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High Gleason grade carcinoma at a positive surgical margin predicts biochemical failure after radical prostatectomy and may guide adjuvant radiotherapy

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Study Type – Prognosis (case series)
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OBJECTIVE

- To establish predictors of biochemical recurrence by analysing the pathological characteristics of positive surgical margins (PSMs), including Gleason grade of the carcinoma at the involved margin.

PATIENTS AND METHODS

- Clinicopathological and outcome data on 940 patients who underwent radical prostatectomy (RP) between 1997 and 2003 were collected.
- Of these, 285 (30.3%) patients with PSMs were identified for pathological review, including assessment of location of margin, linear extent, number of PSMs, plane of margin and Gleason grade (3 vs 4 or 5) at the margin.

RESULTS

- At a median follow-up of 82 months, the biochemical recurrence rate of the PSM cohort was 29%.
- On univariate analysis, the presence of Gleason grade 4 or 5 at the margin (34.4% of cases) was significantly associated with biochemical recurrence (hazard ratio [HR] 2.80, 95% confidence interval [CI] = 1.82–4.32, $P < 0.001$) compared with the presence of Gleason grade 3.
- Linear extent of margin involvement was also associated with recurrence ($P = 0.009$).
- Single vs multiple margin involvement, location, and plane of the involved margin were not significant predictors of recurrence.
- On multivariate analysis, Gleason grade 4 or 5 at the margin remained an independent predictor of recurrence (HR 2.14, 95% CI = 1.29–4.03, $P = 0.003$).

CONCLUSION

- The Gleason grade at the site of a PSM identifies patients at increased risk of biochemical recurrence and should aid stratification of patients for adjuvant radiation therapy.

What's known on the subject? and What does the study add?
Only 30–35% of patients with positive surgical margins after radical prostatectomy develop recurrent disease. Adjuvant radiotherapy reduces the rate of biochemical relapse or metastasis and improves overall survival after radical prostatectomy. Various pathological factors, such as location and extent of positive margins, have been proposed as possible prognostic factors in men with margin-positive prostate cancer, however, the recent International Society of Urological Pathology consensus meeting in Boston noted that there is limited data on the significance of Gleason grade of the carcinoma at a positive margin.

The present study shows that the presence of high grade prostate cancer, i.e. Gleason pattern 4 or 5, at a positive surgical margin is an independent predictor of biochemical recurrence after radical prostatectomy. Moreover, patients with lower grade carcinoma at the margin have a similar prognosis to men with negative margins. Hence, assessment of Gleason grade at the site of positive margin may aid optimal selection of patients for adjuvant radiotherapy.

KEYWORDS

prostatic neoplasms, prostatectomy, surgical margins, pathology, adjuvant radiotherapy

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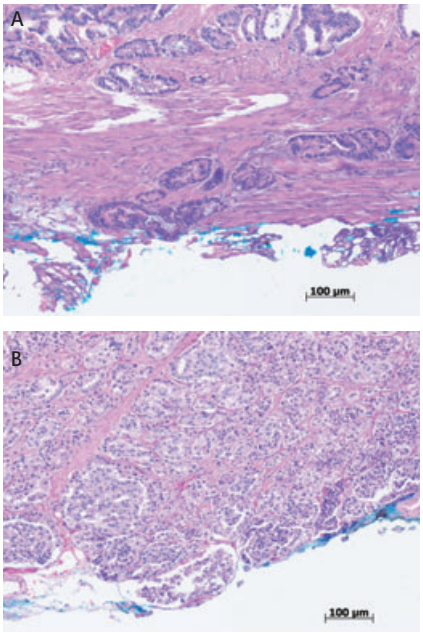
*FIG. 1. Prostatic adenocarcinoma in RP specimens with (**A**) Gleason grade 3 carcinoma involving the margin and (**B**) Gleason grade 4 at margin (H&E stain).*



INTRODUCTION

Prostate cancer (PC) is the most commonly diagnosed carcinoma in men. In the USA, an estimated 217 730 men were diagnosed with PC in 2010, and 32 050 died from PC [1]. Assessment of prognosis is one of the most important issues in localized PC. The identification of clinically significant PC forms the basis of clinical decision-making as to whether or not to proceed to radical prostatectomy (RP) and whether or not to treat with radiotherapy postoperatively.

