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Stage migration in localized prostate cancer has no effect on the post-radical prostatectomy Kattan nomogram

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OBJECTIVE

To investigate the effect of prostate-specific antigen (PSA) testing on stage migration in an Australian population, and its consequences on the prognostic accuracy of the post-radical prostatectomy (RP) Kattan nomogram, as in North America widespread PSA testing has resulted in prostate cancer stage migration, questioning the utility of prognostic nomograms in this setting.

PATIENTS AND METHODS

The study comprised 1008 men who had consecutive RP for localized prostate cancer between 1991 and 2001 at one institution. Two groups were assessed, i.e. those treated in 1991–96 (group 1, the early PSA era), and 1997–2001 (group 2, the contemporary PSA era). Differences in clinicopathological features between the groups were analysed by chi-squared testing and survival modelling. Individual patient data were entered into the post-RP Kattan nomogram and the efficacy assessed by receiver-operating characteristic curve analysis.

RESULTS

Patients in group 2 had lower pathological stage disease ($P = 0.01$) and fewer cancers with Gleason score ≥8 ($P < 0.001$) than group 1. Multivariate analysis identified preoperative serum PSA level ($P < 0.01$) and Gleason score ($P < 0.01$) as strong predictors of biochemical relapse in both groups. In group 2 pathological stage was not significant, but margin involvement became highly significant ($P = 0.004$). There was no difference in the predictive accuracy of the Kattan nomogram between the groups ($P = 0.253$).

CONCLUSIONS

These findings show a downward stage migration towards organ-confined disease after the introduction of widespread PSA testing in an Australian cohort. Despite this, the Kattan nomogram remains a robust prognostic tool in clinical practice.

KEYWORDS

prostate cancer, stage migration, nomogram, prognosis

INTRODUCTION

Prostate cancer is the most common cancer in men in the western world [1], and the second most common cause of male cancer death in Australia [2]. Since its introduction, widespread PSA testing has increased the prevalence of localized prostate cancer, with data showing a migration towards earlier-stage cancer being diagnosed in a younger group of men with lower preoperative PSA levels [3,4]. To date, this has not been reported in an Australian population, where the ethnic diversity of the patients differs from the USA. African-Americans comprise 12.1% of the total population of the USA, compared to African-Australians who comprise <0.01% of the total Australian population [5,6]. This racial disparity is important, as the incidence and mortality rate is higher in African-American men than European-American men [7].

PSA screening has never been formally endorsed by government cancer agencies in Australia, but Medicare (the Australian national health insurance scheme) and epidemiological data show the increased and sustained prevalence of testing since the mid-1990s. The incidence of prostate cancer in Australia has increased significantly since 1988, with a peak in 1994 after the introduction of the PSA testing as a funded Medicare item in 1993. The incidence subsequently declined between 1994 and 1997 to a new baseline [2]. Similarly, Medicare data show increasing use of PSA testing, with 227 499 tests in 1993–94 compared to 800 790 in 2000–2001 (Australian Medicare Data, 2007).

One of the major challenges in localized prostate cancer is predicting prognosis, and numerous prognostic models have been described incorporating a variety of clinicopathological features [8,9]. One of the most widely used is the Kattan nomogram, which predicts a patient's probability of disease-free survival after radical prostatectomy (RP), based on the preoperative PSA level, primary and secondary Gleason

scores and Gleason sum, seminal vesicle involvement (SVI), surgical margin involvement, extracapsular extension (ECE), lymph node involvement, neoadjuvant treatment and year of surgery [9]. The multi-institutional validation study by Graefen *et al.* [10] assessed the predictive accuracy of the post-RP Kattan nomogram across different patient populations, and included patients from our institution as the Australian cohort. More recently, the performance of these prognostic tools has been questioned, as they were developed on cohorts of patients with more advanced disease than that present in the contemporary patient population [11,12]. Although other groups have suggested that nomograms need to be continually updated to reflect the time-related pathological stage migration trends, none have tested the performance of the nomogram in this setting [11,12].

In the present study we aimed to assess the effect of widespread PSA testing on the clinicopathological features of localized prostate cancer treated with RP in an Australian setting, and its effect on the utility of the widely used Kattan nomogram.

