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Extraprostatic extension (EPE) of prostatic carcinoma: is its proximity to the surgical margin or Gleason score important?

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Objective

To examine the association between histopathological factors of extraprostatic prostate cancer and outcome.

Patients and Methods

Patients with extraprostatic extension (EPE) without positive margins, seminal vesicle or lymph node involvement were analysed from a consecutive radical prostatectomy cohort of 1136 (2002–2006) for: (i) distance of EPE from the margin; (ii) Gleason score of the EPE; and (iii) extent of EPE. Log-rank, Kaplan–Meier, and Cox regression analyses were performed.

Results

The study included 194 pT3a, pN0, R0 patients with a median follow-up of 5.4 years, with 37 (19%) patients experiencing biochemical relapse (BCR). On univariable analysis, patients with a Gleason score of ≥8 in the extraprostatic portion showed increased incidence of BCR compared with those with Gleason scores of ≤7 ($P = 0.03$). The proximity of the EPE to the margin (0.01–7.5 mm) did not correlate with BCR. On multivariable analysis, the extent of EPE, the Gleason score of the dominant nodule or of the EPE portion did not correlate with BCR.

Conclusion

Data from this study using current International Society of Urological Pathology Gleason scoring and EPE criteria indicate that close proximity of EPE to the margin is not associated with recurrence. Gleason score ≥8 within EPE is associated with an increased BCR risk on univariable analysis, but larger studies are required to confirm whether extensive Gleason pattern 4 in an EPE indicates increased risk in an otherwise overall Gleason score 7 cancer.

Keywords

prostate, prostatic adenocarcinoma, radical prostatectomy, extraprostatic extension, margins, Gleason scores

Introduction

Extraprostatic extension (EPE) of prostatic adenocarcinoma is a well-recognised adverse prognostic factor resulting in upstaging of prostatic carcinoma [1]. Adjuvant radiotherapy (RT) is often recommended in patients with pathologically advanced prostate cancer after radical prostatectomy (RP) [2]. Although this is an effective adjuvant therapy, it carries a significant risk of toxicity and urologists and radiation oncologists may have divergent views about recommending adjuvant therapy especially in the setting of EPE without other high-risk features [2–4]. Given that ≈50% of patients with EPE do not show disease progression at 10 years [1,5–7], evaluation of various histopathological features of the carcinoma within the periprostatic tissue, such as proximity to the margin of resection or the Gleason score, and their impact on clinical relapse and biochemical (PSA) relapse (BCR) may help in identification of a subset of patients most likely to benefit from postoperative adjuvant therapy.

The International Society of Urological Pathology (ISUP 2011) Consensus recommendations [8] on the handling and staging of RP specimens state that a surgical margin should be considered as negative provided the carcinoma does not reach

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the inked surface of the RP specimen, even if the microscopic clearance is <0.1 mm. This recommendation is supported by studies that have shown lack of postoperative disease progression in patients with very close margins on microscopic examination [6,9,10]. It is speculated that the fibromuscular prostatic stroma may act as a limiting barrier for direct extension of invasive carcinoma [7]. While this may be true for organ-confined prostate cancer, the fibromuscular stroma is lacking in pT3a cancers with EPE. It has been shown that a positive surgical margin at an extraprostatic site is an independent predictor of disease recurrence in pT3a/b patients [5,11,12]. However, the influence of the microscopic distance of the cancer from the inked surface of resection on postoperative BCR and clinical relapse has been evaluated in only a few studies without specific focus on cancers with EPE [9]. The impact of the Gleason score of the extraprostatic portion of the cancer on BCR and clinical relapse has not been evaluated in the literature.

In the present study, we evaluated RP specimens from 194 patients with EPE (pT3a) to determine whether the extent of EPE, the form of EPE, the Gleason score of the extraprostatic carcinoma or the microscopic distance of the closest resection margin from the cancer in an extraprostatic location influences long-term outcome.