In cancers of organs such as the pancreas and rectum, positive surgical resection margins are a key determinant of prognosis and may be associated with either local or distant recurrence [2,3]. A positive surgical margin (PSM) is known to confer a poorer prognosis after RP. PSMs are reported in 11–37% of patients treated by RP [4–7] and men with PSMs have a twofold increase in the risk of biochemical recurrence compared with those with a negative surgical margin [4,5,7]. However, not all patients with a PSM will develop recurrent disease, with most reports suggesting a 30–35% recurrence rate [4,5,7]. Furthermore, the 10-year disease-specific mortality with a PSM remains very low at <10% [4–8]. Adjuvant radiotherapy (within 16 weeks of surgery) reduces the rate of biochemical recurrence and metastasis, and improves overall survival in men with PSMs and/or pT3 tumours [9–11]. Given that there are twice as many grade III toxicities when adjuvant radiotherapy is added to surgery [9,10], there is an urgent need to identify which patients are most likely to benefit from adjuvant treatment.

Various pathological variables, such as location and extent of PSMs, have been proposed as possible prognostic factors in men with margin-positive PC and the recent International Society of Urological Pathology (ISUP) consensus meeting recommended their routine assessment in RP specimens [12–15]. The ISUP report also noted that, although the Gleason grade at the PSM may be a prognostic factor aiding clinical decision-making, supporting evidence is limited [12]. The aim of the present study was, therefore, to assess the relationship between the known pathological characteristics of a PSM, in particular the Gleason grade at the margin, and disease outcome in a large cohort with long clinical follow-up.

PATIENTS AND METHODS

Consecutive patients who underwent open RP between January 1st 1997 and December 31st 2003 at a single institution (St. Vincent's Hospital, Sydney, NSW, Australia) were identified on our database, after institutional ethics approval (Human Research Ethics Committee approval H00/088). All patients were treated by one of six urologists using a similar surgical technique and >90% of specimens were examined by two specialist urological pathologists (W.D. and J.J.T.). Patients with a PSM noted in their pathology report were reviewed.

Although 1077 consecutive patients were identified on the database, patients who received neoadjuvant hormone therapy before RP were excluded ($n = 105$), as were 31 patients with no follow-up data, and one who had squamous cell carcinoma of the prostate, giving a final cohort of 940 patients.

Positive surgical margins were identified in 285 patients and the histopathology sections reviewed by an independent urological pathologist (J.G.K.). A PSM was defined as malignant cells reaching the inked margin [16]. Histopathological review included assessment of other potential prognostic predictors: single vs multiple PSMs, plane of the involved margin (capsular incision vs extraprostatic extension [EPE]), linear extent of the margin (mm), location of the margin (apex vs base vs postero-lateral vs anterior), and the Gleason grade/pattern of the cancer at the involved margin (Fig. 1A,B). In slides where the cancer at the margin was distorted by thermal or crush artifact and could not be reliably assessed, the margin grade was designated as that of the closest, well preserved carcinoma in direct continuity with the distorted neoplastic glands. Where there was carcinoma with more than one Gleason grade/pattern at the surgical margin the highest grade present was used in the analysis.

In 21 (6.8%) cases, an unequivocal PSM was not identified by the reviewing pathologist, strictly applying the definition of unequivocal tumour cells present at the inked margin, and these cases were excluded from the PSM group for analysis and placed in the negative margins group.