PATIENTS AND METHODS

Data collected on 1008 consecutive men who had open RP between January 1991 and December 2001 for localized prostate cancer at one institution (St Vincent's Hospital, Sydney, Australia) were reviewed retrospectively. Surgery was undertaken by one of six urologists using a similar technique. Patients who had had neoadjuvant androgen-ablation therapy were excluded. Two groups were analysed according to the date of RP, with group 1 (1991–1996) representing the early PSA era and group 2 (1997–2001) representing the contemporary PSA era, where 425 and 583 men had RP, respectively. The two periods were chosen based on epidemiological data showing when prostate cancer incidence had reached a new and sustained baseline after the introduction of PSA testing, and Medicare data showing that the use of PSA testing had also reached a plateau at this time [2]. More than 95% of the patients treated were Caucasian. The St Vincent's Campus Research Ethics Committee approved the study (Approval no: H00/088).

To maintain a consistent staging system the attending urologist assigned the patients' clinical stage according to the 1992 TNM staging system, regardless of the year of surgery. The Gleason grading system was used to grade the RP specimen, by a dedicated genitourinary pathologist.

Failure of surgery to provide cancer control was defined by biochemical recurrence or local recurrence detected on a DRE and confirmed by either a positive biopsy or a concurrent or subsequent increase in PSA level. No patient had a PSA-negative relapse. Biochemical recurrence was defined as an initial increase in serum PSA level of ≥0.2 ng/mL, with a second confirmatory level of PSA of >0.2 ng/mL, in accordance with the current AUA guidelines for localized prostate cancer [13]. Progression-free survival (PFS) was defined as the time from the date of RP to the time at which biochemical recurrence occurred.

The differences in clinical and pathological characteristics between the groups were compared using chi-square analyses. Overall survival of the groups was assessed using the Kaplan-Meier method [14]. Data were evaluated for prediction of biochemical relapse using univariate and multivariate analyses in a Cox proportional hazards model [15]. Clinicopathological variables such as Gleason score, pathological stage and preoperative PSA level were modelled as dichotomous or continuous variables as appropriate [4,16].

Individual patient data were entered into the web-based post-RP Kattan nomogram (2007 version). Any patient with focal or extensive ECE was entered as positive and any patient with a positive surgical margin (including apical, focal and extensive) was entered as positive on the nomogram. An absence of pretreatment PSA level or primary and secondary Gleason score precluded the use of the nomogram for a patient. The web-based nomogram would only allow the year of RP to be entered after 1997, thus following consultation with the original author (M. Kattan) we were advised to record the dates of men who had their RP before 1997 as 1997.

The predicted 2- and 5-year PFS rates were compared against the actual PFS data using receiver-operating characteristic (ROC) curve analyses [9,10]. The predictive accuracy of the nomogram was assessed for both groups using area under curve (AUC) estimates from the ROC curve analyses. We accounted for differences in PFS, which could be related to follow-up bias, by censoring the data at 2 and 5 years for both groups. A bootstrap analysis was used to further validate the predictive accuracy of the nomogram. For all statistical analyses we used STATA V9.2 (Stata Corp, College Station, TX, USA) and Statview V5.0 (Abacus Systems, Berkeley, CA). Statistical significance was set at $P < 0.05$, with all reported P values being two-sided.

RESULTS

The clinicopathological characteristics of groups 1 and 2 are summarized in Table 1; there was a statistically significant difference in the preoperative PSA levels between the groups (mean 14.4 vs 8.9 ng/mL), consistent with the change in clinical practice (early vs later era; $P < 0.001$). In addition, the indication for surgery was more often an increased PSA level (48%) in group 2 than in group 1 (33%) ($P < 0.001$).

Patients in group 2 had lower pathological stage disease ($P = 0.01$) with less ECE ($P < 0.001$) and fewer cancers with a Gleason score of ≥8 ($P < 0.001$) than those in group 1. There was a statistically significant difference between the frequency of RP Gleason 6 tumours between groups 1 and 2, at 60% vs 38%, respectively ($P < 0.001$), with a shift towards more men having Gleason 7 disease in group 2. The rate of involved surgical margins also decreased with time, consistent with stage migration and smaller tumours ($P = 0.02$).

