Do Margins Matter? The Influence of Positive Surgical Margins on Prostate Cancer–Specific Mortality

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Abstract

Background: Positive surgical margins (PSMs) in radical prostatectomy (RP) specimens are a frequent indication for adjuvant radiotherapy and are used as a measure of surgical quality. However, the association between PSMs and prostate cancer–specific mortality (CSM) is poorly defined.

Objective: Analyze the association of PSMs with CSM, adjusting for fixed and time-dependent parameters.

Design, setting, and participants: Fine and Gray competing risk regression analysis was used to model the clinical data and follow-up information of 11,521 patients treated by RP between 1987 and 2005. Two extended models were used that adjusted for the use of postoperative radiotherapy, which was handled as a time-dependent covariate. Postoperative radiotherapy was modeled as a single parameter and also as early and late therapy, based on the prostate-specific antigen level at the start of treatment ($\geq 0.5$ vs $<0.5$ ng/ml).

Intervention: RP for clinically localized prostate cancer and selective use of secondary local and/or systemic therapy.

Outcome measurements and statistical analysis: The outcome measure was prostate cancer-specific mortality.

Results and limitations: The 15-yr CSM rates for patients with PSMs and negative surgical margins were 10% and 6%, respectively ($p < 0.001$). No significant association between PSM and CSM was observed in the conventional model with fixed covariates (hazard ratio [HR]: 1.04; 95% confidence interval [CI], 0.7–1.5; $p = 0.8$) or in the two extended models that adjusted for postoperative radiotherapy (HR: 0.96; 95% CI, 0.7–1.4; $p = 0.9$), or early and late postoperative radiotherapy (HR: 1.01; 95% CI, 0.7–1.4; $p = 0.9$).

Conclusions: PSMs alone are not associated with a significantly increased risk of CSM within 15 yr of RP. However, urologists should continue to strive to avoid PSMs, as they increase a man’s risk of biochemical recurrence and need for secondary therapy and may be a source of considerable patient anxiety.

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1. Introduction

Positive surgical margins (PSMs) in radical prostatectomy (RP) specimens for the treatment of localized prostate cancer (PCa) are reported in 11–48% of men and are a recognized risk factor for prostate-specific antigen (PSA)-defined biochemical recurrence (BCR) [1–6]. We recently reported a 2.3-fold increased risk of BCR among men with PSMs treated in the later PSA era after adjusting for all standard parameters [1]. To improve the outcome of men with non–organ-confined cancer and/or PSMs after RP, three randomized trials have investigated the role of adjuvant radiotherapy [7–9]. Compared to observation, adjuvant radiotherapy significantly reduced the risk of BCR in all three trials, and one has reported a significantly improved metastasis-free and overall survival [7]. Given these results, some have advocated adjuvant radiotherapy as the standard of care for men with non–organ-confined cancer or PSMs [10,11].

In two of the randomized trials, the benefit of adjuvant radiotherapy was most evident in men with PSMs [9–12], consistent with its association with local recurrence [13]. However, a policy of adjuvant radiotherapy for all men with PSMs represents overtreatment for the majority, as an estimated 60% will be free of cancer recurrence after RP alone [1]. As with external-beam radiotherapy as primary therapy, adjuvant radiotherapy may adversely affect urinary, bowel, and sexual function and may increase the risk of secondary pelvic malignancies [14–18]. Furthermore, in the one trial that has reported an improved metastasis-free and overall survival, a major effect of adjuvant radiotherapy was reducing deaths from competing causes (93 vs 114 events), and there was a smaller effect on preventing distant metastases (20 vs 37 events) [7]. A recent update of a larger European trial of similar design but composed of more contemporary patients reported no significant difference in the rate of distant metastasis or overall survival over a median follow-up of 10.6 yr [8]. Thus, close observation and salvage radiotherapy at the earliest sign of BCR (ie, when the PSA first reaches detectable levels) is a reasonable alternative strategy [13,19,20].