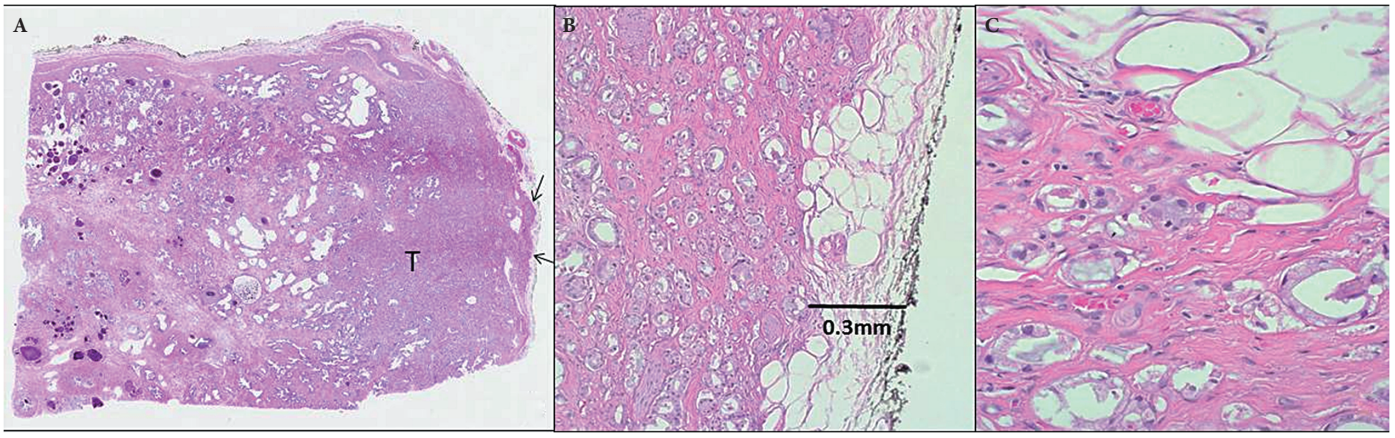
Patients and Methods

The study was undertaken after Institutional Human Research Ethics Committee approval (Ethics approval: St Vincent's Hospital File Number 12/231). In all, 1136 consecutive patients from a single institution (St. Vincent's Hospital, Sydney, NSW, Australia) were identified as having undergone an open RP between 1 January 2002 and 31 December 2006, in a single Urology Department using similar surgical techniques.

The details of patients with EPE (pT3) were extracted from the cohort of 1136 consecutive patients for this analysis and patients recorded as having positive surgical margins, seminal vesicle invasion or lymph node metastases were excluded; leaving 277 patients (24.4%) who fulfilled these criteria in the database. Of the 277 patients, nine patients were excluded due to lack of clinical follow-up and 37 patients were excluded as the relevant slides and blocks were not available in the archives for review. A further 37 (12.2%) patients from this 2002–2006 cohort in which EPE/capsular penetration was reported as per the criteria prevalent at that time [13] were excluded because unequivocal EPE as per the ISUP 2011 Consensus recommendations [1] was not identified following histopathological review or because the EPE reported in the original histopathology reports was located at the apex, or in the bladder neck region. Hence a total of 194 cases (pT3a, N0, R0) were available for analysis.

The histopathology sections were reviewed by two uropathologists (R.G and J.G.K.). EPE was defined as per the ISUP Consensus recommendations (ISUP 2011) on the handling and staging of RP specimens and was considered present when the cancer was identified within periprostatic adipose tissue or loose connective tissue, or the cancer invested the neurovascular bundles in the loose connective tissue beyond the confines of the prostate gland or cancer in fibrous tissue was seen bulging beyond the contours of the prostate gland [1]. The sections were reviewed and the following parameters were assessed (Fig. 1): (i) measurement of closest microscopic distance of the cancer in the extraprostatic location from the inked resection margin using an ocular micrometer (Fig. 1B); (ii) determination of extent of EPE as per the Wheeler et al. [13] definition (where the extent of EPE was defined as focal when the cancer involved no more than one high-power field in no more than two separate

Fig. 1 Evaluation of histopathological parameters: (**A**) Section from RP specimen showing prostatic parenchyma and cancer (T) along the peripheral aspect with foci of EPE (arrows) [haematoxylin and eosin (H&E) × 2]. (**B**) Higher power image showing carcinoma in direct contact with adipocytes. Measurement of the distance of extraprostatic carcinoma to the overlying margin of resection (H&E × 100). (**C**) Extraprostatic carcinoma, Gleason score 3 + 3 = 6 (H&E × 400).



sections, and non-focal when it was more extensive); (iii) Gleason score of the cancer in EPE as per the ISUP 2005 consensus conference recommendations [14]; (iv) determination of the nature of EPE as direct invasion, invasion in the form of perineural invasion (PNI) or lymphovascular invasion (LVI). Discrepancies, if any, were resolved by consensus microscopy.

