

Positive surgical margins at radical prostatectomy: Population-based averages within PSA and Gleason strata

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Abstract

Background: Positive surgical margins (PSM) are an important determinant of biochemical recurrence after radical prostatectomy (RP). We use a population-based cancer registry to evaluate PSM by stage, Gleason and prostate-specific antigen (PSA).

Methods: We identified men undergoing RP from the Surveillance, Epidemiology and End Results (SEER) database between 2004 and 2007. Differences between those with and without PSM were compared with chi-squared tests. The proportion of cases with PSM were stratified by PSA and Gleason sum for both pT2 and pT3a tumours. Factors associated with PSM were analyzed using chi square and multivariate logistic regression analysis. A composite variable was used in a second multivariate analysis to display the odds ratio (OR) for a PSM for each discrete combination of PSA, Gleason score and pT stage

Results: In total, 28 461 RP patients were identified and a PSM was present in 19.5%. PSM were 42% in pT3a and 16% in pT2 cases. Higher PSAs (<4.0, 4-9.9, >10) were associated with higher proportions of PSM (12%, 20% and 28%, $p < 0.001$). Similarly, higher Gleason scores (≤ 6 , 3+4, 4+3, ≥ 8) were associated with higher PSM (12%, 22%, 27% and 33%, $p < 0.001$). For pT2 tumours, the proportion of PSM ranged from 8% (Gleason ≤ 6 , PSA <4.0) to 28% (Gleason 8-10, PSA ≥ 10). For pT3a tumours, the PSM was higher in each Gleason/PSA strata compared to those with pT2 tumours, reaching 63% for those with pT3a, Gleason 8-10, PSA >10 disease. On multivariate analysis, stage was the largest predictor for PSM (OR 3.05, 95% confidence interval 2.81-3.30), although Gleason score and PSA remained statistically significant.

Conclusion: In this population-based study of PSM after RP, the proportion of PSM vary significantly within different PSA and Gleason strata for organ-confined and extracapsular disease. These data can be used as a reference for urologist self-assessment.

Introduction

Positive surgical margins (PSM) at the time of radical prostatectomy (RP) are independent predictors of biochemical recurrence, local recurrence, distant metastasis and, in some series, have been shown to predict for prostate cancer specific mortality.¹⁻⁶ The occurrence of PSM often prompts adjuvant treatments, such as radiotherapy, which has been shown to improve biochemical recurrence-free survival and overall survival in this population.⁷⁻⁹ In fact, a PSM may be the strongest predictor of the utility of radiotherapy in the adjuvant setting.¹⁰ As such, avoiding a PSM is a clear goal of surgery; a PSM is perhaps the only risk factor for poor outcomes that can be affected by the surgeon.

Recent quality improvement initiatives in Canada have focused on accurate reporting of PSM rates. A publication by Cancer Care Ontario has mandated that less than a 25% PSM rate for T2 disease should be achieved.¹¹ Yet, a previously published report indicated that the median PSM rate in the province was 33%.¹² The most recent meeting of the Canadian Urologic Association contained numerous presentations showing highly variable rates of PSM between presenters.

Rates of PSM vary significantly in the literature and are dependent on a number of factors, including surgical expertise, pathological stage, Gleason grade, percent of positive cores, serum PSA, prostate volume and the interobserver variability between pathologists.¹³⁻¹⁸ However, much of the data used to derive rates of PSM are based on information from single institutions and tertiary care centres of excellence. They are, therefore, of limited utility to the practicing urologist who is seeking to compare his or her own results against a normative sample. Additionally, not all tumours are created equally even within the same pathological stage. Rates of PSM may be profoundly affected by other risk factors generating varying PSM rates within each pathological stage.

We explore the rates of PSM within PSA, Gleason and pathologic stage strata for its occurrence in a large population-based study. This was done to generate a tool to be used by urologists for their own self-assessment.