A strong argument against adjuvant radiotherapy for PSMs is the lack of evidence that the latter significantly increases a man’s risk of PCa-specific mortality. In an analysis of 23,910 men treated by RP at five high-volume hospitals, we previously identified the presence of pathologic Gleason 8–10 cancer and seminal vesicle invasion as the prime determinants of cancer-specific mortality (CSM) [21]. Neither PSM nor extraprostatic extension was significantly associated with CSM in the multivariable analysis. The lack of association between PSMs and CSM may be due to the variable natural history of BCR; within 15 yr, only one-third of men with BCR will die of PCa, which is similar to the risk of death from competing causes [22]. Alternatively, we hypothesized that this lack of association may be due to the protective effect of postoperative radiotherapy. To explore this possibility, we analyzed the long-term risk of CSM based on the pathologic features of PCa, adjusting for the use and timing of postoperative radiotherapy.

2. Patients and methods

Between 1987 and 2006, 12,310 consecutive men with localized PCa were treated by RP at Cleveland Clinic (Cleveland, OH, USA), Memorial Sloan-Kettering Cancer Center (New York, NY, USA), University of Michigan (Ann Arbor, MI, USA), and Baylor College of Medicine (Houston, TX, USA). We excluded 462 patients (3.7%) who received prior androgen deprivation therapy or radiation therapy or who had missing information for PSA values, pathologic Gleason score, or pathologic stage. Thus, a total of 11,521 patients were available for analysis. Clinical information was obtained from prospectively maintained, institutional review board-approved data bases.

Surgical specimens were totally embedded and step-sectioned at 3- to 5-mm intervals from apex to base, examined as whole or quarter mounts, and evaluated by genitourinary pathologists at each institution. Pathologic stage was assigned according to the American Joint Committee on Cancer criteria [23]. A PSM was defined as tumor at the inked margin of the resected specimen. In general, patients were followed for recurrence postoperatively with serum PSA level determinations and clinical assessment at 3- to 6-mo intervals for the first 3–5 yr, then annually thereafter. Secondary therapy was uncommonly administered in the absence of BCR. Death was attributed to PCa if, upon review of the medical record, there was evidence of progressive metastases and PCa was listed as the primary cause of death on the death certificate.

Estimates of CSM were calculated using the competing risk method [24]. Univariable and multivariable analyses of CSM were performed with Fine and Gray competing risk regression analysis [24]. The PSA levels before RP and year of surgery were modeled with restricted cubic splines because of a skewed distribution and/or suspected nonlinear effects. Primary and secondary Gleason grades were modeled as binary categorical variables (≤ 3 and >4). The presence of extraprostatic extension, PSM, seminal vesicle invasion, and lymph node metastasis were modeled as binary categorical variables.

PSM is a frequent indication for postoperative radiotherapy, which substantially alters the risk of BCR and/or survival following RP [7–9,13,19,25]. As such, we endeavored to explore whether PSM is associated with CSM after adjusting for the use of postoperative radiotherapy. Given that the use and timing of postoperative radiotherapy was not standardized, an extended competing risk regression model was used to adjust for postoperative radiotherapy, which was handled as a time-dependent covariate [26]. As the benefit of postoperative radiotherapy appears to be greatest when administered at preradiotherapy PSA level ≤0.5–0.6 ng/ml [13,19], it was also modeled as early and late therapy based on a preradiotherapy PSA level ≤0.5 and >0.5 ng/ml, respectively.

All decisions with respect to variable coding were made a priori without knowledge of CSM association. All statistical analyses were performed using S-Plus software (S-plus 2000; Insightful Corp, Redmond, WA, USA) with additional functions (called “Design” added). All p values resulted from use of two-sided statistical tests. The study was conducted according to Health Insurance Portability and Accountability Act guidelines.