Clinicopathological data were available and included patients' age, preoperative PSA concentration, and 5–10 years follow-up for adjuvant treatment, BCR (PSA), clinical relapse and death. Patients were followed after RP by their surgeons on a monthly basis until satisfactory urinary continence was obtained and then at 3-month intervals until the end of the first year, at 6-monthly intervals to 5 years, and yearly thereafter. BCR was defined by the following criteria: biochemical disease progression with a serum PSA concentration of ≥0.2 ng/mL increasing over a 3-month period or local recurrence on DRE confirmed by biopsy or by subsequent rise in PSA concentration. Time to BCR was defined as interval between RP and the event.

Statistical Analysis

Log-rank tests were used to evaluate the influence of various pathological factors on BCR- and clinical relapse-free survival; Kaplan–Meier curves were constructed for graphical display. The median follow-up was calculated using the reverse Kaplan–Meier method in which deaths are censored [15]. Actuarial (Kaplan–Meier) event-free survival rates were calculated at 5 years. To explore the nature of the relationship between distance to resection margins and outcome, the distance was initially analysed using a five category variable (i.e. <0.1, 0.1–<0.2, 0.2–<0.3, 0.3–<0.4, 0.4–<0.5 and ≥0.5 mm) and was later dichotomised to <0.1 vs ≥0.1 mm. Gleason scores were analysed as categorical variables initially using all attainable scores and subsequently dichotomised using categorisation of Gleason scores 6–7 vs ≥8. Univariable and multivariable analyses were performed using Cox proportional hazards regression modeling to calculate hazard ratios (HRs) with 95% CIs. Variables were included in the multivariable Cox proportional hazards model if they had a $P < 0.10$ on univariable testing. A nominal $P = 0.05$ was used to indicate statistical significance. All P values are two-sided. Statistical analyses were performed using SAS®software Version 9.3 of the SAS System for Windows (SAS institute Inc, Cary, NC, USA).

Results

The study included 194 cases of prostatic adenocarcinoma with EPE with a median (range) follow-up of 5.4 (0.4–10.3) years. The median (range) patient age was 62.8 (47.7–74.1) years and the preoperative serum PSA concentration was 7.3 (2–31.9) ng/mL (Table 1). BCR was seen in 37 (19%) patients. Various forms of adjuvant therapies were given to 19 patients (10 RT and nine hormonal therapy). Clinical relapse including bony and visceral metastases was seen in only six (3.1%) patients, thus precluding meaningful statistical analysis.

Log-rank and Cox methods were used to assess the impact of standard clinicopathological variables, such as preoperative PSA concentration, Gleason score of the dominant nodule, adjuvant therapy, and of the histopathological factors associated with EPE on BCR-free survival (Table 1). The preoperative PSA concentration did not correlate with BCR in this cohort; however, adjuvant therapy was found to have significant correlation with BCR. The Gleason scores of the dominant nodules in the RP specimens were recorded and patients with Gleason scores of ≥8 in the dominant nodules

Table 1 Clinicopathological features of the cohort and BCR (unadjusted Cox model).

Characteristic	Median (range)	*N*	BCR		
			N (%)	HR (95% CI)	*P* (log-rank)
Age, years	62.8 (47.7–74.1)				
<65		126	26 (20.6)	1	
≥65		68	11 (16.2)	0.88 (0.43–1.78)	0.72
Preoperative serum PSA concentration, ng/mL	7.3 (2–31.9)				
<10		142	23 (16.2)	1	
≥10		49	14 (28.6)	1.82 (0.93–3.54)	0.07
Gleason score of dominant nodule in RP specimen:					
6 and 7		153	23 (15.2)	1	
≥8		41	13 (31.7)	2.24 (1.13–4.42)	0.02
Gleason score of extraprostatic portion of adenocarcinoma:					
6 and 7		163	27 (16.6)	1	
≥8		31	10 (32.3)	2.20 (1.07–4.56)	0.03
Adjuvant therapy:					
No		175	24 (13.7)	1	
Yes		19	13 (68.4)	5.52 (2.81–10.88)	<0.001

**Data available in 191 patients.*

Table 2 Histopathological features of EPE and BCR (unadjusted Cox model).