Methods

Data source

The cohort was identified from the Surveillance, Epidemiology, and End Results (SEER) Program database. SEER collects cancer incidence, primary treatment and other variables from 17 population-based cancer registries in the United States accounting for about 26% of the population.¹⁹ Data from 2004 to 2007 from 13 SEER registries were used (metropolitan areas of San Francisco-Oakland, San Jose-Monterey, Los Angeles, Atlanta, Detroit, Seattle-Puget Sound and the states of Connecticut, Hawaii, New Mexico, Utah, Iowa). Cases before 2004 were excluded since PSA and Gleason scores was not reported prior to that date. The Alaska and Rural Georgia registries were also excluded since they provided less than 0.3% of the total cases.

Study population

Subjects were identified using the International Classification of Diseases for Oncology (ICD-O-3) site codes for the prostate (C61.9) and ICD-O-3 histology codes for adenocarcinoma (8550) and acinar cell carcinoma (8140). There were 33 758 eligible cases undergoing RP during the study period. Margin status is not reported for pathologic stage pT3b (seminal vesicle invasion) or pT4 (adjacent organ invasion) and therefore were excluded (pT3b: 1,612 (4.6%); pT4: 425 (1.2%)). Those with missing Gleason score ($n = 85$ [0.3%]) or PSA ($n = 3692$ [11.6%]) were also excluded.

Statistical analysis

Clinical and pathologic characteristics were compared between those with and without PSM with chi-squared tests. The proportion of PSM were determined within each strata of Gleason sum (2-6, 3+4, 4+3, 8-10) and PSA (<4.0, 4.0-9.9, 10+) for both organ-confined (pT2) and extracapsular (pT3a) tumours. Chi-squared tests were used to test for differences within these strata. Multivariate logistic regression analysis was used to determine factors which significantly predicted for PSM. Included in the model were Gleason score, preoperative PSA, age, race, registry site and year of diagnosis. A composite variable composed of PSA, Gleason score and pathological T stage was then developed. This was added to our multivariate model to display the odds ratio for a PSM for each discrete combination of PSA, Gleason score and

T stage. All statistical analyses were conducted using Stata software version 11.0 (StataCorp LP, College Station, TX).

Results

The analytic cohort consisted of 28 459 men who underwent RP with complete data available between 2004 and 2007. PSM were reported in 19.5%. We tallied the clinical and pathological characteristics of the men who underwent RP (Table 1). Pathologic tumour stage was highly associated with PSM, as 15.8% of men with pT2 tumours, and 41.8% of men with pT3a tumours ($p < 0.001$) had PSM (Table 1). The proportion of PSM declined annually during the study period.

PSM were more commonly observed with higher PSA levels (Table 1). The proportion of men with a PSM rose for each level of PSA, from 12.4% to 19.5% to 29.1% for PSAs <4.0 ng/mL, 4-9.9, and ≥ 10 , respectively ($p < 0.001$). Similarly, higher Gleason scores were associated with PSM (Table 1). PSM were observed in 12.3%, 22.3%, 26.8% and 32.6% of men with Gleason ≤ 6 , 3+4, 4+3 and 8-10 disease, respectively ($p < 0.001$).

To determine the role of preoperative PSA and pathologic Gleason score by pathologic stage, we grouped PSM into PSA and Gleason sum strata within each pTstage (Table 2). For pT2 tumours, the lowest PSM were seen in those with PSAs <4.0 and Gleason 2-6 cancer (7.9%). The proportion of PSM rose with increasing PSA levels and Gleason aggressiveness to a high of 28.4% for those with Gleason 8-10 tumours with PSAs ≥ 10 . A similar trend was seen for pT3 tumours, although for each respective strata, the corresponding PSM proportion was higher than observed for pT2 tumours.

Multivariate logistic regression analysis showed that pathological stage was the strongest predictor for a PSM (odds ratio 3.04, 95% confidence interval 2.81-3.30). PSA and Gleason score maintained statistical power in the multivariate model as did tumour registry location and year of diagnosis (data not shown). Our composite variable showed an increase risk of PSM with increasing PSA, Gleason and pathological T stage (Fig. 1).

Discussion

Our study augments previous studies that have linked grade, PSA and pathological stage to PSM by stratifying patient cohorts by these parameters. While these results may seem intuitive, we present the data as a benchmarking tool for urologists to assess their operative results as a quality measure.