3. Results

The clinical and pathologic features of patients in this study are summarized in Table 1. Overall, 2,607 (23%) patients had PSMs, including 1,291 of 8,064 (16%) with organ-confined cancer and 1,316 of 3,457 (38%) with non–organ-confined cancer. A total of 788 men received postoperative radiotherapy, 756 (96%) of whom had a detectable preradiotherapy PSA level (median: 0.50 ng/ml; interquartile range [IQR]: 0.24–1.10). Overall, 1,045 (9%) men received androgen deprivation therapy after RP for BCR or clinical progression.
Table 1 – Clinical and pathologic features of 11,521 patients treated by radical prostatectomy with complete information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (IQR)</td>
<td>60 (56–65)</td>
</tr>
<tr>
<td>PSA, ng/ml, median (IQR)</td>
<td>6.0 (4.4–8.8)</td>
</tr>
<tr>
<td>Year of surgery, no. (%)</td>
<td></td>
</tr>
<tr>
<td>1987–1990</td>
<td>1073 (9)</td>
</tr>
<tr>
<td>1991–1998</td>
<td>3169 (28)</td>
</tr>
<tr>
<td>1999–2006</td>
<td>7279 (63)</td>
</tr>
<tr>
<td>Pathologic Gleason score, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Gleason 2–6</td>
<td>4305 (37)</td>
</tr>
<tr>
<td>Gleason 7 (3 + 4)</td>
<td>4866 (42)</td>
</tr>
<tr>
<td>Gleason 7 (4 + 3)</td>
<td>1303 (11)</td>
</tr>
<tr>
<td>Gleason 8–10</td>
<td>631 (6)</td>
</tr>
<tr>
<td>Pathologic stage, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Organ confined</td>
<td>8441 (70)</td>
</tr>
<tr>
<td>Extraprostatic extension</td>
<td>2501 (21)</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>650 (5)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>207 (23)</td>
</tr>
<tr>
<td>Positive surgical margins, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Preradiotherapy PSA ≤0.5 ng/ml</td>
<td>417 (4)</td>
</tr>
<tr>
<td>Preradiotherapy PSA &gt;0.5 ng/ml</td>
<td>371 (3)</td>
</tr>
<tr>
<td>Postoperative androgen deprivation therapy, no. (%)</td>
<td>1045 (9)</td>
</tr>
<tr>
<td>Mortality events, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Death from prostate cancer</td>
<td>157 (1.4)</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>621 (5)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; PSA = prostate-specific antigen.

Over a median follow-up of 56 mo (IQR: 24–93), 778 men have died, including 157 of PCa and 621 from competing causes; the number of patients at risk at 10 and 15 yr was 1558 and 205 patients, respectively. The 15-yr CSM and all-cause mortality rates were 7% (95% confidence interval [CI], 6–9) and 33% (95% CI, 30–36), respectively. In univariable analysis, men with PSMs had a significantly increased risk of CSM compared with those with negative surgical margins (NSMs; 15-yr CSM: 10% [95% CI, 7–14] vs 6% [95% CI, 4–8]; p < 0.001) (Fig. 1).

In multivariable competing risk regression analysis, PSMs were not significantly associated with CSM (HR: 0.96; 95% CI, 0.7–1.4; p = 0.9). Postoperative radiotherapy was associated with CSM (HR: 1.8; 95% CI, 1.3–2.6; p < 0.001), although this is likely due to the fact that it was administered for (and thereby associated with) BCR. The extended model that adjusted for early and late postoperative radiotherapy also did not identify a significant association between PSM and CSM (HR: 1.01; 95% CI, 0.7–1.4; p = 0.9). Early postoperative radiotherapy was not associated with CSM (HR: 1.1; 95% CI, 0.6–2.0; p = 0.8) and late postoperative radiotherapy was associated with CSM (HR: 2.6; 95% CI, 1.7–3.9; p < 0.001). Similar results were obtained using an extended Cox proportional hazards regression analysis model (data not shown) [27]. The latter’s association with increased CSM may due to the fact that most men with postprostatectomy PSA >0.5 ng/ml have coexisting systemic disease. Men receiving late postoperative radiotherapy also had significantly more adverse features in terms of pathologic Gleason.