Clinicopathological data were available including age, preoperative PSA, RP Gleason score, pathological stage, seminal vesicle invasion (SVI), pelvic lymph node involvement and adjuvant treatment. Biochemical recurrence-free survival was the primary endpoint. Patients who had a PSA nadir (≤0.1 ng/mL) within 12 weeks of RP were recorded as a PSA recurrence if the PSA subsequently had a sustained rise to 0.2 ng/mL or higher. Time to recurrence was defined as the time from date of RP to the date of PSA recurrence.

STATISTICAL ANALYSIS

Kaplan–Meier analyses were performed to examine the relationships between pathological variables and biochemical recurrence-free survival [17]. Univariate and multivariate analyses were performed using a Cox proportional hazards model [18]. All margin variables of interest, as well as clinicopathological variables known to influence PSA recurrence, were analysed as dichotomous or continuous variables where appropriate. Variables were included in the

multivariate Cox proportional hazards model if they had a *P* value of <0.1 on univariate testing and a stepwise selection procedure was used to define the model. The predictive discrimination of the multivariate models was assessed using a Harrell's C statistic. Chi-squared testing was used to assess the correlation between Gleason score RP and Gleason grade at the margin. Hazard ratios (HRs) were generated with 95% CIs, the null hypothesis that no predictive value existed for the variable evaluated was rejected if $P < 0.05$. All *P* values corresponded to two-sided tests. Statistical analyses were performed using SPSS statistics (version 17.0), STATA statistics (version 11) and ACCorD (V. Gebski, NHMRC Clinical Trials Centre, University of Sydney).

RESULTS

Of the 940 patients who had undergone RP, 285 patients had at least one PSM. The patient characteristics of the whole RP cohort, the subset of men with PSM and the subset with negative surgical margins are shown in Table 1. Compared with men with negative surgical margins, the group with margin-positive PC had a higher rate of preoperative PSA >10 ng/mL, higher stage disease, a greater percentage of RP Gleason score ≥7 and, consequently, a higher rate of adjuvant treatment (Table 1). At a median (range) follow-up of 82 (5–146) months, the biochemical recurrence rate of the PSM cohort was 29% (83/285). A PSM was associated with a HR of 1.61 (95% CI: 1.20–2.16, $P = 0.002$) for biochemical recurrence compared with negative margins. There were 10 clinical recurrences (3.5%) and death occurred in 11 men (3.8%), seven from PC (2.5%).

A single PSM was found in 76.8% men (Table 1). PSMs were located at the apex (47%), anterior (11.2%), base (bladder neck) (10.9%) and postero-lateral (30.9%) surfaces (Table 1). EPE was present (with or without an associated PSM) in 177 (62.1%) men. PSMs were associated with capsular incision in 34 (11.9%) and EPE in 117 (41.1%) men. The remaining 47% were specimens with apical PSMs where capsular incision could not be reliably differentiated from EPE. The mean linear extent of a PSM was 3.3 mm, with a median (range) of 2.4 (0.1–16) mm. Gleason grade 3 was found at the site of 65.6% PSMs, Gleason grade 4

TABLE 1 Clinicopathological characteristics of patients with PSMs, patients with negative surgical margins and all patients with localized PC treated by RP

