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Clinicopathological predictors of systemic progression and prostate cancer mortality in patients with a positive surgical margin at radical prostatectomy

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BACKGROUND: Although a positive surgical margin (PSM) at radical prostatectomy (RRP) has been consistently linked to an increased risk of biochemical recurrence, the impact of margin status on patient survival continues to be debated. We evaluated long-term outcomes of patients with a PSM at RRP and determined predictors of systemic progression (SP) and mortality in these men.

METHODS: We reviewed our institutional registry of 16,749 patients who underwent RRP between 1990 and 2008 to identify 2,895 patients with a PSM. Median follow-up was 10.6 years. Postoperative survival was estimated using the Kaplan–Meier method. Cox proportional hazard regression models were used to analyze clinicopathological variables associated with SP and death from prostate cancer.

RESULTS: A 15-year SP-free and cancer-specific survival was 90 and 93%, respectively. On multivariate analysis, higher tumor volume, increased pathological Gleason score and advanced pathological tumor stage were associated with significantly increased risks of SP and death from prostate cancer, whereas number and location of PSM did not predict mortality.

CONCLUSIONS: The risks of SP and prostate cancer death in patients with a PSM remain low on long-term follow-up. Tumor variables are the primary determinants of cancer death. These results should be considered when evaluating patients with a PSM for adjuvant therapy.

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Keywords: radical prostatectomy; PSA; surgical margin; disease-specific survival

Introduction

The presence of a positive surgical margin (PSM) at the time of radical prostatectomy (RRP) has been cited as an adverse pathological feature.1 As such, margin status has been incorporated as a component of multiple prostate cancer outcome predictive models,2,3 and as a criterion for enrollment in adjuvant therapy trials.4,5 However, as surgical margin status has been linked to other clinicopathological features such as tumor stage, Gleason score, tumor volume and even year of surgery,1,6–9 the independent impact of margin status on patient outcome has been challenged.10

In particular, the rate of postoperative disease recurrence for patients with a PSM has been reported as between 19 and 50%, reflecting a lack of consistency in the association of margin status with cancer progression.11,12 Moreover, the primary endpoint which reports on margin status have assessed has been biochemical recurrence (BCR).1,7,8,10–15 Importantly, the use of BCR as a clinical outcome measure remains questionable, as the natural history of BCR is variable. That is, although approximately 35% of patients experience PSA failure within 10 years following RRP,16,17 BCR does not always translate into systemic progression (SP) and prostate cancer death.16,18,19 Furthermore, given the sensitivity of PSA to detect disease recurrence following RRP, the clinical course of patients with BCR is generally prolonged, and in fact, median survival has been found not to have reached 15 years after initial PSA failure in previous studies.18,19 Thus, as men with prostate cancer are generally over the age of 60, competing causes of mortality may obscure the ability of BCR to predict death from prostate cancer.20

At the same time, the few series to date which have evaluated the impact of surgical margin status on endpoints other than BCR have met with conflicting results, with series demonstrating an association of
positive margins with metastases and death from prostate cancer, whereas a large, single-institution study found that the presence of a positive margin was not independently associated with SP or cancer-specific mortality. Given the heterogeneous natural history of patients with a PSM, and the uncertain link between margin status and disease-specific mortality, determining additional clinicopathological features to identify those patients with a PSM, who are at the highest risk for subsequent clinical progression, may guide the judicious application of secondary therapy and may thereby spare patients not likely to experience disease-related mortality from the toxicity of additional treatment. Indeed, the recent Southwest Oncology Group trial of adjuvant radiation (RT) after RRP reported rectal proctitis and bleeding in 3.2% of patients, urethral stricture in 17%, urinary incontinence in 6.5%, and a significantly higher overall rate of adverse events among men treated with adjuvant RT than in the observation cohort (28.8 versus 11.9%).

Here, we then evaluated the long-term outcomes of patients with a PSM at RRP and determined predictors of SP and mortality in these men.

Materials and methods

After Institutional Review Board approval was obtained, we reviewed our Prostatectomy Registry of 16749 consecutive patients who underwent RRP at the Mayo Clinic between 1990 and 2008, to identify 4535 patients who were found to have a PSM at RRP. Patients with positive lymph nodes at surgery (n = 455), as well as patients who received neoadjuvant treatment (n = 346) or adjuvant androgen deprivation therapy alone (n = 750) were excluded from analysis. In addition, 52 foreign patients without postoperative follow-up and 37 patients who refused release of their records were excluded as well.