A limitation of the existing literature on PSM is that the work comes from single institution series or pooled results from a few centres of prostate cancer excellence which may not reflect the average urologist's experience. A recent review article of PSM reported rates from 11% to 38% over-

Table 1. Distribution of clinical and pathological characteristics of 28 459 radical prostatectomy patients by surgical margin status

	Negative margin N (%)	Positive margin N (%)	p value
Overall	22 921 (80.5)	5538 (19.5)	
Age (years)			
<55	4514 (80.7)	1082 (19.3)	0.003
55-59	5408 (81.6)	1219 (18.4)	
60-64	5744 (81.1)	1341 (18.9)	
65-70	4649 (79.5)	1201 (20.5)	
70+	2605 (78.9)	695 (20.1)	
Race			
Caucasian	19 019 (80.7)	4552 (19.3)	0.3
African-American	2216 (79.5)	572 (20.5)	
Other	1686 (80.3)	414 (19.7)	
Year of diagnosis			
2004	5667 (77.7)	1629 (22.3)	<0.001
2005	5180 (79.5)	1325 (20.4)	
2006	5734 (81.9)	1267 (18.1)	
2007	6340 (82.8)	1317 (17.2)	
Clinical stage			
T1c	13 031 (81.1)	3031 (18.9)	<0.001
cT2	9293 (79.5)	2400 (20.5)	
cT3	234 (75.7)	75 (24.3)	
Pathologic stage			
pT2	20 608 (84.2)	3871 (15.8)	<0.001
pT3	2313 (58.1)	1667 (41.8)	
PSA			
<4.0 ng/mL	4690 (87.6)	662 (12.4)	<0.001
4-9.9	15 160 (80.5)	3674 (19.5)	
10+	3071 (71.9)	1202 (28.1)	
Gleason sum			
2-6	10 426 (87.7)	1465 (12.3)	<0.001
3+4	8705(77.7)	2492 (22.3)	
4+3	2154 (73.1)	790 (26.8)	
8-10	1636 (67.4)	791 (32.6)	

all with organ-confined and non-organ-confined disease, with ranges of 3% to 18% and 17% to 53%, respectively.²⁰ In our study, organ-confined tumours had PSM in 16% of cases compared to 42% in tumours that extended through the capsule. Recently, Patel and colleagues analyzed the records of 8418 patients with pathological organ-confined disease undergoing robotic RP from 7 institutions.²¹ Their PSM rates were 9.45% and 37.2% for pT2 and pT3a disease, respectively. They found on multivariate analysis that pathological T stage, preoperative PSA, elevated body mass index and smaller prostates were predictive of PSM. In those with organ-confined disease, preoperative PSA was the most important predictor of PSM.

Other studies have specifically examined PSM in organ-confined disease. Ahyai and colleagues studied 932 men

with pathological T2 disease undergoing RPs over a 12-year span at a German institution. They found that preoperative PSA was not predictive of PSM.²² Their series had an overall rate of PSM of 12.9%, which was similar to the 15.8% seen in the organ-confined subset of our study. On their univariate and multivariate analysis, predictors of a PSM were tumour volume, nerve-sparing procedure and surgeon volume. Interestingly, their study showed neither Gleason score nor PSA level predictive of PSM. Both Gleason score and preoperative PSA predicted biochemical recurrence in univariate models, but not multivariable models where tumour volume, percent high-grade tumour volume and surgical margin status were the only predictors of biochemical recurrence.

Lawrensckuk and colleagues established a population-based assessment of PSM in organ-confined disease in a Canadian cohort.¹² The Ontario province-wide PSM rate in pT2 disease was 33%, which is considerably higher than in our series. PSA and Gleason grade, however, were not included in the analysis. Surgical volume fell short of predicting for PSM in a statistically significant manner, although this association has been shown in other series.^{13,23} Information regarding surgeon volume is not available within the SEER dataset and could not be included in our analysis. However, tumour registry location significantly affected PSM rates even after controlling for all other factors in the multivariate model, indicating significant geographic variability among providers.