Cox proportional hazards analysis was used to assess independent predictors of prognosis in the two groups. The median follow-up for patients after RP was 103 months (>8 years) with a relapse rate of 42% (179/425) in group 1, and 68 months (>5 years) with a relapse rate of 22% (128/583) in group 2; 62% of men in group 2 had ≥5 years of follow-up and only 10% had <2 years. The 5-year biochemical relapse-free survival was 65% in group 1 and 78% in group 2, consistent with the lead-time bias seen in PSA-screened cohorts (Fig. 1A,B). Significant predictors of biochemical relapse in univariate analysis for both groups were preoperative serum PSA level (≥10 ng/mL), pathological stage (≥pT3), positive surgical margins, ECE, SVI and Gleason score (Table 2). Although adjuvant treatment was variably used in the two periods (Table 1) and was associated with relapse on univariate analysis,

TABLE 1 A comparison of clinicopathological characteristics for patients with localized prostate cancer treated with RP in groups 1 and 2

Variable	Group 1 (1990-1996)	Group 2 (1997-2001)	*P*
RP in period	1990–96	1997–2001	
No. of men	425	583	
Median (range):			
age, years	64 (41–77)	61 (42–75)	<0.001
follow-up, months	103 (0–191)	68 (1–117)	
Mean (range) PSA level, ng/mL	14.4 (0.2–194)	8.9 (0.1–63	<0.001
Indication for surgery, *n* (%)			
PSA level	138 (33)	274 (48)	<0.001
Clinical examination	259 (61)	273 (48)	
Pathological examination	27 (6)	26 (4)	
Clinical stage, *n* (%)			
T1	145 (34)	277 (48)	<0.001
T2	263 (62)	278 (48)	
T3	15 (4)	14 (2)	
Pathological stage, *n* (%)			
pT2	226 (53)	356 (61)	0.01
pT3a,b	136 (32)	161 (28)	
pT3c	63 (15)	66 (11)	
Lymph node involvement	6 (1.5)	6 (1)	0.60
Gleason score			
≤6	251 (60)	218 (38)	<0.001
7	109 (26)	281 (48)	
≥8	61 (14)	63 (11)	
Adjuvant treatment			
Hormonal	47 (11)	21 (3.5)	<0.001
Radiotherapy	18 (4)	20 (3.5)	
Combined	3 (1)	10 (2)	
Margins positive	207 (49)	240 (41)	0.02

*FIG. 1. Kaplan-Meier analysis of biochemical PFS in **A**, group 1 (1990–1996) and **B**, group 2 (1997–2001).*

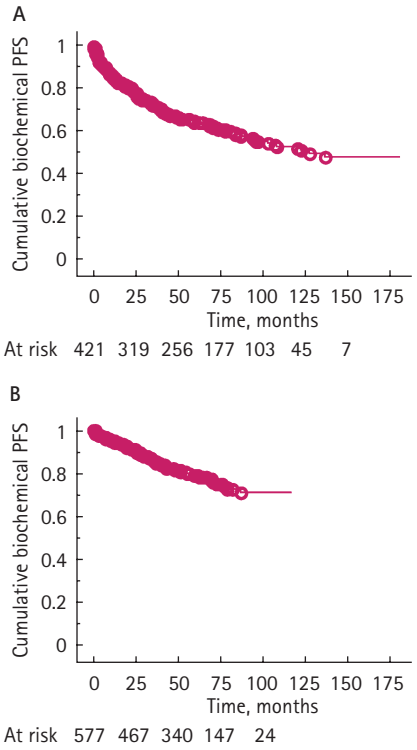
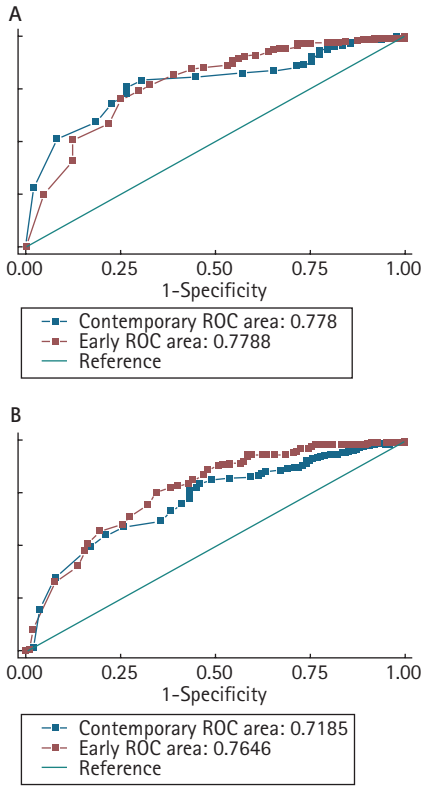