Surgical procedures were performed by different surgeons using standardized techniques. The Mayo Clinic protocol for preparing and reporting serially sectioned prostates has been previously reported. Briefly, RRP specimens are microscopically examined and inked by the pathologist immediately after resection, and multiple frozen sections from the prostate are examined, including margins at the prostate base, apex/urethra, bladder neck, left and right anterior, left and right posterior and seminal vesicles. All sections are separately examined by routine formalin-fixed paraffin-embedded sections the following day. A positive margin was defined as tumor extension to the inked surface of the resected specimen.

Adjuvant therapy was defined as treatment received within 90 days of RRP and was given at the discretion of the treating physician. Salvage treatment was defined as secondary therapy initiated greater than 90 days after RRP and was likewise administered per individual physician. BCR was defined here as a PSA ≥ 0.4 ng ml⁻¹. SP involved demonstratable metastases on radionucleotide bone scan or on biopsies outside of the prostatic bed. Vital status was identified from death certificates or physician correspondence. For patients followed elsewhere, the Mayo Clinic Prostatectomy Registry monitors outcomes annually by correspondence.

Postoperative survival was estimated using the Kaplan–Meier method and compared with the log-rank test. Patients were censored at last follow-up or death if the end point of interest had not been attained. Cox proportional hazard regression models were used to analyze the impact of patient-related variables, tumor features and margin characteristics on SP and survival. All tests were two-sided with a P-value < 0.05 considered significant. Statistical analyses were done using the SAS version 9.1.3 software package (SAS Institute, Cary, NC, USA).

Results

Overall, 2895 patients with a PSM met the criteria for analysis here. Of these men, 2737 (94.5%) underwent an open retropubic approach to RRP, whereas 158 (5.5%) were treated with a robotic-assisted laparoscopic approach. Median age at RRP was 64 years (interquartile range (IQR) 59.0, 69.0). Median preoperative PSA was 7.4 ng ml⁻¹ (IQR 5.1, 11.5), whereas the median prostate volume was 31.4 cc (IQR 23.6, 42.4) and the median tumor volume was 2.8 cc (IQR 1.0, 6.5). Additional clinicopathological features are detailed in Table 1. As noted, the majority of patients (66%) had organ-confined disease at surgery and a single PSM (76%). In particular, 1546 patients had an apical positive margin, including 1040/2210 (47.1%) men who had a single-site positive margin.

Following surgery, 439 (15%) men received adjuvant RT, including 88 men who were treated with concurrent adjuvant androgen deprivation therapy. Patient demographics stratified by receipt of adjuvant RT are detailed in Table 1. Not surprisingly, patients who received adjuvant RT had more aggressive disease characteristics, including a greater preoperative PSA, higher Gleason scores and more advanced tumor stage. These men were also significantly more likely to have ≥ 2 sites of positive margins (P < 0.0001).

A total of 560 (19.3%) men who had a PSM underwent salvage RT, whereas 583 (20.1%) received salvage androgen deprivation therapy. At a median postoperative follow-up of 10.6 years (IQR 6.0, 13.9), 1206 (41.7%) patients experienced BCR, 196 (6.8%) developed SP and 651 (22.5%) had died, with 106 (3.7%) dying from prostate cancer. The estimated 15-year SP-free and cancer-specific survival for patients with a positive margin at RRP was 90% and 93%, respectively (Figure 1). These survival rates did not change appreciably when patients who received postoperative adjuvant RT were excluded from the analysis (91% and 94%, respectively, Figure 2).

On multivariate analysis controlling for clinicopathological variables (Table 2), we found that, among men with a PSM at RRP, higher tumor volume (P = 0.0002), increased pathological Gleason score (P < 0.0001) and advanced pathological tumor stage (P < 0.0001) were significantly associated with an increased risk of SP. These features remained associated with greater risks of death from prostate cancer and overall mortality as well. Indeed, pathological Gleason score was noted to...
Table 1  Clinicopathologic demographics of patients with a positive surgical margin at RRP

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients with a positive margin (n = 2895)</th>
<th>No adjuvant radiotherapy (n = 2456)</th>
<th>Received adjuvant radiotherapy (n = 439)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at RRP (IQR)</td>
<td>64 (59, 69)</td>
<td>64 (59, 69)</td>
<td>64 (59, 68)</td>
<td>0.12</td>
</tr>
<tr>
<td>Median preoperative PSA (IQR)</td>
<td>7.4 (5.1, 11.5)</td>
<td>7.3 (5.0, 11.1)</td>
<td>8.3 (5.5, 14.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median prostate volume (IQR)</td>
<td>31.4 (23.6, 42.4)</td>
<td>31.4 (23.6, 42.4)</td>
<td>32.1 (23.6, 44.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Median tumor volume (IQR)</td>
<td>2.8 (1.0, 6.5)</td>
<td>2.6 (1.0, 6.2)</td>
<td>4.0 (1.9, 9.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Clinical tumor stage, number (%; n = 2867)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1125 (39.3)</td>
</tr>
<tr>
<td>T2</td>
<td>1560 (54.4)</td>
</tr>
<tr>
<td>T3/4</td>
<td>182 (6.3)</td>
</tr>
</tbody>
</table>