In our study, PSM rates declined over the 4-year interval. Other groups have noted similar decreases over time. Han and colleagues analyzed the changes in pathologic surgical margin status over a 20-year period at a single institution.²⁴ They noted a significant decrease in PSM overall, but explained this phenomenon by a corresponding increase in the percentage of patients with organ-confined disease. Their data included prostatectomies performed up to 2001 and may, therefore, represent a different underlying cause for the change in PSM seen in our study. In our analysis, there was no statistical difference in the number of patients presenting with lower stage disease over the 4-year period (data not shown). It is possible that this decrease may be the result of refinement in surgical technique over time or may represent a change in surgical approach with the increasing utilization of robot assisted techniques. Unfortunately, information on surgical approach is not available in the SEER registry.

Williams and colleagues recently analyzed the SEER-Medicare dataset and found that individual surgical volume did not predict PSM in a dataset of 4247 men.²⁵ To produce a meaningful predictive and quality control tool for urologists, our study had several advantages over the Williams study. First, our dataset contained the results of over 28 000 RPs which may have given it power to detect differences that were not statistically significant given their small sample size

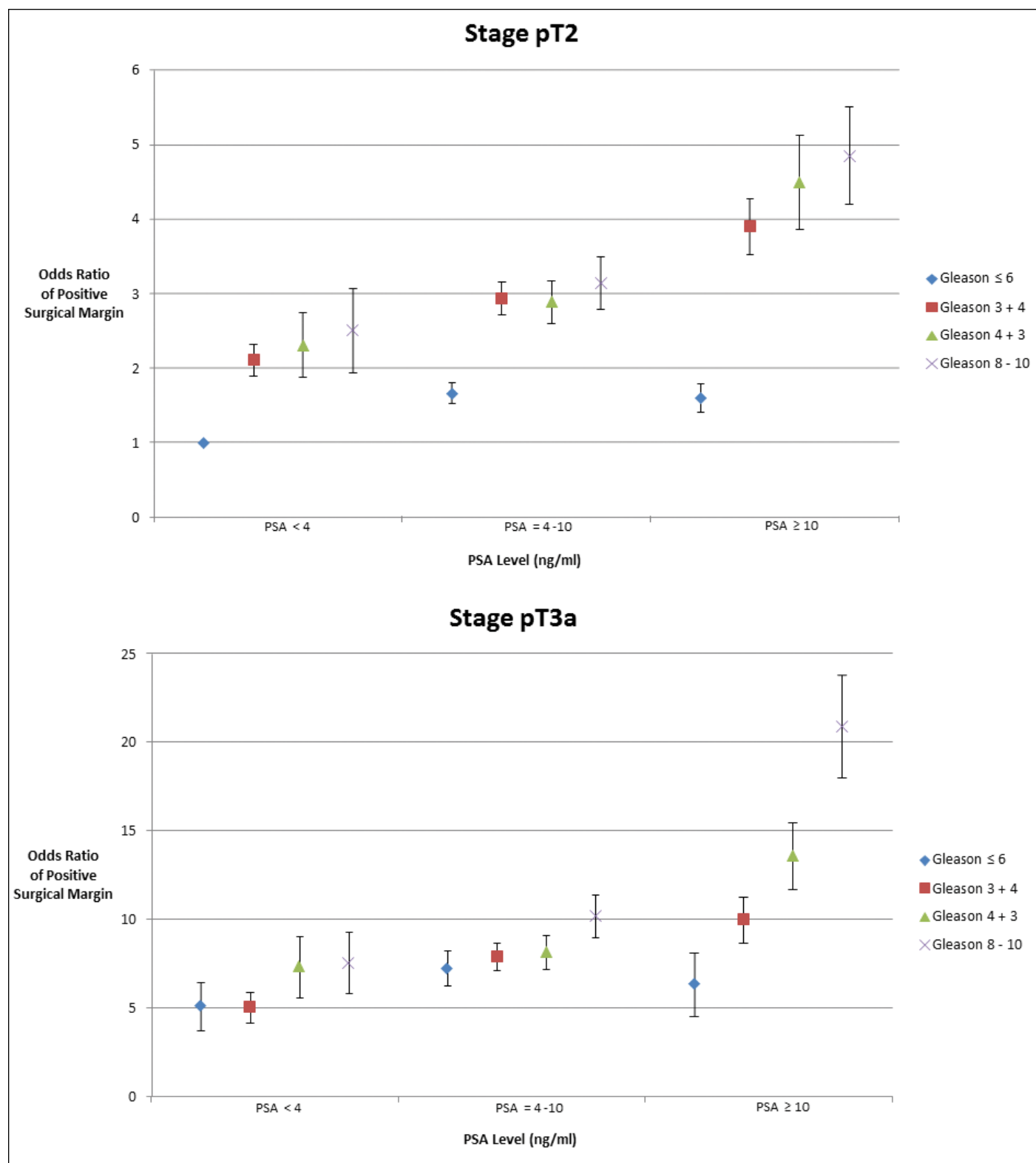


Fig. 1. Odds ratio of a positive surgical margin stratified by stage, grade and Gleason sum. Data were derived using multivariate logistic regression analysis adjusting for age, race, stage, Gleason sum, prostate-specific antigen (PSA), registry site and year of diagnosis. Data are displayed as odd ratios with standard errors of a positive surgical margin using Gleason 6, PSA <4 ng/mL and pathological stage T2 as the referent.

Table 2. Radical prostatectomy positive margin rate by pathologic stage by PSA and Gleason sum

PSA level	Organ confined (pT2)								p value
	Gleason 2-6		Gleason 3+4		Gleason 4+3		Gleason 8-10		
	N	% Positive margin	N	% Positive margin	N	% Positive margin	N	% Positive margin	
<4.0	2903	7.9	1529	14.1	278	15.1	169	16.6	<0.001
4-9.9	7305	12.6	6681	19.4	1416	19.4	942	20.2	<0.001
10+	1207	12.1	1283	24.7	379	26.7	387	28.4	<0.001
p value	<0.001		<0.001		0.002		<0.001		

PSA level	Extra-capsular extension (pT3a)								p value
	Gleason 2-6		Gleason 3+4		Gleason 4+3		Gleason 8-10		
	N	% Positive margin	N	% Positive margin	N	% Positive margin	N	% Positive margin	