	PSM cohort *N* = 285	Negative surgical margin cohort *N* = 655	All consecutive patients treated by RP *N* = 940
Age, years			
Median (range)	61.7 (46.4–81)	61.2 (42.2–77.4)	61.4 (42.2–81)
Preoperative PSA, ng/mL			
Median (range)	8.7 (2–63)	7.5 (0.4–84)	8 (0.4–84)
≤10, *n* (%)	174 (61.1)	476 (72.7)	650 (69.1)
>10, *n* (%)	110 (38.6)	173 (26.4)	283 (30.1)
Not reported, *n* (%)	1 (0.4)	6 (0.9)	7 (0.8)
pT stage			
pT2, *n* (%)	105 (36.9)	438 (66.9)	543 (57.8)
pT3, *n* (%)	166 (58.2)	212 (32.4)	378 (40.2)
pT4, *n* (%)	14 (4.9)	5 (0.8)	19 (2.0)
EPE			
Absent, *n* (%)	107 (37.5)	442 (67.5)	549 (58.4)
Present, *n* (%)	177 (62.1)	213 (32.5)	390 (41.5)
Not reported, *n* (%)	1 (0.4)	0	1 (0.1)
Pathological Gleason sum			
≤6, *n* (%)	75 (26.3)	241 (36.8)	316 (33.6)
7, *n* (%)	177 (62.1)	349 (53.3)	526 (56.0)
≥8, *n* (%)	33 (11.6)	63 (9.6)	96 (10.2)
Not reported, *n* (%)	0	2 (0.3)	2 (0.2)
SVI			
Absent, *n* (%)	243 (85.3)	612 (93.4)	855 (91.0)
Present, *n* (%)	41 (14.4)	41 (6.3)	82 (8.7)
Not reported, *n* (%)	1 (0.4)	2 (0.3)	3 (0.3)
Node involvement			
Absent, *n* (%)	256 (89.8)	556 (84.9)	812 (86.4)
Present, *n* (%)	5 (1.8)	7 (1.1)	12 (1.3)
Not done, *n* (%)	17 (6.0)	76 (11.6)	93 (9.9)
Not reported, *n* (%)	7 (2.5)	16 (2.4)	23 (2.4)
Adjuvant treatment			
None, *n* (%)	207 (72.6)	632 (96.5)	839 (89.3)
Hormone, *n* (%)	21 (7.4)	15 (2.3)	36 (3.8)
Radiotherapy, *n* (%)	36 (12.6)	5 (0.8)	41 (4.4)
Both, *n* (%)	21 (7.4)	3 (0.5)	24 (2.6)
Number of PSMs			
Single, *n* (%)	219 (76.8)	–	–
Multiple, *n* (%)	66 (23.2)	–	–
Location of PSM			
Anterior, *n* (%)	32 (11.2)	–	–
Apex, *n* (%)	134 (47)	–	–
Base (Bladder neck) , *n* (%)	31 (10.9)	–	–
Posterior-lateral, *n* (%)	88 (30.9)	–	–
Linear extent			
Median (range)	2.4 mm (0.1–16)	–	–
Gleason grade at PSM			
3, *n* (%)	187 (65.6)	–	–
4, *n* (%)	89 (31.2)	–	–
5, *n* (%)	9 (3.2)	–	–

TABLE 2 Cox proportional hazards analysis of the clinicopathological features predicting biochemical recurrence-free survival in men with margin-positive, localized PC

Variable	Univariate analysis HR (95% CI)	*P*	Multivariate analysis HR (95% CI)	*P*
PREOPERATIVE PSA				
Continuous (per 1 ng/mL)	1.03 (1.00–1.05)	0.03	1.01 (0.98–1.04)	0.43
Categorical >10 vs ≤10 ng/mL)	1.40 (0.90–2.17)	0.13		
Pathologic stage				
≥ pT3 vs pT2	1.10 (0 .70–1.71)	0.68	–	–
SVI				
Yes vs no	2.70 (1.64–4.45)	<0.001	1.90 (1.08–3.34)	0.03
EPE				
Yes vs no	1.07 (0.69–1.67)	0.77	–	–
Gleason Score RP				
5–6	1		1	
7	1.57 (0.89–2.76)	0.12	1.06 (0.57–1.97)	0.85
8–10	3.58 (1.82–7.05)	<0.001	1.31 (0.57–3.05)	0.53
Adjuvant Treatment				
Yes vs no	0.79 (0.48–1.32)	0.38	–	–
Nodes				
Positive vs negative	1.77 (0.43–7.19)	0.43	–	–
Number of Margins				
Multiple vs single	1.36 (0.73–1.97)	0.21	–	–
Location				
Anterior vs apical	0.55 (0.10–0.99)	0.21		
Base vs apical	1.06 (0 .51–2.18)	0.88	–	–
Posterior vs apical	1.18 (0 .73–1.89)	0.50		
Linear extent				
Continuous (per 1 mm)	1.09 (1.02–1.15)	0.009	1.05 (0.99–1.12)	0.09
Plane of margin				
Apex vs EPE	0.81 (0.52–1.26)	0.34	–	–
Capsular incision vs EPE	0.48 (0.20–1.13)	0.09		
Gleason Grade at margin				
Grade 4/5 vs Grade 3	2.80 (1.82–4.32)	<0.001	2.14 (1.29–4.03)	0.003