TABLE 2 Cox proportional hazards analyses of the relationship between clinicopathological characteristics and biochemical recurrence after RP between groups 1 and 2

Variable	Hazard ratio (95% CI), *P*			
	Group 1 (1990–1996)		Group 2 (1997–2001)	
	Univariate	Multivariate	Univariate	Multivariate
pT stage, pT3 vs pT2	3.2 (2.3–4.4), <0.001	2.2 (1.5–3.2), <0.001	2.6 (1.8–3.7), <0.001	1.4 (0.9–2.1), 0.10
C stage, T3 vs T1/2	2.6 (1.4–4.8), 0.002	–	2.3 (1.0–5.2), 0.04	–
ECE, yes vs no	2.9 (2.1–3.9), <0.001	–	2.6 (1.8–3.7), <0.001	–
Margins involved, yes vs no	2.0 (1.5–2.8), <0.001	1.1 (0.8–1.6), 0.50	2.3 (1.6–2.3), <0.001	1.8 (1.2–2.6), 0.004
SVI, yes vs no	3.5 (2.5–4.9), <0.001	–	3.8 (2.5–5.9), <0.001	–
Pre-op PSA level, ≥10 vs <10 ng/mL	1.9 (1.4–2.6), <0.001	1.6 (1.1–2.1), 0.005	2.4 (1.7–3.5), <0.001	1.9 (1.3–2.7), 0.001
Gleason score				
7 vs ≤6	2.5 (1.8–3.5), <0.001	2.0 (1.4–2.9), <0.001	2.7 (1.7–4.3), <0.001	2.1 (1.3–3.4), <0.001
≥8 vs ≤6	3.3 (2.2–4.8), <0.001	2.2 (1.5–3.3), <0.001	6.1 (3.5–10), <0.001	4.3 (2.3–7.8), <0.001
Adjuvant treatment, no vs yes	0.4 (0.3–0.6), <0.001	0.9 (0.6–1.5), 0.90	0.6 (0.3–0.9), 0.03	1.4 (0.8–2.3), 0.20

*FIG. 2. ROC curve analyses comparing actual vs predicted PFS (using the post-RP Kattan nomogram) at **A**, 2 years, and **B**, 5 years after RP.*



it was not an independent predictor of outcome in the multivariate models (Table 2).

Preoperative PSA level and Gleason score were both independent prognostic markers in the two groups. Despite the overall decline in preoperative PSA level between the groups (Table 1), it remained a significant predictor of relapse (Table 2). A higher Gleason score was also positively associated with biochemical recurrence in both group 1 ($P < 0.001$) and 2 ($P < 0.001$) in multivariate analyses, but with higher hazard ratios in group 2, suggesting increasing prognostic importance.

In keeping with stage migration, pathological stage no longer had prognostic value in group 2, although margin involvement became an independent prognostic marker. A higher pathological stage significantly increased the risk of biochemical relapse on multivariate analysis in group 1 (hazard ratio 2.2; 95% CI, 1.5–3.2; $P < 0.001$), but was not an independent predictor of outcome in group 2 ($P = 0.10$). However, the presence of a positive margin was only an independent predictor of outcome in group 2 (hazard ratio 1.8; 95% CI 1.2–2.6, $P = 0.004$), not in group 1 ($P = 0.5$).

The 2- and 5-year time points for the Kattan post-RP nomogram were assessed for both groups. As a result of missing data, 166 patients in group 1 and one from group 2 were excluded from the study. Most patients (94%) who were excluded from group 1 were omitted because only the Gleason sum score was available, as the pathologists who were reporting on the specimens from 1991–2 did not record the primary and secondary Gleason score. The excluded patients in group 1 were compared to the 254 included in the analysis. The 166 patients excluded had a lower rate of margin involvement (26% vs 55%) and a high rate of Gleason 6 disease (75% vs 49%) but other clinicopathological variables were similar, with no statistically significant differences between the groups.

