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Impact of surgical margin status on prostate-cancer-specific mortality

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Abstract

OBJECTIVE—

- To examine the relative impact of a positive surgical margin (PSM) and other clinicopathological variables on prostate-cancer-specific mortality (PCSM) in a large retrospective cohort of patients undergoing radical prostatectomy (RP).

PATIENTS AND METHODS—

- Between 1982 and 2011, 4569 men underwent RP performed by a single surgeon.
- Of the patient population, 4461 (97.6%) met all the inclusion criteria.
- The median (range) age was 58 (33–75) years and the median prostate-specific antigen (PSA) was 5.4 ng/mL; RP Gleason score was 6 in 2834 (63.7%), 7 in 1351 (30.3%), and 8–10 in 260 (6.0%) patients; PSMs were found in 462 (10.4%) patients.
- Cox proportional hazards models were used to determine the impact of a PSM on PCSM.

RESULTS—

- At a median (range) follow-up of 10 years (1–29), 187 men (4.3%) had died from prostate cancer.
- The 20-year prostate-cancer-specific survival rate was 75% for those with a PSM and 93% for those without.
- Compared with those with a negative surgical margin, men with a PSM were more likely to be older (median age 60 vs 58 years) and to have undergone RP in the pre-PSA era (36.6% vs 11.8%). Additionally, they were more likely to have a higher PSA level (median 7.6 vs 5.2 ng/mL), a Gleason score of 7 (58.7% vs 33.7%), and a non-organ-confined tumour (90.9% vs 30.6% [$P < 0.001$ for all]).
- In a univariate model for PCSM, PSM was highly significant (hazard ratio [HR] 5.0, 95% confidence interval [CI] 3.7–6.7, $P < 0.001$).
- In a multivariable model, adjusting for pathological variables and RP year, PSM remained an independent predictor of PCSM (HR 1.4, 95% CI 1.0–1.9, $P = 0.036$) with a modest effect relative to RP Gleason score (HR 5.7–12.6) and pathological stage (HR 2.2–11.0 [$P < 0.001$]).

CONCLUSION—

- Although a PSM has a statistically significant adverse effect on prostate-cancer-specific survival in multivariable analysis, Gleason grade and pathological stage were stronger predictors.

Keywords

surgical margin; prostatectomy; prostate cancer; survival

INTRODUCTION

There is no better way to cure a cancer that is confined to the prostate than total surgical removal, but the surgical procedure must remove all of the tumour. Surgical margin status at radical prostatectomy (RP) is shown to be a predictor of disease progression [1,2] and can be useful in deciding if adjuvant therapy is necessary. The positive surgical margin (PSM) rate varies greatly according to many factors such as surgical technique [3,4]. More importantly, the PSM rate is dependent on the pathological stage of the cancer [5].

While PSM status increases the risk of biochemical recurrence (BCR) after RP [2,6,7], a nomogram that predicts BCR has shown that Gleason grade and pathological stage were much stronger predictors of recurrence-free survival after surgery compared with surgical margin status [8]. Also, BCR does not necessarily translate into systemic progression and prostate-cancer-specific mortality (PCSM), so it is important to study PCSM directly [9–11]. At this time it is not well understood whether a PSM has prognostic value for PCSM. Even less is understood about the relative importance of a PSM compared with established prognostic variables such as Gleason grade and pathological stage.

In the present study, we evaluated the impact of surgical margin status on long-term PCSM using a large cohort of patients who underwent RP by a single surgeon with standardized pathological examination of surgical specimens. The independent predictive value of a PSM on PCSM was investigated in a multivariable model with commonly available perioperative variables.

MATERIALS AND METHODS

STUDY POPULATION

We conducted a retrospective cohort analysis of 4569 patients who underwent RP for clinically localized prostate cancer between 1982 and 2011. RP was performed by a single experienced surgeon (P.C.W.) using the retropubic approach as described [12]. RP specimens were inked and examined microscopically by experienced urological pathologists to determine surgical margin status. Surgical margins were considered positive if tumour cells extended to the inked surface of the prostate. Mortality status and cause of death information were updated using medical records after RP. Death was considered to be attributable to prostate cancer if prostate cancer was listed as the underlying cause of death or the patient had hormone refractory metastatic disease at the time of death. Cause-of-death information was sourced from the Centers for Disease Control and Prevention's National Death Index (NDI). Neoadjuvant and adjuvant therapy were not commonly performed in this series and 62 men who received adjuvant therapy and 29 men who received neoadjuvant therapy were excluded from the analysis, as previously described (Mullins *et al.* submitted).