TABLE 3 A comparison of the Gleason score of the carcinoma and the Gleason grade at the PSM

	Gleason grade at PSM		
	3	4	5
Gleason score (RP)			
5	18	–	–
6	52	5	–
7	113	64	–
8	–	11	3
9	4	9	6

at 31.2% and Gleason grade 5 at 3.2% (Table 1).

Cox proportional hazards analysis was used to assess predictors of prognosis in the PSM cohort. On univariate analysis, pretreatment PSA ($P = 0.03$), SVI ($P < 0.001$) and RP Gleason score ($P < 0.001$) were associated with an increase in the biochemical recurrence rate (Table 2). The presence of EPE in the specimen as a whole did not influence biochemical recurrence rate ($P = 0.77$), nor did the use of adjuvant treatment ($P = 0.38$). Of the PSM variables, single vs multiple margins, the location of the margin, and the plane of the margin were not significantly associated with prognosis (Table 2), but there was a significant association between increased linear extent ($P = 0.009$) and a higher Gleason grade at the PSM ($P < 0.001$) and a poorer prognosis (Table 2).

On multivariate analysis, Gleason grade at the PSM ($P = 0.003$) and SVI ($P = 0.026$) were independent predictors of biochemical recurrence in men with PSM, when modelled with Gleason score ($P = 0.53$), pretreatment PSA ($P = 0.43$) and linear extent ($P = 0.09$) (Table 2). Although Gleason grade at the margin was correlated with Gleason score (contingency co-efficient 0.5, $P < 0.001$), Table 3 shows that Gleason grade at the margin was quite heterogeneous across the Gleason scores, in particular in the intermediate risk group of Gleason score 7 cancer. When Gleason grade at margin and Gleason score were modelled together, there was no evidence of a co-linearity problem as suggested by a co-linearity diagnostic (largest condition index was 2.94). The predictive discrimination of the multivariate model including Gleason grade at margin, Gleason score RP, SVI, preoperative PSA and linear extent was higher (Harrell's C statistic 0.696) than in the same model excluding Gleason grade at margin (Harrell's C statistic 0.676). These data suggest that Gleason grade at the margin is an independent prognostic factor, not merely a surrogate marker of the Gleason score of the whole surgical specimen.

Kaplan–Meier analysis was used to assess the actuarial biochemical recurrence-free survival rates for the different groups. The rate of PSA recurrence was significantly higher in those with PSMs than in the group with negative surgical margins ($P = 0.002$; Fig. 2A). The 5-year actuarial biochemical recurrence-free survival for negative margins, PSM with Gleason grade 3 at the margin and PSM with Gleason grade 4/5 at the margin were 85.6%, 83.8% and 65.2%, respectively (corresponding to 5-year recurrence rates of 14.4%, 16.2% and 34.8%) (Fig. 2A,B). This suggests that a cancer with positive margins of Gleason grade 3 has a similar prognosis to a cancer with negative margins.