Characteristic	Category	*N*	BCR		
			N (%)	HR (95% CI)	*P*
Extent of EPE	Focal	78	13 (16.7)	1	
	Non-focal	116	24 (20.7)	1.02 (0.52, 2.02)	0.95
Form of EPE	Direct	166	34 (20.5)	2.29 (0.70, 7.46)	0.17
	PNI/LVI**	28	3 (10.71)	1	
Associated PNI in EPE	Yes	145	29 (20)	1.69 (0.70, 4.10)	0.24
	No	49	6 (12.2)	1	
Associated LVI in EPE	Yes	17	5 (29.4)	1.60 (0.62, 4.14)	0.33
	No	177	30 (16.9)	1	
Distance to margin, mm	<0.1	15	2 (13.3)	1	
	0.1–<0.2	23	6 (26.1)	1.80 (0.36, 8.97)	0.48
	0.2–<0.3	19	5 (26.3)	1.69 (0.33, 8.72)	0.53
	0.3–<0.4	5	1 (20.0)	1.37 (0.12, 15.08)	0.80
	0.4–<0.5	13	1 (7.7)	0.43 (0.04, 4.79)	0.50
	≥0.5	119	22 (18.5)	1.18 (0.28, 5.06)	0.82
Gleason score of EPE	3 + 3	84	12 (14.3)	1	
	3 + 4	48	10 (20.8)	1.48 (0.64, 3.43)	0.36
	4 + 3	31	5 (16.1)	0.94 (0.33, 2.69)	0.91
	4 + 4	15	5 (33.3)	2.48 (0.87, 7.05)	0.09
	4 + 5/ 5 + 4/ 5 + 5	16	5 (31.3)	2.46 (0.87, 7.00)	0.09
Gleason score of EPE closest to the margin	3 + 3	100	15 (15.0)	1	
	3 + 4	36	9 (25.0)	1.88 (0.82, 4.30)	0.13
	4 + 3	23	2 (8.7)	0.52 (0.12, 2.29)	0.39
	4 + 4	25	8 (32.0)	2.10 (0.89, 4.96)	0.09
	4 + 5/ 5 + 4/ 5 + 5	10	3 (30.0)	2.41 (0.70, 8.33)	0.17

***Only two cases showed EPE in the form of lymphovascular emboli (LVI).*

had an increased incidence of BCR vs those with Gleason scores of 6 or 7 (HR 2.24, 95% CI 1.13–4.42; $P = 0.02$) (Table 1).

Focal EPE was seen in 78 (40%) cases and non-focal in 116 (60%) cases. The extent of EPE, i.e. whether focal or non-focal EPE as per the Wheeler et al. criteria [13], did not show correlation with BCR in this cohort over a median follow-up of 5 years (Table 2). Direct invasion of the extraprostatic adipose tissue was the most common form of EPE and was seen in 166 (86%) patients, while extension in the form of PNI only was seen in 26 (13%) patients, and only two patients had EPE in the form of lymphovascular emboli (LVI). The form of EPE or its association with PNI did not correlate with BCR in this cohort (Table 2).

The Gleason score of the cancer within the extraprostatic tissue was 6 in 84 (43.3%) patients, 7 in 79 (40.7%) and ≥8 in 31 (16%). The 5-year actuarial survival for patients with Gleason score ≥8 in the EPE was 70 months (95% CI 50–83), while that of patients with Gleason scores 6 or 7 in the EPE was 86 months (95% CI 79–91) (Fig. 2). Univariable analysis showed that the patients with Gleason scores of ≥8 in their EPE cancer showed an increased incidence of BCR vs those with Gleason scores of 6 or 7 at the extraprostatic site (HR 2.20, 95% CI 1.07–4.56; $P = 0.03$) (Table 1). The subgroup of patients with Gleason score 7 in the extraprostatic cancer were further stratified as Gleason scores 3 + 4 = 7 (48 patients) and 4 + 3 = 7 (31) (Table 2). Univariable analysis did not show a statistically significantly different rate of BCR in patients with Gleason scores 3 + 4 = 7 and Gleason scores 4 + 3 = 7 in their EPE cancers (HR 0.6, 95% CI 0.2–1.7; $P = 0.32$). Only eight patients with the dominant nodule showing Gleason score 7 showed Gleason score 8 in the extraprostatic carcinoma. While

Fig. 2 Kaplan–Meier survival curve showing that patients with Gleason scores of ≥8 in their EPE cancers showed increased incidence of BCR as compared with those with Gleason scores of 6 or 7 at the extraprostatic site.