STATISTICAL ANALYSIS

Patients with and without PSMs were compared using Student's *t*-test or Wilcoxon rank-sum test for continuous variables, and a chi-squared test for categorical variables. The log-rank test was used to compare Kaplan–Meier estimates of PCSM by PSM status. A Cox proportional hazards regression model was used to evaluate the effect of PSM while adjusting for other prognostic factors. All analyses were performed using Stata version 11 software (College Station, TX, USA) and SAS (Cary, NC, USA).

RESULTS

Of the 4569 patients who underwent RP, 4461 (97.6%) met the inclusion criteria of available surgical margin status and no adjuvant or neoadjuvant therapy. The median PSA level was 5.4 ng/mL and the median (range) age at time of surgery was 58 (33–75) years. RP Gleason score was 6 in 2834 (63.7%), 7 in 1351 (30.3%) and 8–10 in 260 (6.0%) patients. The median (range) follow-up time was 10 (1–29) years. In all, 187 patients (4.3%) had died from prostate cancer. Overall, PSMs were identified in 462 patients (10.4%).

Several significant differences were found between the PSM and negative surgical margin (NSM) subgroups (Table 1). Compared with those with a NSM, men with a PSM were more likely to be older (median age 60 vs 58 years) and to have undergone RP in the pre-PSA era (36.6% vs 11.8%). Additionally, they were more likely to have a higher PSA level (median 7.6 vs 5.2 ng/mL), a Gleason score of 7 (58.7% vs 33.7%), and a non-organ-confined tumour (90.9% vs 30.6%; $P < 0.001$ for all).

Kaplan–Meier estimates of PCSM were compared between patients with and without PSMs; survival was significantly lower among patients with PSMs, $P < 0.001$ (log-rank chi-squared 143.2, 1 degree of freedom; Fig. 1). In the univariate proportional hazards model a PSM was significantly associated with PCSM (hazard ratio [HR] 5.0, 95% CI 3.7–6.7, $P < 0.001$). In a multivariable model adjusting for RP Gleason score, pathological stage and year of RP, PSM remained an independent predictor of PCSM (HR 1.4, 95% CI 1.0–1.9, $P = 0.036$) with a modest effect relative to RP Gleason score (HR 5.7–12.6, $P < 0.001$) and pathological stage (HR 2.2–11.0, $P = 0.011$ – < 0.001). Year of surgery was also a significant predictor of PCSM (HR 0.92, 95% CI 0.88–0.95, $P < 0.001$ [Table 2]).

DISCUSSION

The presence of a PSM is an independent predictor of BCR after RP [2,13]; however, BCR does not always lead to PCSM. In one study, only 34% of patients with BCR eventually had metastatic disease [14] and in another, the difference in 10-year overall survival between those with and without BCR was only 5% [15]. Given this information, it may be more clinically relevant to study PCSM as the primary endpoint, rather than BCR after definitive treatment.

We performed a retrospective analysis of the association of PSMs with long-term PCSM. A single surgeon performed all prostatectomies using a uniform technique and all surgical specimens were examined in a standardized fashion by experienced urological pathologists at a single institution, minimizing the variation in surgical technique and the risk of misclassification. This is an important detail as surgical artifacts and varying pathologist methods can lead to false-positive or false-negative margins for prostatectomy specimens [16–18].

We found a significant difference in long-term PCSM by surgical margin status on univariate analysis (HR 5.0, 95% CI 3.7–6.7, $P < 0.001$); however, there are many factors

that correlate with PSM, such as pathological grade, stage and tumour size [19]. To determine the independent prognostic contribution of a PSM, multivariable regression analysis was performed while controlling for clinicopathological covariates that are known to be associated with an increased risk of PCSM. After adjustment for RP Gleason grade and pathological stage as well as year of surgery, PSM remained an independent predictor of PCSM (HR 1.4, 95% CI 1.0–1.9), $P = 0.036$) with a modest effect relative to RP Gleason score (HR 5.7–12.6, $P < 0.001$) and pathological stage (HR 2.2–11.0, $P = 0.011$ – <0.001).

A nomogram that predicts BCR has already shown that Gleason grade and pathological stage were much stronger predictors of recurrence-free survival after surgery than surgical margin status [8]. Boorjian *et al.* [13] found that PSM was not an independent predictor of PCSM at their institution but did not report on the prognostic value of Gleason grade and pathological stage. In a recent nomogram for 15-year PCSM after RP, PSM status was not significantly associated with PCSM, while Gleason score and pathological stage were the only significant predictors [20]. As the nomogram was generated using multi-institutional data, potentially introducing variability in evaluation of margin status, it was important to evaluate PSM as a prognostic indicator in a standardized fashion.

