Impact of Positive Surgical Margins After Radical Prostatectomy Differs by Disease Risk Group

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Purpose: Positive surgical margins have a negative impact on disease outcomes after radical prostatectomy, yet their prognostic value may vary depending on specific pathological characteristics. We examined the relationship of positive surgical margins to biochemical progression according to several clinicopathological features.

Materials and Methods: We analyzed data from 1,268 patients who underwent radical prostatectomy for clinically localized prostate cancer at our center between 1992 and 2008, and did not receive any neoadjuvant or adjuvant treatment. We examined the relation of age, pretreatment prostate specific antigen, pathological T stage, radical prostatectomy Gleason score, disease risk group and surgical margin status to biochemical progression-free survival.

Results: The overall positive surgical margin rate was 20.8% and median followup was 79 months. The impact of positive surgical margins was dependent on risk group. Biochemical progression-free survival was 99.6% for the negative surgical margin group vs 94.9% for the positive surgical margin group in low risk disease (log rank p = 0.53), 93.5% for the negative surgical margin group vs 83% for the positive surgical margin group in intermediate risk disease (log rank p <0.001) and 78.5% for the negative surgical margin group vs 57.1% for the positive surgical margin group in high risk disease (log rank p = 0.003). These differences remained significant in a multivariate Cox regression model adjusting for other clinicopathological features.

Conclusions: Positive surgical margins are an independent predictor of biochemical progression in patients with intermediate and high risk prostate cancer. Patients with low risk disease have a favorable long-term outcome regardless of margin status and may be candidates for expectant management even with positive surgical margins, sparing them the side effects and costs of treatment.

Key Words: disease progression, prostatic neoplasms, prostatectomy

Abbreviations and Acronyms

BPFS = biochemical progression-free survival
NSM = negative surgical margin
PSA = prostate specific antigen
PSM = positive surgical margin
RP = radical prostatectomy

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RADICAL prostatectomy is one of the main treatment options for clinically localized prostate cancer.[1] Several factors have been found to impact the outcome after RP. A positive surgical margin, identified as the presence of cancer at the inked resection margin of the RP specimen, is considered one of the most important factors in predicting outcomes and it occurs with an incidence that ranges from 6% to 41%.[2]

The prognostic impact of PSMs on outcomes after RP is still controversial. While several studies have shown a higher rate of biochemical

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progression and/or local recurrence and distant metastasis in association with PSMs,[3–6] others have shown no such relationship.[7–9] Moreover some reports showed that the impact of PSMs on prognosis depends on certain clinical and pathological features of the disease (eg preoperative PSA, pathological T stage, pathological Gleason score and percentage of disease in the RP specimen).[3–5]

In this study we investigated the impact of PSMs on biochemical progression after RP. We selected biochemical progression because it is the outcome most commonly used to trigger intervention after surgery. A secondary goal was to identify clinical and pathological features that have an impact on the outcome in addition to PSMs.

MATERIALS AND METHODS

Patients and Followup

Using our prospective database of consecutive patients undergoing RP, we identified all patients who underwent RP (including open and laparoscopic) by multiple experienced uro-oncological surgeons at our institution for clinically localized prostate cancer (cT1/cT2) between 1992 and 2008.[12] Patients who received any form of neoadjuvant or adjuvant treatment and those with incomplete records were excluded from study.

We examined several clinical variables including patient age, preoperative PSA and PSA doubling time (less than 3 vs 3 or more months). Surgical margin status was determined using the original pathology report for which all surgical specimens were originally reviewed by a dedicated urological oncology pathologist at our institution using standard techniques and reporting. Pathological variables included pathological T stage and Gleason total score as well as surgical margin status (PSM vs NSM).

Patients were followed postoperatively every 3 months for the first year, every 6 months for the second year and annually thereafter. Followup consisted of clinic visits that included history and physical examination, International Prostate Symptom Score[10] and International Index of Erectile Function[11] questionnaires at least once a year, and PSA testing. Median followup was defined as the last available followup of individual patients from the time of surgery until the last recorded visit and biochemical progression was defined as a post-prostatectomy serum PSA of 0.4 ng/ml or greater.[12,13]

Statistical Analysis

Patients were stratified into 3 disease risk categories according to pretreatment PSA and pathological Gleason score. The low risk group had a PSA less than 10 ng/ml and Gleason sum 6 or less, the intermediate risk group had a PSA of 10 to 20 ng/ml or Gleason sum 7 and the high risk group had a PSA greater than 20 ng/ml, or Gleason sum 8 or greater. Clinicopathological features were compared between patients with PSMs and NSMs using ANOVA for continuous variables (age and preoperative PSA) and the chi-square test for categorical variables (pT stage, PSA doubling time and disease risk category).

BPFS was estimated using the Kaplan-Meier survival technique and the log rank test was used to determine statistical significance. A Cox proportional hazards model was used to determine which clinical and pathological features were significant predictors of biochemical progression, and whether BPFS differed between disease risk groups. The proportional hazards assumption was tested by examining Schoenfeld residuals. Statistical analyses were performed using SPSS® software (version 16.0).

RESULTS

A total of 2,542 patients were identified and of these 1,268 met our inclusion criteria (139 patients were excluded from study for receiving neoadjuvant treatment, 158 were excluded for receiving adjuvant treatment, 167 patients were lost to followup and the remainder had incomplete clinical records). Median (SD) patient age at surgery was 62 (6.6) years (mean 61.5, range 39 to 77), median preoperative PSA was 6.2 (6.1) ng/ml (mean 7.7, range 0.1 to 65.9) and median preoperative PSA doubling time was 10.5 (458.4) months (mean 22.7, range 0 to 1,672.2). There were 853 patients (67.3%) with pT2 disease and 415 (32.4%) with pT3 disease. Based on the risk stratification criteria 317 patients (25.0%) were low risk, 809 (63.8%) were intermediate risk and 142 (11.2%) were high risk (table 1).

The overall PSM rate was 20.8%, and it was significantly lower in patients with pT2 disease (13.6%) compared to pT3 (35.7%) ($p < 0.0001$). It was also significantly lower in the low risk group (12.3%) compared to the intermediate (21.8%) and high risk groups (34.5%) ($p < 0.0001$). On average patients with NSMs were slightly younger than those with PSMs (mean [SD] age 61.3 [6.7] vs 62.3 [6.4] years, respectively, $p = 0.004$) and had a lower mean preoperative PSA (7.04 [5.2] vs 10.08 [8.4] ng/ml, respectively, $p = 0.04$), while there was no statistically significant difference in preoperative PSA doubling time between those with PSMs and NSMs (table 2).

At a median (SD) followup of 79 (56.5) months (mean 78.1, range 3 to 192) patients with NSMs had a significantly higher BPFS rate (93.8%) compared to those with PSMs (79.9%) and the Kaplan-Meier survival curves separated almost immediately (log rank

Table 1. *Baseline cohort characteristics*

	No. (%)
Ng/ml preop PSA:	
Less than 10	1,002 (79.0)
10–20	218 (17.2)
Greater than 20	48 (3.8)
Pathological Gleason score:	
6 or Less	352 (27.8)
7	807 (63.3)
8 or More	109 (8.6)