DISCUSSION

The 2009 ISUP Consensus Conference in Boston drew attention to the limited data published on the prognostic influence of the Gleason grade of the carcinoma at a PSM after RP [19], representing a significant gap in the evidence base for the management of patients with PC [12]. In the present study, we have addressed this issue in a well

characterized cohort with long follow-up and found that the Gleason grade of the carcinoma at the PSM is an independent predictor of biochemical recurrence. The 5-year actuarial biochemical recurrence-free survival was significantly lower for patients with Gleason grade 4 or 5 carcinoma at the margin (65.2%) than for patients with Gleason grade 3 at the margin (83.8%) or clear margins (85.6%). Given that the Gleason grade of carcinoma at a PSM can be readily assessed in standard histological sections and is associated with relatively large differences in recurrence rates, we suggest that this factor should be routinely included in RP pathology reports to facilitate the optimum selection of patients for adjuvant therapy.

Recently, Cao *et al.* [20] reported an association between Gleason score (derived from the sum of the most dominant and second most prevalent grades/patterns) of the tumour at the margin and biochemical recurrence in a cohort with a median follow-up of 32 months. However, assessment of the proportion of different grades at a PSM can be problematic when there is thermal or crush artifact present, a common occurrence in RP specimens. In the present study, we showed that a simplified assessment of the highest Gleason grade of the tumour present at the margin is predictive of biochemical recurrence in a cohort of consecutive margin-positive cases with long follow-up (median 82 months). Furthermore, in Cao *et al*'s paper Kaplan–Meier analysis showed no difference between recurrence-free survival in patients with a Gleason margin score of 3 + 4 = 7 vs 4 + 3 = 7, supporting the proposal that it is the highest grade of tumour at the PSM which is predictive of recurrence [20]. Another recent study addressed this issue in a different way. In a cohort of 108 patients, restricted to patients with Gleason score 7 tumours, extensive (non-focal) EPE and no capsular incision, the grade of cancer at the site of a PSM was shown to significantly influence outcome [21].

Studies assessing the association between the extent of the PSM and the risk of disease progression have yielded varying results. Babaian *et al.* [22] found that patients with PSM of >3 mm in linear extent had a significantly greater PSA-recurrence risk, as did Chuang *et al.* [19] in their analysis of a cohort with capsular incision.

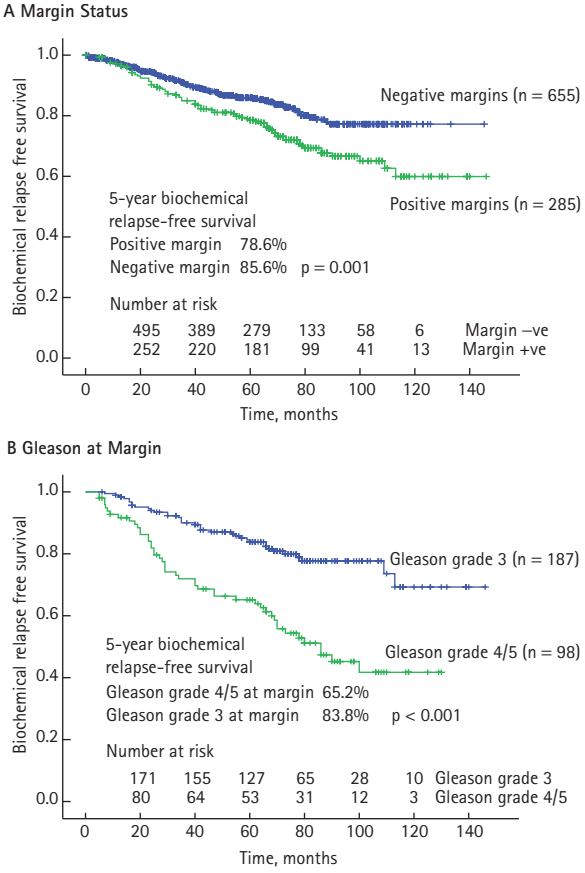


FIG. 2.
*Kaplan–Meier curves assessing the association between biochemical recurrence-free survival and (**A**) surgical margin status in men with localized PC and (**B**) the Gleason grade at the margin in men with margin-positive, localized PC.*