The present analysis is the only study of the PSM–PCSM interaction in a single surgeon's cohort. The surgeon variable has been linked to the rate of PSM, and the elimination of this variability may have allowed us to appreciate the modest independent prognostic value of a PSM [21]. Furthermore, men routinely did not receive adjuvant or neoadjuvant therapy in the present cohort. The very few exceptions were *a priori* eliminated from the analysis, allowing the unique opportunity to study the long-term meaning of a PSM. In other cohorts the decision to give adjuvant therapy was probably influenced by the presence of a PSM [22]. Finally, other authors have used salvage therapy as a variable in their multivariable analysis, and in the present study we did not. By definition, all men who receive salvage therapy have experienced BCR. Thus the salvage therapy variable acts as a surrogate marker of BCR, producing a biased analysis of outcomes in any model that includes all patients who have undergone surgery [23,24].

As many patients undergo surgery for prostate cancer, it is necessary to determine the implications of a PSM. The clinical significance of a PSM depends on the context in which it is being considered. When discussing long-term prognosis, the present analysis and other nomograms suggest that Gleason grade and pathological stage are the best predictors of PCSM, while PSM provides limited additional insight. Conversely, when determining a management plan for the individual patient, the finding of a PSM is very important. In fact, Van der Kwast *et al.* [22] showed that PSM was the strongest predictor of benefit from immediate postoperative radiotherapy, where benefit was measured as recurrence-free survival.

Potential limitations of the present study should be mentioned. The present analysis treated surgical margin as a binary variable, being either positive or negative. Neither the number, extent, location, nor cancer grade at PSM were considered, all of which have been associated with recurrence [9,25–28]. Also, in the present analysis the independent predictive value of PSM for PCSM was determined for the entire cohort, which included men with pT3b and lymph node involvement. It is possible that there exists a stratification based on perioperative variables where PSM attains a stronger prognostic value for some subgroups of patients. In fact, in patients in the Surveillance, Epidemiology and End Results database, limited to pT2/pT3a tumours, Wright *et al.* [23] found that a PSM was an independent predictive variable (HR 1.70, 95% CI 1.32–2.18) and, for comparison, in their subgroup with pT3 and high grade disease the association was 2.72. Similarly, in a subset of patients in the high D'Amico risk group, Boorjian *et al.* [29] found the HR for PSM (HR

2.1, 95% CI 1.2–3.6, $P < 0.008$) to be of similar magnitude to pathological stage (HR 1.8–2.3). It will be interesting to further stratify the cohort as well as different measures of PSM in future studies.

In conclusion, overall prostate-cancer-specific survival is excellent in a large cohort of men who underwent RP by a single surgeon. Univariate analysis of this cohort determined that PSM was a significant predictor of PCSM. Upon adjustment for clinicopathological variables in a multivariable model, surgical margin status remained modestly associated with increased PCSM, while RP Gleason score and pathological stage were strong predictors of PCSM. The present results are consistent with established multicentre nomograms for BCR and PCSM.

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Abbreviations

PSM	positive surgical margin
PCSM	prostate-cancer-specific mortality
RP	radical prostatectomy
HR	hazard ratio
BCR	biochemical recurrence

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What's known on the subject? and What does the study add?

Surgical margin status at radical prostatectomy (RP) has been shown to be a predictor of disease progression and the strongest predictor of benefit from adjuvant therapy, but the impact of a positive surgical margin (PSM) on long-term prostate-cancer-specific survival is unknown. The PSM rate is dependent on the pathological stage of the cancer. In a recent multicentre nomogram for 15-year prostate-cancer-specific mortality (PCSM) after RP, PSM was not significantly associated with PCSM, while Gleason score and pathological stage were the only significant predictors. This has not been validated in a single centre, and PSM has been shown to vary greatly with surgical technique.

This is the first study on the impact of PSM on PCSM in a single surgeon's cohort.

In other centres, the decision to administer adjuvant therapy may be influenced by surgical margin status. In this cohort, men routinely did not receive adjuvant therapy, affording the unique opportunity to study the long-term implications of a PSM.

FIG. 1.
Prostate-cancer-specific survival by surgical margin status.

