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

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

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

Submitted for publication April 14, 2009.
* Nothing to disclose.
† Financial interest and/or other relationship with Bio-Advantex Pharma, AstraZeneca, Sanofi- Aventis, GlaxoSmithKline, Merck, Novartis and Pfizer.
‡ Financial interest and/or other relationship with Wyeth, Wyeth/Canadian Institutes of Health Research, Pfizer, Viventia, Gyrus ACM, Angos and Antigenics.
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Editor’s Note: This article is the fourth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 404 and 405.
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 Score10 and International Index of Erectile Function11 questionnaires at least once a year, and PSA testing. Median followup was defined as 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. Clinico-pathological 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 63.6 [7.6] 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

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<th>Table 1. Baseline cohort characteristics</th>
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<td>No. (%)</td>
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BPFS was also higher in patients with pT2 disease compared to those with pT3 disease at 95.1% vs 82.4%, respectively (log rank p < 0.0001), as well as for patients with low risk disease compared to those with intermediate and high risk disease at 99.1% vs 91.2% and 71.1%, respectively (log rank p < 0.0001, fig. 2). BPFS rates were not different between patients with a preoperative PSA doubling time of less than 3 months compared to those with a doubling time of 3 or more months at 91.1% vs 93.7%, respectively (log rank p = 0.32).

When BPFS rates were compared for each disease risk group based on surgical margin status, they were 99.6% for NSMs vs 94.9% for PSMs in the low risk disease group (log rank p = 0.53), 93.5% for NSMs vs 83% for PSMs in intermediate risk disease group (log rank p < 0.001) and 78.5% for NSMs vs 57.1% for PSMs in high risk disease group (log rank p = 0.003, fig. 3).

A multivariate Cox proportional hazards regression model was developed to identify the independent predictors of biochemical progression, and those predictors were pathological T stage (HR 2.05, 95% CI 1.37–3.08, p < 0.001), surgical margin status (HR 2.51, 95% CI 1.72–3.67, p < 0.001) and disease risk (intermediate risk HR 6.27, 95% CI 1.96–20.04; high risk HR 15.42, 95% CI 4.68–50.78, p < 0.001, table 3).

**DISCUSSION**

After radical prostatectomy the reported incidence of PSMs ranged from 6% to 41%. The difference in surgical margin rates was attributed to several factors including pathological stage and grade, cancer volume and location, surgical technique, specimen processing and pathological examination, and lymph node invasion. We reported an overall PSM rate of 20.8% in keeping with other large series. In a 20-year review of patients from Memorial Sloan-Kettering Cancer Center and Baylor College of Medicine, the PSM rate was 20% and ranged from 10% to 48% for individual surgeons. PSM rates were significantly higher in cases of pathological T3 disease (35.7%) compared to T2 disease (13.6%). Similar findings were reported by Vis et al in a population based cohort with a PSM rate of 18% in pT2 disease vs 40% in pT3 (p < 0.01), and these results were confirmed by others in single institution experiences.

We found a difference in mean age and mean preoperative PSA between patients with PSMs and NSMs, which demonstrates that differences in surgical margin rates may depend on variables other than pathological stage, similar to what was shown by Cheng et al. We also found that pretreatment PSA and pathological Gleason score are related to PSM rates, and that when patients were stratified into disease risk categories using these factors the PSM rates in patients with low risk disease were significantly lower than in those with intermediate or high risk disease (12.3% vs 21.8% and 34.5%, respectively, p < 0.001). The same finding was reported by Eastham et al but we combined these 2 factors in a simple and practical way using the original D’Amico classification.

Our data demonstrate that the presence of PSMs has a significant impact on the incidence of biochemical progression independent of other clinical and pathological features. The negative impact of PSMs on biochemical progression was shown by others. Furthermore, PSMs were also shown to have a negative impact on local and distant recurrence.