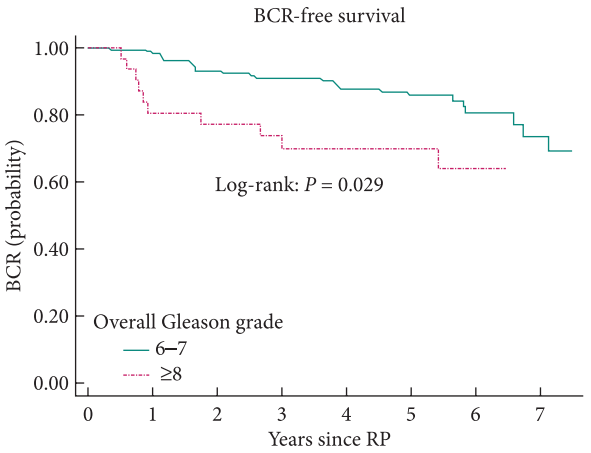
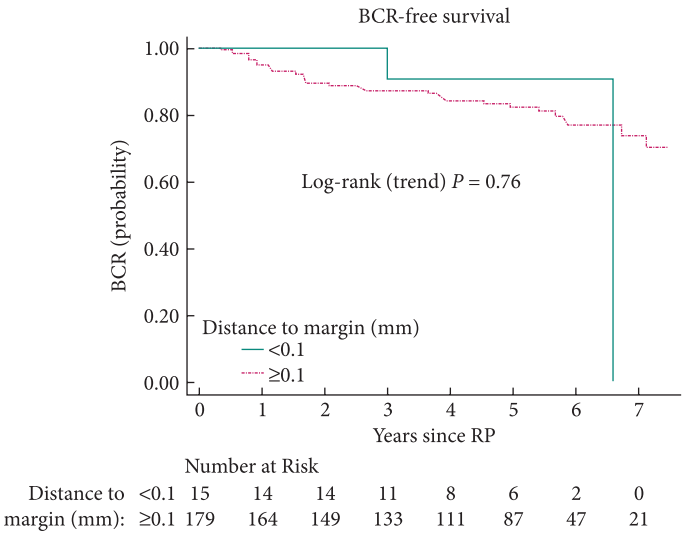


Table 3 Multivariable Cox proportional hazards model for BCR.

	HR (95% CI)	β	Standard error	*P*
Gleason score of the extraprostatic portion of the tumour (EPE) (≥8 vs 6–7)	1.88 (0.80–4.45)	0.63	0.44	0.15
Gleason score of the dominant nodule (≥8 vs 6–7)	0.95 (0.39–2.28)	−0.05	0.45	0.9
Preoperative serum PSA (logged)	1.47 (0.7–3.07)	0.38	0.38	0.3
Adjuvant therapy	4.3 (1.9–9.8)	1.46	0.42	<0.001

Estimates are adjusted for all other covariates listed.

Fig. 3 Kaplan–Meier survival curves evaluating the impact of the proximity of the extraprostatic component of the tumour to the resection margin.



one of these eight patients developed BCR, meaningful statistical analysis was not possible.

The distance of the cancer in the EPE from the resection margin ranged from 0.01 to 7.5 mm. In 75 patients, the cancer in the EPE extended to 0.5 mm from the margin of resection (Table 2). The proximity of the extraprostatic cancer to the resection margin did not correlate with BCR (HR 0.69; 95% CI 0.19–2.47) in this cohort at a median follow up of 5.4 years (Table 2; Fig. 3).