TABLE 1

Clinical and pathological characteristics of the RP study cohort

Variable	NSM, N = 3999	PSM, N = 462	Total, N = 4461	P
Age, n (%)				<0.001
<40 years	58 (1.4)	3 (0.6)	61 (1.4)	
41–50 years	626 (15.7)	40 (8.7)	666 (14.9)	
51–60 years	1973 (49.3)	208 (45.0)	2181 (48.9)	
61–70 years	1311 (32.8)	206 (44.6)	1517 (34.0)	
>70 years	31 (0.8)	5 (1.1)	36 (0.8)	
Mean age	57.1	59.1	57.3	<0.001
Median (range) age	58 (33–75)	60 (38–75)	58 (33–75)	
Preoperative PSA, n (%)				<0.001
0–4 ng/mL	1214 (31.9)	49 (13.4)	1263 (30.3)	
4.1–10 ng/mL	2132 (56.0)	187 (51.1)	2319 (55.6)	
10.1–20 ng/mL	382 (10.0)	79 (21.6)	461 (11.0)	
>20 ng/mL	79 (2.1)	51 (13.9)	130 (3.1)	
Preoperative PSA, n (%)	3807	366	4173	<0.001
Mean	6.3	12.0	6.8	
Median (range)	5.2 (0.1–69.0)	7.6 (0.6–151.0)	5.4 (0.1–151.0)	
Year of RP				<0.001
Mean	1998.0	1992.7	1997.5	
Median (range)	1998 (1982–2011)	1991 (1982–2011)	1998 (1982–2010)	
Clinical stage, n (%)				<0.001
T1a/b	157 (3.9)	28 (6.1)	185 (4.2)	
T1c	2244 (56.4)	143 (31.2)	2387 (53.8)	
T2	1544 (38.8)	277 (60.5)	1821 (41.0)	
T3	36 (0.9)	10 (2.2)	46 (1.0)	
Biopsy Gleason score, n (%)				<0.001
2–6	3170 (79.7)	307 (68.4)	3477 (78.6)	
7	708 (17.8)	107 (23.8)	815 (18.4)	
8–10	98 (2.5)	35 (7.8)	133 (3.0)	
Performed in pre-PSA era, n (%)				<0.001
Yes	478 (12.0)	174 (37.7)	652 (14.6)	
No	3521 (88.0)	288 (62.3)	3809 (85.4)	
Pathological stage, n (%)				<0.001
OC	2770 (69.4)	41 (9.1)	2811 (63.2)	
FCP/ECP	985 (24.6)	281 (62.2)	1266 (28.5)	
SVI	115 (2.9)	53 (11.7)	168 (3.8)	
LN+	123 (3.1)	77 (17.0)	200 (4.5)	
Pathology Gleason score, n (%)				<0.001
2–6	2643 (66.3)	191 (41.3)	2834 (63.7)	
7	1159 (29.0)	192 (41.6)	1351 (30.3)	

Variable	NSM, N = 3999	PSM, N = 462	Total, N = 4461	P
8–10	187 (4.7)	79 (17.1)	266 (6.0)	
Progression, n (%)				<0.001
No	3461 (87.5)	203 (44.6)	364 (83.1)	
Yes	493 (12.5)	252 (55.4)	745 (16.9)	
Metastasis, n (%)				<0.001
No	3735 (95.5)	337 (75.7)	4072 (93.5)	
Yes	174 (4.5)	108 (24.3)	282 (6.5)	
Prostate cancer death, n (%)				<0.001
No	3851 (97.4)	374 (82.0)	4182 (95.7)	
Yes	103 (2.6)	82 (18.0)	187 (4.3)	
Mean follow-up, years	10.5	13.1	10.8	< 0.001
Median (range) follow-up, years	10 (1–29)	13 (1–29)	10 (1–29)	

OC, organ-confined; FCP, focal capsular penetration; EPE, extraprostatic extension; SVI, seminal vesicle invasion; LN+, micrometastases to pelvic lymph nodes.

TABLE 2

Cox proportional hazard model predicting PCSM

Variable	Univariate model		Multivariate model, <i>N</i> = 4385	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Surgical margin				
Negative (reference)	1	<0.001	1	0.036
Positive	5.0 (3.7–6.7)		1.4 (1.0–1.9)	
RP Gleason score				
2–6, reference	1	<0.001	1	<0.001
7	12.4 (7.4–20.8)		5.7 (3.3–9.8),	
8–10	45.5 (26.8–77.1)		12.6 (7.1–22.5)	
Year of surgery	0.88 (0.85–0.91)	<0.001	0.92 (0.88–0.95),	<0.001
Pathological stage				
OC (reference)	1		1	
FCP/ECP	5.5 (3.0–9.8),	<0.001	2.2 (1.2–4.1)	0.011
SVI	37.6 (20.6–68.6),		8.5 (4.4–16.3),	<0.001
LN+	58.8 (33.1–104.4)		11.0 (5.8–20.9),	<0.001

OC, organ-confined; FCP, focal capsular penetration; EPE, extraprostatic extension; SVI, seminal vesicle invasion; LN+, micrometastases to pelvic lymph nodes.