Table 2 – Multivariable competing risk regression analysis of parameters associated with prostate cancer-specific mortality considering fixed covariates only (model 1), fixed covariates and postoperative radiotherapy (model 2), and fixed covariates and early and late postoperative radiotherapy (model 3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Gleason score ≥4</td>
<td>4.8 (3.4–6.8)</td>
<td>&lt;0.001</td>
<td>4.5 (3.2–6.4)</td>
<td>&lt;0.001</td>
<td>4.4 (3.1–6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary Gleason score ≥4</td>
<td>2.4 (1.7–3.3)</td>
<td>&lt;0.001</td>
<td>2.2 (1.6–3.1)</td>
<td>&lt;0.001</td>
<td>2.2 (1.5–3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>3.8 (2.6–5.7)</td>
<td>&lt;0.001</td>
<td>3.7 (2.5–5.3)</td>
<td>&lt;0.001</td>
<td>3.8 (2.6–5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year of surgery</td>
<td>0.9 (0.85–0.95)</td>
<td>&lt;0.001</td>
<td>0.9 (0.86–0.95)</td>
<td>&lt;0.001</td>
<td>0.9 (0.86–0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>1.4 (0.9–2.1)</td>
<td>0.18</td>
<td>1.6 (1.1–2.5)</td>
<td>0.028</td>
<td>1.7 (1.1–2.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Extraprostatic extension</td>
<td>2.0 (1.3–3.2)</td>
<td>0.003</td>
<td>1.9 (1.2–2.9)</td>
<td>0.005</td>
<td>1.9 (1.2–3.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.97–1.01)</td>
<td>0.5</td>
<td>0.99 (0.97–1.02)</td>
<td>0.6</td>
<td>0.99 (0.97–1.01)</td>
<td>0.4</td>
</tr>
<tr>
<td>PSA</td>
<td>1.0 (0.99–1.01)</td>
<td>0.7</td>
<td>0.99 (0.98–1.01)</td>
<td>0.4</td>
<td>0.99 (0.98–1.00)</td>
<td>0.2</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td>1.04 (0.7–1.5)</td>
<td>0.9</td>
<td>0.96 (0.7–1.4)</td>
<td>0.9</td>
<td>1.01 (0.7–1.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Postoperative radiotherapy</td>
<td>–</td>
<td>–</td>
<td>1.8 (1.3–2.6)</td>
<td>&lt;0.001</td>
<td>Early 1.1 (0.6–2.0)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>Late 2.6 (1.7–3.9)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval.
8–10 and high preoperative PSA levels, and a higher percentage were diagnosed in the early PSA era \( (p < 0.01 \) for all comparisons).

4. Discussion

In the largest published series of men treated by RP in the PSA era, we previously reported that pathologic Gleason score 8–10 and advanced pathologic features (seminal vesicle invasion and lymph node metastasis) are the prime determinants of CSM [21]. Men with PSMs had marginally increased CSM compared with those with NSMs, but PSM was not an independent predictor of CSM. However, this study considered only fixed covariates and did not consider secondary treatments that may influence the natural history of progressive PCa. After adjusting for the use of postoperative radiotherapy (including early and late administration based on the preradiotherapy PSA level), we were unable to demonstrate a significant association between PSM and CSM. While PSMs significantly increase the risk of BCR and should be avoided, the lack of an association between PSMs and CSM has important implications. First, it calls into question the rationale for postoperative radiotherapy for PSMs in the absence of other adverse features such as seminal vesicle invasion, pathologic Gleason score 8–10, or a short PSA doubling time after BCR. Second, it calls into question the relevance of PSM rates as a measure of surgical proficiency.