On multivariable analysis, adjuvant therapy was found to be the only factor that correlated with BCR in patients with EPE (HR 4.3, 95% CI 1.88–9.84; $P < 0.001$). The Gleason score of the dominant nodule in the RP specimen (HR 0.95, 95% CI 0.39–2.28; $P = 0.9$) or the Gleason score of the cancer in EPE (HR 1.88, 95% CI 0.80–4.45; $P = 0.15$) did not achieve statistical significance (Table 3). These parameters also failed to achieve statistical significance after exclusion of patients with adjuvant therapy from the analysis.

Discussion

The present study of RP cases with EPE, evaluated the prognostic significance of key histopathological factors within the extraprostatic portion of the cancer, separately from those pertaining to the prostatic cancer as a whole. Using a well-characterised cohort of patients with EPE (pT3a, pN0, R0) with a relatively long follow-up, we found that the proximity of the resection margin to the cancer in an extraprostatic location did not significantly influence prognosis and that the Gleason score of the extraprostatic cancer significantly correlated with BCR in univariable analysis. These findings address a significant gap in our understanding of disease progression and biochemical failure in patients with pT3a prostatic adenocarcinomas.

The current international recommendations and guidelines for histopathological reporting of RP specimens do not require measurement or reporting of the distance of the cancer from its closest resection margin in organ-confined cancers or in cancers with EPE [16,17]. While there is evidence to support this practice guideline in organ-confined prostate cancer [9,10,18,19], similar evidence-based support is scant for cancers with EPE. The results of our present study evaluating 194 patients with EPE over a median follow up of 5.4 years showed that close proximity of the cancer at an extraprostatic location to the surgical margin does not convey an adverse prognosis, thus providing evidentiary support to the conventionally accepted paradigm. Previous studies, such as that by Emerson et al. [9], have provided a limited evaluation of this parameter as their cohort of 278 patients included only 44 patients with EPE (pT3a) with a relatively short median follow-up of 1 year. A recent meta-analysis by Yossepowitch et al. [4] including 74 publications discussing the impact of positive surgical margins in men undergoing RP indicates that the long-term impact of positive surgical margins on survival is highly variable and influenced by other risk factors. While the implications of some of the risk factors, e.g. intraprostatic incision resulting in a positive margin, have been well evaluated in the studies reviewed, the significance of EPE or its proximity to the margin were not discussed by Yossepowitch et al. [4], presumably due to paucity of data. Thus, our present data generate hypotheses that require prospective validation through multi-institutional studies including larger cohorts with sufficient power.

The Gleason score of the dominant nodule in the RP specimens has been shown to influence BCR in patients with

prostatic adenocarcinoma with EPE [20]. However, the influence of the Gleason score specifically relating to the extraprostatic component of the carcinoma has not been evaluated, nor is a comment on this parameter required in the pathology report datasets [16,17]. Univariable analysis in the present study suggests that patients with Gleason scores of ≥8 within the EPE of the cancer have an increased risk of BCR vs those with Gleason scores of 6 and 7. This finding suggests that presence of extensive or exclusive Gleason pattern 4 in an extraprostatic location in patients with Gleason scores of 7 in the entire radical dominant nodule may be of prognostic significance and further studies of this parameter in a larger cohort are warranted. However, the present study includes only eight patients fulfilling these criteria, thus precluding meaningful statistical evaluation.

Wheeler et al. [13] and Danneman et al. [21] have shown that patients with non-focal EPE are at higher risk of BCR and clinical relapse on both univariable and multivariable analysis of their cohorts including patients with seminal vesicle invasion and lymph node metastases. Billis et al. [22], using a slightly different semiquantitation method for EPE, have reported similar findings on univariable analysis including patients with positive surgical margins. However, positive surgical margins emerged as the most important prognostic factor on multivariable analysis in their cohort [22]. Similarly, stratification of the extent of the EPE into focal and non-focal using the criteria proposed by Wheeler et al. [13], was not significant on univariable analysis in this cohort of patients restricted to those with EPE without positive surgical margins, seminal vesicle involvement or lymph node metastases (pT3a, R0, N0). These findings bear similarity to those initially reported by Epstein et al. [23], although the definitions of EPE and Gleason scoring system have since evolved. Furthermore, these results suggest that the extent of EPE may not be of prognostic significance in completely resected cancers.