Biopsy Gleason, number (%; n = 2466)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1596 (64.7)</td>
</tr>
<tr>
<td>7</td>
<td>702 (28.5)</td>
</tr>
<tr>
<td>8–10</td>
<td>168 (6.8)</td>
</tr>
</tbody>
</table>

Pathological tumor stage, number (%; n = 2893)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2</td>
<td>1915 (66.2)</td>
</tr>
<tr>
<td>pT3a</td>
<td>652 (22.5)</td>
</tr>
<tr>
<td>pT3b/4</td>
<td>326 (11.3)</td>
</tr>
</tbody>
</table>

Pathological Gleason, number (%; n = 2889)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1505 (52.1)</td>
</tr>
<tr>
<td>7</td>
<td>1130 (39.1)</td>
</tr>
<tr>
<td>8–10</td>
<td>254 (8.8)</td>
</tr>
</tbody>
</table>

Number of positive margins (%)

<table>
<thead>
<tr>
<th>Number</th>
<th>Number (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single site</td>
<td>2210 (76.3)</td>
</tr>
<tr>
<td>≥2</td>
<td>685 (23.7)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; RRP, radical prostatectomy.

Figure 1  Kaplan–Meier estimates for postoperative systemic-progression free (a), cancer-specific (b) and overall (c) survival following radical prostatectomy (RRP) for patients with a positive surgical margin.
represent the highest risk for disease-specific death among patients with a PSM, such that each unit increase in Gleason score portended a nearly four-fold increase in the risk of death from prostate cancer. Meanwhile, receipt of adjuvant RT was associated with a 24% decreased risk of death from prostate cancer, although this association did not reach statistical significance ($P = 0.32$). Interestingly, adjuvant RT was associated with a significantly protective effect on the outcome measure of receipt of salvage therapy or progression (hazard ratio $0.34; P < 0.0001$; Table 3). Lastly, when patients who received postoperative adjuvant RT were excluded from the multivariate analysis, the variables of tumor volume, pathological tumor stage and pathological Gleason score remained associated with significantly increased risks of SP and death from prostate cancer, whereas margin features again did not predict mortality (data not shown).

### Discussion

We found here that the majority of men with a PSM at RRP experienced long-term cancer-specific survival, with only 7% having died from prostate cancer at 15

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**Figure 2** Kaplan–Meier estimates for postoperative systemic-progression free (a), cancer-specific (b) and overall (c) survival following radical prostatectomy (RRP) for patients with a positive surgical margin who did not receive adjuvant therapy.

**Table 2** Multivariate analysis of predictors of systemic progression, death from prostate cancer, and all-cause mortality in patients with a positive surgical margin at RRP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Systemic progression</th>
<th>Death from prostate cancer</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age at surgery (year increase)</td>
<td>1.00</td>
<td>0.97, 1.02</td>
<td>0.69</td>
</tr>
<tr>
<td>Year of surgery (year increase)</td>
<td>0.96</td>
<td>0.91, 1.01</td>
<td>0.12</td>
</tr>
<tr>
<td>Log$_2$ preoperative PSA</td>
<td>1.02</td>
<td>0.88, 1.19</td>
<td>0.77</td>
</tr>
<tr>
<td>Log$_2$ prostate volume</td>
<td>1.17</td>
<td>0.92, 1.49</td>
<td>0.19</td>
</tr>
<tr>
<td>Log$_2$ tumor volume</td>
<td>1.24</td>
<td>1.11, 1.39</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pathologic tumor stage (≥pT3 versus pT2)</td>
<td>2.12</td>
<td>1.48, 3.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pathologic Gleason score (≥7 versus 6)</td>
<td>3.88</td>
<td>2.56, 5.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of positive margins (≥2 versus 1)</td>
<td>0.87</td>
<td>0.59, 1.26</td>
<td>0.45</td>
</tr>
<tr>
<td>Location of positive margin (apex versus other)</td>
<td>0.93</td>
<td>0.66, 1.31</td>
<td>0.69</td>
</tr>
<tr>
<td>Adjuvant RT</td>
<td>1.03</td>
<td>0.71, 1.50</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; RRP, radical prostatectomy; RT, radiation.
years after surgery. The primary determinants of clinical progression and prostate cancer death in these patients were tumor variables, particularly pathological Gleason score, tumor stage and tumor volume. Meanwhile, margin-related features, including number and location, were not significantly associated with mortality.