The AUC (Fig. 2A) for group 1 at 2 years was 0.778 (95% CI 0.71–0.85) compared with 0.779 (95% CI 0.72–0.83) for those in group 2, and this difference was not significant. Similarly, the AUC for group 1 at 5 years was 0.765 (95% CI 0.70–0.82) compared with 0.719 (95% CI 0.67–0.77) for those in group 2 (Fig. 2B). There was also no statistically significant difference between the two AUC at 5 years ($P = 0.253$).

The bootstrap analysis concurred with the ROC curves, showing that the AUC was the same for the 2-year PFS in group 1 (AUC 0.78, 95% CI 0.64–0.92) and group 2 (AUC 0.78, 95% CI 0.62–0.93). Similarly, the AUC for the 5-year PFS in group 1 was 0.76 (95% CI 0.65–0.88) and for group 2 was 0.72 (95% CI 0.61–0.83).

DISCUSSION

Our study showed a continued stage migration towards an earlier pathological stage and more localized disease after the introduction of widespread PSA testing in Australia. It also confirms several important relationships between prognostic clinicopathological characteristics and biochemical relapse that were reported previously [4,12,16,17]. Importantly, our results indicate that despite the evidence of a pathological stage migration, there was no statistical difference in the predictive accuracy of the post-RP Kattan nomogram in predicting progression-free probability after surgery at 2 and 5 years, indicating that it remains a clinically useful tool.

The stage migration we observed was consistent with that in other series, apart from the changes in Gleason score. Most groups, including ours, showed a decrease in the percentage of surgically treated cancers that were Gleason score ≥8 after the introduction of widespread PSA testing [4,16,17]. Some smaller studies showed little difference in the rate of Gleason 7 cancers after the advent of PSA screening [4,16,17], although a recent large collaborative study comparing European and USA stage migration patterns reported a decrease in Gleason score 2–5 on both continents, but an increase in Gleason score 7 cancers in the USA only, similar to the present findings [16].

The positive margin rates of 49% and 41% in group 1 and 2, respectively, initially appear to be higher than rates in the present urological context [18–23]. However, other international studies conducted during a similar period to that used here (1991–2001) reflected positive margin rates similar to those in the present analyses [24–29].

The importance of prognostic assessment has increased since evidence emerged for the role of adjuvant radiotherapy for high-risk localized prostate cancer. Bolla *et al.* [30] showed that men who undergo RP and whose pathological examination showed capsular penetration or a positive margin, benefit from adjuvant external beam radiotherapy. In that study, biochemical PFS (74% vs 52.6%, $P < 0.001$) and clinical PFS (85.1% vs 77.5%, $P < 0.001$) significantly improved in the irradiated group at a median follow-up of 5 years. A similar study by Thompson *et al.* [31] showed a significant reduction in PSA relapse ($P < 0.001$) and clinical disease recurrence ($P = 0.001$) when patients received adjuvant radiotherapy. There is now significant evidence for effective adjuvant treatment in patients with high-risk prostate cancer, emphasizing the need for accurate prediction of risk by prognostic models.

The performance of prognostic nomograms has been questioned because of the pathological stage migration, leading to contemporary cohorts having an increasingly homogenous population of prostate cancers, where the tumours are at an earlier stage than during the era in which the nomograms were developed [11,32]. Thus it is increasingly

important to establish the validity of prognostic models in the modern setting. The Kattan post-RP nomogram is one of the most well-validated and commonly used prognostic tools in clinical practice, which is why it was chosen for evaluation in the present study. Our data closely reflect the findings of the multi-institutional validation [10] despite the presence of a pathological stage migration. This provides strong evidence for the ongoing clinical utility of this model in a contemporary context.

In conclusion, this study shows a continued downward stage migration towards organ-confined disease in an Australian population after the introduction of widespread PSA testing. Consequently, the pathological stage is less predictive of outcome than the Gleason score and surgical margin involvement. Despite this, the post-RP Kattan nomogram remains a robust prognostic tool in these patients and can confidently be used in the contemporary context.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **PFS**, progression-free survival; **ROC**, receiver-operating characteristic; **AUC**, area under the ROC curve; **RP**, radical prostatectomy; **SVI**, seminal vesicle involvement; **ECE**, extracapsular extension.