The most common form of EPE in our present cohort was direct infiltration of the adipose tissue or loose connective tissue investing neurovascular bundles beyond the confines of the prostate gland. EPE purely in the form of PNI was seen in 15 patients while that purely in the form of LVI was very rare and was seen in only two cases. Associated PNI and LVI were seen in cancers directly invading into the adipose tissue. However, the presence of PNI or LVI did not carry prognostic significance, as has also been reported by Danneman et al. [21].

It has been previously observed that variable consideration of postoperative adjuvant therapy can cause discordant findings when evaluating the prognostic significance of histopathological parameters [24]. In the present study, 19 (9.7%) patients received adjuvant therapy, including 10 (5.1%) patients being treated with adjuvant RT. On multivariable analysis, these patients were found to be at significantly higher risk of BCR. We think that a combination of high-risk factors, such as large dominant nodule with extensive EPE with high Gleason scores, led to the selection of these patients for adjuvant therapy from a relatively homogenous cohort of pT3a, R0, N0 patients. While the numbers are small making it difficult to exclude type II error, it is reasonable to assume that adjuvant therapy reflects the presence of a combination of multiple high-risk features and is thus statistically significant on multivariate analysis as opposed to each individual factor. Multivariate analysis was performed both with and without the inclusion of patients with adjuvant therapy. Histopathological parameters such as the overall Gleason score of the entire RP specimen, Gleason score of the extraprostatic cancer or its proximity to resection margin, failed to correlate with BCR even after exclusion of adjuvant therapy, possibly due to selection bias.

Adjuvant RT, although an effective treatment option, carries significant acute and late rectal and genitourinary toxicities and may adversely affect potency [20]. Considering that >50% of patients with EPE show freedom from disease at 10 years, several attempts have been made to identify subsets of patients most likely to benefit from adjuvant therapy, particularly in patients more likely to have long life-expectancy [20,25,26]. Phase III trials such as 'Radiotherapy-Adjuvant vs Early Salvage (RAVES) trial are underway to test the hypothesis that observation with early salvage RT triggered by rise in PSA level to 0.20 ng/mL are not inferior to currently established practice of adjuvant therapy in patients with EPE or positive surgical margins [27]. The RAVES trial plans to complete accrual in early 2018 [27]. The clinical and the tissue repository arms of RAVES trial will be an excellent bio-resource for prospective validation of studies such as ours, particularly due to their sample size and focus on high-risk features. It will also be interesting to see whether the trial provides a clear solution to the question of adjuvant therapy vs observation with salvage RT or identifies that assessment of additional histological features (e.g. Gleason score of extraprostatic carcinoma or Gleason score of the carcinoma at a positive surgical margin) are important for improved risk stratification.

It is accepted that patients with EPE and positive surgical margins are at intermediate risk of relapse [26]; however, detailed evaluation of histopathological parameters of the extraprostatic component of cancer have not been performed. Our present study addresses a gap in the evidence-base underpinning the current recommendations for assessing EPE and surgical margin involvement in prostatic adenocarcinoma. Using a well-characterised pT3a, pN0, R0 cohort, of the type that is frequently encountered in routine clinical practice, comprising 194 patients with a median follow-up of 5.4 years and applying current definitions of EPE and contemporary Gleason scoring methods, we found that proximity of cancer in an extraprostatic location to the margin of resection does

not convey prognostic significance. The Gleason scores of the extraprostatic component of cancer were associated with poor prognosis on univariable analysis, but larger studies are required to confirm whether extensive or exclusive presence of Gleason pattern 4 in an EPE connotes increased risk of relapse in an otherwise overall Gleason score 7 carcinoma. It may be useful to consider the implications of these histopathological factors, particularly the Gleason score of the cancer in the extraprostatic location, when selecting parameters for nomogram development, risk stratification and clinical trials.

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Conflict of Interest

J.G.K. reports personal fees from Pfizer, Australia, outside the submitted work.

No other conflicts of interest declared.

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Abbreviations: BCR, biochemical relapse; EPE, extraprostatic extension; H&E, haematoxylin and eosin; HR, hazard ratio; ISUP, International Society of Urological Pathology; LVI, lymphovascular invasion; PNI, perineural invasion; RAVES, Radiotherapy-Adjuvant vs Early Salvage (trial); RP, radical prostatectomy; RT, radiotherapy.