A unique finding of our study was that the impact of surgical margin status on biochemical progression differed according to risk group. Patients with low risk
disease had a similar outcome in terms of biochemical progression-free survival regardless of surgical margin status (99.6% in NSM vs 94.9% in PSM group, p = 0.53) and this remained unchanged on multivariate analysis adjusting for other disease features. This finding contributes to the theory that the impact of the margin status influences outcome in only a subset of patients. Ohori et al have shown that margin status is an independent predictor in pT3a disease but not in organ confined disease.17 Stamey et al also found that margin status was not an independent predictor of biochemical progression when adjusted for other factors such as Gleason score and PSA.7 It was also shown by others that once the total and high grade cancer volume were included in the analysis, margin status was no longer independently associated with biochemical progression.4,18 This finding suggests that margin status is rather a product and an expression of a large cancer but that it does not independently alter prognosis.

Nomograms were developed to predict biochemical progression after RP. They have a strong predictive ability and serve as an excellent tool to clinicians in stratifying patients into different risk groups for progression.19 By using a simple, broad and readily available risk stratification system we were able to show differences in outcomes among risk groups. Before broad clinical implementation these findings need to be validated in an independent sample using the same risk stratification system we used and/or one of the available postoperative nomograms.

The European Organisation for Research and Treatment of Cancer trial 22911 has shown a clear benefit in terms of BPFS in favor of adjuvant radiotherapy compared to salvage treatment in patients with PSMs,20 and the Southwest Oncology Group trial has shown better BPFS as well as overall survival with adjuvant radiotherapy in patients with pT3 disease.21,22 In view of the favorable outcome of patients with PSMs and low risk disease that we have shown, we believe that this particular group of patients could be spared any adjuvant treatment unless they experience disease progression. These patients constituted approximately 12.3% of our total cohort and in other reports the proportion of this type of patient was as high as 41%, especially after the widespread use of PSA screening, which resulted in a higher proportion of patients diagnosed at an early stage of disease.4–6 Therefore, a significant proportion of patients could be treated conservatively, and spared the side effects and cost of radiotherapy that has a moderate to severe long-term complication rate of 11.9% on average.23

Figure 2. Kaplan-Meier curve showing difference in biochemical progression rates between patients with pathological T2 vs T3 stage disease (A) and those with low risk vs intermediate and high risk disease (B) (log rank p <0.0001 for both).

Figure 3. Kaplan-Meier survival curves showing biochemical progression rates for disease risk groups according to surgical margin status.
Our study has several limitations. It is a retrospective analysis with the inherent limitations of such studies. In addition, we excluded from analysis patients who received immediate adjuvant therapy, and this represented a good number of patients with pT3 disease. However, 415 patients in our cohort had pT3 disease (35.7% with PSMs) which is a fair representation of this group. Another limitation is that we performed lymphadenectomy in highly selected patients which constituted a small number of our cohort. When lymph node status was considered in the original analysis it did not show any impact on BPFS on univariate or multivariate analysis, which might be due to the large percentage of patients with unknown lymph node status (Nx). We also did not include the location and number of margins as variables. The impact of margin location is still controversial. It has been shown to have no effect on the outcome by some groups, while others have demonstrated that posterolateral margins are associated with a worse prognosis. Another limitation is the lack of data regarding local progression and distant metastases. However, biochemical progression alone is usually the single most commonly used clinical parameter to initiate radiation or hormonal therapy and, thus, it is the most commonly used parameter in assessing outcome after radical prostatectomy.

The definition of biochemical progression is controversial and the most appropriate PSA to define progression after RP has not been standardized among institutions. We believe that a cut point of 0.4 ng/ml is reasonable because several groups have shown that PSA levels below this point tend to remain stable over time and not progress.

This study is a single institution experience with results representing multiple surgeons with different levels of experience, and includes different types of surgery (open and laparoscopic). Despite this heterogeneity the PSM and disease progression rates were similar to those in published multi-institutional and larger cohort studies. We believe that a median followup of 79 months is appropriate since biochemical progression usually develops during the first 2 years of followup and more than 90% of patients who will eventually experience relapse do so within 5 years after surgery.

CONCLUSIONS
A positive surgical margin after radical prostatectomy is an independent predictor of biochemical progression only in patients with intermediate and high risk disease. Patients with low risk disease and PSMs show a favorable outcome and may be appropriate candidates for expectant management without immediate adjuvant therapy to spare them the side effects of treatment. Prospective, controlled studies are needed to confirm these findings.

REFERENCES