Our results, with regard to the prognostic interaction of pathological Gleason score, tumor stage and tumor volume in patients with a positive margin, are consistent with findings from previous studies.\(^\text{12,22,26,28}\) Similarly, Alkhateeb et al.\(^\text{29}\) noted that positive margins predicted recurrence for patients with intermediate- and high-risk disease, but not for patients with low-risk tumors. On the other hand, conflicting data has been reported with regard to the independent association of preoperative PSA, as well as the number and location of margins, with outcome for patients with a PSA at RRP.\(^\text{8,12,26,27}\) We did not find these factors to be significantly associated with death from prostate cancer in patients with a PSA, and in fact it is important to note that previous series correlated these features with BCR.

Given the documented heterogeneous natural history of BCR,\(^\text{6,18,19}\) we sought to identify the association of various clinicopathological features with SP and mortality.

Determining prognostic subclassifications for patients with a PSA may assist with patient counseling and guide the selective application of adjuvant therapy. That is, up to 60–75% of contemporary patients with a positive margin remain disease-free at 7 years following RRP alone.\(^\text{8,12,13,15,30}\) Such patients are therefore unlikely to benefit from immediate secondary prostate cancer treatment, which is not without attendant cost and treatment-related toxicity.\(^\text{5}\) The potential multifactorial causality of positive margins, which may result from cancer extent, technical error (capsulotomy), surgical artifact or pathological processing, likely underlies the conflicting reports on the link between surgical margin status and subsequent patient outcome, both in terms of BCR rates\(^\text{8,12,13,15,30}\) and SP.\(^\text{9,21,22}\)

Indeed, then, the continued debate around the optimal postoperative management of patients with a PSA is not surprising. In fact, a subset analysis of the European Organization for Research and Treatment of Cancer randomized trial 22911 found that the presence of a positive margin was the strongest predictor of prolonged BCR-free survival in patients who received adjuvant RT after RRP, although in the manuscript the authors also conceded that ‘it is not certain that PSMs add to the risk of actual local recurrence or systemic disease.\(^\text{31}\) Meanwhile, a recent retrospective investigation noted improved overall survival in patients with organ-confined, margin-positive disease who received adjuvant RT, although only 17 patients were included in the treatment group.\(^\text{32}\) Further fueling the controversy regarding the timing of secondary treatment for patients with a positive margin at RRP are contemporary data, suggesting that SD\(^\text{33}\) and prostate cancer mortality\(^\text{34}\) may be decreased with the administration of salvage RT in patients who experience BCR after RRP. In fact, Stephenson et al.\(^\text{35}\) determined that surgical margin status was an independent predictor of treatment success for patients treated with salvage RT for recurrence after RRP.

We recognize that our study is limited by its retrospective, non-randomized nature. As such, decisions to treat with adjuvant and salvage therapies were based on patient preference and physician counseling, and were thereby subject to inherent selection bias. Thus, our findings, in particular, regarding the non-significant association of adjuvant RT with disease progression and mortality must be interpreted in light of this study design, particularly as prospective randomized trials have demonstrated a benefit to adjuvant RT on reducing the risk of BCR\(^\text{4,5,36}\) and, in one series, mortality.\(^\text{37}\) Indeed, we did find here that adjuvant RT was associated with a significant decrease in the risk of the outcome measure receipt of salvage therapy or progression. These data likely reflect the previously-documented protective effect of adjuvant RT on BCR,\(^\text{4,5,36}\) an outcome measure which has been linked to utilization of secondary cancer treatments.\(^\text{38}\)

Moreover, additional pathological features, which may have impacted outcome, such as the presence of focal versus extensive positive margins, were not separately analyzed. Notably, however, this feature was not found to increase the accuracy of a predictive nomogram compared with surgical margin status modeled as positive or negative.\(^\text{30}\) Likewise, outcomes were not stratified by individual surgeon, a variable which may impact clinical outcomes independent of margin status. Furthermore, as only a small minority (5.5%) of the patients were treated with robotic prostatectomy, the impact of surgical approach on the outcomes of patients with a positive margin could not be assessed here as well.

Nevertheless, in a large patient dataset with extended follow-up, we found that higher tumor volume, increased pathological Gleason score and advanced pathological tumor stage represent clinicopathological features associated with clinical progression and death from prostate cancer among patients with a PSA at RRP. As the overall long-term risks of SP and mortality in these men remain low, these results should be considered when evaluating such patients for adjuvant therapy.

### Conflict of interest

The authors declare no conflict of interest.
References