<4.0	78	28.2	211	28.9	87	34.5	97	36.1	0.50
4-9.9	334	37.7	1132	38.7	507	38.7	517	44.7	0.09
10+	64	34.4	361	44.9	277	53.1	315	62.5	<0.001
p value	0.28		0.001		<0.001		<0.001		

PSA: prostate-specific antigen.

limited to the Medicare population. Second, they provide estimated thresholds for PSM within pathologic stage strata based on surgeon volume. Our analysis is different because we report on the actual rates of PSM within pathologic stages stratified by Gleason and PSA, which both strongly predict margin status. This distinction will allow urologists to stratify their patients with respect to risk factors for PSM to more accurately judge and monitor their own quality control.

There are several limitations associated with our analysis. First, recent work from one of the SEER sites has suggested that the SEER data may underreport PSM.²⁶ Information regarding comorbidities was not available and several groups have reported that increased body mass index is associated with an increased risk of PSM.^{21,27,28} The location and number of positive cores from transrectal ultrasound (TRUS) guided biopsies of the prostate guide surgeons with surgical planning. They have been shown in various series to affect surgical margin status.^{29,30} Patient information regarding the results from TRUS biopsies are not contained within the SEER dataset. Not all PSM may convey the same risk of biochemical recurrence.^{31,32} Our analysis does not stratify patients based on location, size or multifocality of surgical margins. Finally, surgical details, such as robotic or open approach, nerve-sparing status and surgeon volume, are not available in SEER.

Despite these limitations, we believe we have developed an important tool to assist urologists in assessing surgical quality within their own practice. While it does not incorporate all factors associated with PSM, the strength of our study lies in the simplicity of the tool and its ability to stratify patients into easily discernible categories for quick comparisons of surgical outcomes.

Conclusion

We report on the rates of PSM from a contemporary population-based cohort of over 28 000 men with prostate cancer treated with RP. We developed a simple table that stratified the risk of PSM based on PSA, Gleason score and pathological T stage. These data provide valuable information regarding population-based rates of PSM, which can serve as a quality benchmark for urologists to compare their results.

Competing interests: None declared.

This paper has been peer-reviewed.

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