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Influence of pathologist experience on positive surgical margins following radical prostatectomy

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Abstract

Background: A positive surgical margin (PSM) following radical prostatectomy (RP) for prostate cancer is associated with increased risk of biochemical recurrence. We sought to examine whether the pathologist is an independent predictor of PSMs.

Methods: We performed a retrospective review of 3,557 men who underwent RP for localized prostate cancer at our institution from 2003 to 2015. We evaluated 29 separate pathologists. Univariate and multivariable logistic regression were used to test variables previously shown to influence PSM rates.

Results: Overall rate of PSM was 18.9%. Compared with patients without PSM, patients with PSM had higher body mass index (mean: 28.8 vs. 28.3), Gleason score ≥ 7 (84% vs. 66%), extracapsular extension (51% vs. 20%), and median prostate-specific antigen (5.9 vs. 5.1 ng/ml) (all $P < 0.05$). Univariate logistic regression showed that surgeon experience, pathologist experience, and pathologist genitourinary fellowship training were all predictors of PSMs (all $P < 0.05$). Multivariable regression analysis confirmed that decreased surgeon experience, increased pathologist experience, higher pathologic Gleason score, higher pathologic stage, and higher prostate-specific antigen were significant predictors of PSMs. Increasing surgeon experience was associated with decreased odds of PSM (odds ratio = 0.79 per 1 standard deviation increase, 95% CI [0.70–0.89]). In contrast, increasing pathologist experience was associated with increased odds of PSM (odds ratio = 1.11 per 1 standard deviation increase, 95% CI [1.03–1.19]). The relationship between pathologist experience and PSM appeared to be nonlinear (Fig. 2).

Conclusions: Greater pathologist experience appears to be associated with greater odds of PSMs following radical prostatectomy, even after controlling for case mix, pathologist fellowship training, and surgeon experience. Based on these findings, pathologists with less experience reviewing RP specimens may consider requesting rereview by a dedicated genitourinary pathologist.

Keywords: Prostate cancer; Urology; Pathology; Interobserver variability

1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed nonskin cancer in the United States and radical prostatectomy (RP) is the most common treatment option for men with localized disease [1]. Analysis of the surgical margin following RP, defined as tumor cells present at the inked margin of a resected specimen [2], is frequently used to assist in risk stratification and guide subsequent therapies. Over several decades, there has been continued downward stage migration due to prostate-specific antigen (PSA) screening [3]. Consequently, the rates of positive surgical margins (PSM) after RP have been decreasing over the last 25 years and contemporary rates range from 10% to 30% [4,5].

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PSMs following RP can be a significant source of anxiety for patients and increases the risk of biochemical recurrence [6,7] and secondary therapies [8]. Although some data suggest PSMs to independently predict PCa-specific mortality [9], most adjusted analyses do not show similar observations [10,11]. Some expert guidelines (American Society of Clinical Oncology/American Urological Association/European Association of Urology) suggest that men with PSMs should consider adjuvant radiation therapy [12,13]; however, this is not commonly done [14,15]. For these reasons, accurate interpretation of the surgical margin has a critical role for patient counseling, prognosis, and treatment decisions [16].

PSA, clinical stage, pathologic stage, and volume of tumor are consistently associated with a higher PSM rate [5,17–19]. The role of the pathologist on PSMs has also been examined. Interpretation of surgical margins is subject to interobserver variability with multiple studies suggesting 8% to 26% rates of discordance among pathologists [20,21].

We hypothesize that the individual pathologist and pathologist experience are associated with PSMs following RP.

2. Methods

2.1. Study design and data collection

We performed a retrospective, single-center, observational cohort study on 3,557 men who were treated with robotic-assisted laparoscopic prostatectomy for localized PCa at the University of Chicago Medical Center and Weiss Hospital between April 2003 and January 2015. Men were excluded if surgery was aborted ($n = 38$, 1%), most often due to intraoperative positive lymph nodes, or if they received neoadjuvant therapy ($n = 57$, 1.5%).

All patients provided informed consent. Data were collected and stored in an Institutional Review Board-approved Health Insurance Portability and Accountability Act-compliant database [22]. Data include patient demographics, preoperative variables, biopsy data, intraoperative information, pathological variables, patient-reported quality-of-life outcomes, and recurrence information.

The RP specimens were processed in accordance to the College of American Pathologists and International Society of Urological Pathology recommendations [23,24]. Briefly, the entire outer surface of the prostate was inked using 2 different colors to identify right and left outer margins. The prostatic apex was amputated and sectioned perpendicular to the inked surface, and the prostatic base was submitted serially in a perpendicular fashion. The remainder of the prostate was serially sectioned transversely at 3 to 5 mm intervals and submitted for processing either partially (at least 50%) or entirely (100%) in quadrants. Partial sampling is by submitting alternate slices. Sections of bilateral seminal vesicles, including its proximal portions, were also submitted. A margin was considered as positive if a cancer gland extends into the inked outer surface.

2.2. Statistical analysis

A PSM was defined as tumor at the inked margin of the resected specimen. We included variables shown to be associated with PSM [5,19,25–27], including age, race, body mass index (BMI), pathologic Gleason score, pathologic tumor stage, preoperative PSA level, surgeon and pathologist experience (defined as the number of cases the surgeon/pathologist had performed before the date of each case), fellowship training in genitourinary (GU) pathology, and year of surgery. Pathologist and surgeon experience and BMI were standardized to their respective means, such that the values of each variable corresponded to their standard deviation (SD) from the mean. PSA values were log transformed for use in regression analyses.

There were 19 pathologists who evaluated at least 25 cases during the study period with 9 pathologists having <25 cases and therefore grouped together in the "low-volume" group. The number of cases seen by each pathologist who evaluated >25 cases varied from 39 to 606 cases. Pathologist #10 represents a consolidation of multiple low-volume pathologists from an affiliated hospital.

Mean and SD were used to report continuous normally distributed variables; median and interquartile range were used for continuous nonnormally distributed variables. We used univariate logistic regression to analyze the relationship between each variable of interest and PSMs, followed by multivariable logistic regression using predictor variables with $P < 0.1$ from univariate models to control for confounders and assess the relationship between the individual pathologist and PSMs. To account for the clustering due to multiple cases seen by each pathologist, the standard errors were adjusted with the use of the sandwich estimator of variance. The models produced were assessed for interactions between individual pathologists and surgeons, and between individual pathologists and pathologic parameters. To further explore its effects, pathologist experience was also modeled as a restricted cubic spline with 5 knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles [28], and plots of the probability of PSM vs. pathologist experience were generated with all other variables in the model set to their means (for continuous variables) and to the most common category (for categorical variables). All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX) with a 2-sided significance level set at $P < 0.05$.

3. Results

3.1. Cohort description

The mean age was 60 years (SD = 7.1) and median PSA was 5.2 ng/ml (interquartile range: 4.1–7.2;