although CR/IDC status in our predictive model led to significantly better discriminative ability, the absolute c-indices in the models with and without CR/IDC status only differed marginally. CR/IDC status might not affect clinical decision-making in patients with Gleason score 8–10 since these patients will undergo active treatment either way. CR/IDC status could, however, be useful to stratify Gleason score 3+4 = 7 patients for active surveillance or treatment. A drawback of the current Gleason grading system is its considerable inter-observer variability, in particular when distinguishing Gleason score 3+4 = 7 from Gleason score 6 prostate cancer.[19,20] Variability in assignment of grade is significantly related to the presence of ill-formed and fused growth patterns; these represented the majority of Gleason score 3+4 = 7 prostate cancers in this study. Egevad *et al*[21] found that cribriform growth was not statistically associated with Gleason score inter-observer variability among 337 pathologists. This indicates that CR/IDC status may be a more robust parameter for patient stratification than grading as either Gleason score 6 or 3+4 = 7.

Although invasive cribriform carcinoma and intraductal carcinoma are two different pathologic entities, they may be related on a pathological and biological level.[22,23] Their morphologic distinction is often difficult requiring immunohistochemical staining for basal cells. Although presence of basal cells is strongly supportive of intraductal carcinoma, lack of basal cells is not pathognomonic for invasive cribriform growth; basal cells can be scattered and not be sampled in the tissue section, which is also known to occur in HGPIN.[24] The use of combined CR/IDC status is practical for pathologic diagnosis since it does not affect prognostic value of separate entities nor requires additional immunohistochemistry. This is also in line with the latest 2014 ISUP recommendations on Gleason grading, in which Epstein *et al*[1] advised that immunohistochemistry to distinguish invasive cribriform from intraductal carcinoma should only be considered in cases where the results of the studies would change the overall grade of the case, for example, in cases lacking other Gleason grade 4 patterns.

Several studies have reported on genetic abnormalities related to CR/IDC growth. Qian *et al* found gain of chromosome 7, 12, and Y, loss of chromosome 8, and extra copies of *c-MYC* in both cribriform HGPIN and invasive cribriform carcinoma, suggesting that these growth patterns are genetically more alike to Gleason grade 5 than Gleason grade 3 or 4 prostate cancer.[25,26] Dawkins *et al*[27] reported frequent losses of 8p22 and 16q23.1 in intraductal carcinoma. Bettendorf *et al*[28] found that intraductal carcinoma has more frequent loss of *TP53*, *RB1*, and *PTEN*. Using break-point regions to infer phylogenetic relationships, Lindberg *et al*[29] showed that the clone closely related to the metastases was found in intraductal carcinoma. We hypothesize that both invasive cribriform and intraductal carcinoma are architectural substrates of genetic aberrations associated with aggressive disease behavior. The fact

that small CR/IDC components were already associated with worse outcome, could be explained by the emergence of aggressive tumor clones irrespective of their volume.

A limitation of the current study is the fact that the original ERSPC biopsy protocol included sextant biopsies, while current biopsy schemes are more extensive and increasingly MRI targeted reducing the chance of sampling artifact. Future research is needed to confirm that the prognostic value of CR/IDC status is similar in contemporary biopsy protocols. Another limitation is the difference in treatment modalities nowadays as compared to the 1990s. Low-risk patients in this study had mostly received active treatment, while active surveillance would have been an acceptable strategy nowadays. The strengths of the present study are its large number of patients with long-term follow-up, the use of disease-specific survival as an outcome measure, and the meticulous pathologic review. In conclusion, CR/IDC+ status in prostate cancer biopsies is independently associated with poorer disease-specific survival. Our findings indicate that men with biopsy CR/IDC – Gleason score 3+4 = 7 prostate cancer could be candidates for active surveillance, as these patients have similar survival probabilities to those with Gleason score 6.

Disclosure/conflict of interest

MJR has had travel, accommodations, or other expenses paid or reimbursed by Novartis, currently or during the past 2 years.

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