In contrast, Marks *et al.* [23] found no significant association between the extent of PSM and biochemical recurrence, possibly because of differences in the pathological interpretation of PSMs and the method of assessing the linear extent of margin involvement when multiple margins were involved. Recently, Cao *et al.* [24] reported that the linear length of a PSM was an independent prognostic factor for biochemical recurrence in stage pT2 cancers but not in pT3 cancers after RP. Most studies have described the extent of involvement subjectively as 'focal' or 'extensive' [9,25]. Our analysis of this variable was based on independent measurement of the length of the PSM using an ocular micrometer which showed a significant association between increase in linear extent and poorer prognosis on univariate, but not multivariate analysis.

Other variables previously reported as being associated with PSMs, including single vs multiple margins, location of margin, and plane of the margin, were not significantly associated with prognosis in the present study. It is possible that our cohort was not sufficiently large to detect weak associations between subgroups, and it is worth noting that the published studies have produced variable results [13,15,26–30]. For instance, a PSM involving the bladder neck or posterolateral surface of the prostate has been reported as having a more significant adverse impact on prognosis than an involved apical or anterior PSM [26–29]. In contrast, other investigators have found no association between the location of PSMs and recurrence rates [13,15,30]. Likewise, initial reports suggested that when the PSM occurred at a site of capsular incision it did not have an adverse prognostic significance, while more recent series have shown a significantly lower 5-year biochemical recurrence-free survival in patients with capsular incision compared with those with negative margins [19,31,32].

Adjuvant radiotherapy after RP for patients with high risk localized PC improves biochemical recurrence-free, metastasis-free and overall survival in men with one or more of the high risk features: PSM, SVI or

EPE [9–11]. In one study, at a median follow-up of 5 years, men with PSMs had a 48% 5-year biochemical recurrence-free rate without radiotherapy compared with 76% in the irradiated group ($P < 0.001$) [9]. The SWOG8794 trial with 20 years follow-up has now shown a significant improvement in overall survival after adjuvant radiotherapy (10-year overall survival 74% vs 66%, $P = 0.02$) [11]; however, there are significantly more Grade 2/3 late effects in the irradiated groups, with complications twice as likely for those men receiving radiotherapy [9,10]. In addition, surgical margin status is more predictive than EPE and SVI of a treatment benefit with adjuvant radiotherapy [33]. Irrespective of other clinicopathological features, patients with negative margins do not benefit from postoperative radiotherapy. Based on these data, for every 1000 patients with PSMs, adjuvant radiotherapy would prevent biochemical recurrence in 291 patients by year 5 ($P < 0.01$) [33]. Since the present study has shown that men with Gleason grade 3 at the PSM have the same prognosis as men with negative margins, we suggest that the former group of men are also candidates for a 'watch-and-wait' approach, potentially allowing almost two thirds of patients with PSMs to avoid radiotherapy and its associated toxicities.

In conclusion, the present study shows that the Gleason grade of the carcinoma at a PSM after RP is an independent predictor of biochemical recurrence. Patients with Gleason grade 4 or 5 carcinoma at a PSM have double the risk of PSA recurrence compared with patients with Gleason grade 3 at the margin, suggesting that this factor should be routinely assessed. Moreover, we found that men with Gleason grade 3 carcinoma at the PSM have a similar prognosis to men with negative margins and may not need further treatment. Assessment of Gleason grade at the margin may aid the optimum selection of patients for adjuvant radiotherapy after RP.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **PSM**, positive surgical margin; **RP**, radical prostatectomy; **PC**, prostate cancer; **ISUP**, International Society of Urological Pathology; **EPE**, extraprostatic extension; **SVI**, seminal vesicle invasion; **HR**, hazard ratio.