A PSM suggests that the primary tumor has not been completely excised due to the extension of cancer outside the prostate to the margins of resection or from violation of the prostatic capsule, thereby exposing neoplastic glands. However, a residual focus of cancer resulting from a PSM may not possess the biologic properties necessary for cancer progression. PSMs may also be a pathologic artifact caused by tissue trauma during retraction of the prostate intraoperatively or during the processing of pathologic specimens. There is also substantial interobserver variability in identifying PSMs, even among expert pathologists [28]. As such, the majority of men with PSMs will not manifest BCR [1]. While PSMs are widely regarded as a risk factor for BCR, PSMs in the absence of other adverse features may be associated with an indolent form of BCR: 15-yr CSM for men with a long PSA doubling time is low [29]. PSMs are caused, in part, by technical errors, and may not necessarily reflect aggressive tumor biology [6]. Thus, it is important to question the clinical relevance of PSMs for CSM and overall survival—the outcomes of greatest importance to the patient.

Our study demonstrates that PSM is not associated with an increased risk of CSM after controlling for important clinical and pathologic parameters, including the use of postoperatively radiotherapy. This finding conflicts with prior publications. In a single-surgeon perineal prostatectomy series from the pre-PSA era, Paulson reported a significantly higher CSM in men with PSMs compared with those with organ-confined disease, although multivariable regression analysis was not used to adjust for other parameters [30]. However, in a single-institution study of 1712 patients treated by RP in the PSA era, Mauermann et al. reported no significant association between PSMs (either solitary or multiple) with distant metastasis or CSM [31]. The statistical power of this study was limited by few events for analysis of metastatic progression \( (n = 19) \) and CSM \( (n = 13) \). In a recent population-based study using the Surveillance Epidemiology and End Results (SEER) registry from 1998–2006, Wright et al. reported that PSM was a significant predictor of CSM \( (HR: 1.7; 95\% CI, 1.3–2.2) \) after adjusting for Gleason score, pathologic stage, and the use of postoperative radiotherapy [32]. While the study population was large \( (N = 65 633) \), no patients were followed for >10 yr and the risk of CSM within 10 yr is low, particularly in the absence of seminal vesicle invasion and lymph node metastasis (patients with these features were excluded from this study). Indeed, only 291 (0.4%) CSM events were observed and the 7-yr CSM was <2% for men with either PSMs or NSMs. This analysis had other important limitations. In the SEER registry, information on preoperative PSA is not available and Gleason 7 tumors are grouped with Gleason 5–6 tumors. Thus, the association of PSM with CSM in this study may simply be associated with higher PSA values and/or Gleason 7 cancer. Last, inaccurate pathologic information in the SEER registry has been identified in up to 30% of cases, often related to inaccurate assignment of surgical margin status [33].

Our study has important strengths over that of Wright et al. [32]. Information on all relevant parameters was available, including the timing of postoperative radiotherapy and the PSA level when it was administered. We also used competing risk regression analysis and modeled postoperative radiotherapy as a time-dependent covariate, which is preferable to using Cox proportional hazards regression analysis and considering postoperative radiotherapy as a fixed covariate. While the median follow-up in both studies was short for analyzing CSM \( (<5 \text{ yr}) \), the short follow-up in our study is partly related to the fact that most patients were treated since 1999. However, we did have 1538 and 205 patients at risk at 10 yr and 15 yr, respectively. Last, all pathologic specimens were reviewed by genitourinary pathologists at each institution. Thus, our patients are more likely to have accurate assessments of the pathologic features of their cancer. An important weakness of our study is that all patients were treated at high-volume hospitals and the SEER registry contains patients treated at high- and low-volume hospitals in 17 regions accounting for approximately 26% of the US population. Thus, it is possible that a PSM may have different prognostic implications, depending on whether a patient was treated at a high- versus low-volume hospital. Another limitation of our study is the lack of information on the length and number of PSMs. However, we and others have shown the PSMs classified by their extent, length, and/or number provide little empiric prognostic information for predicting BCR and CSM [1,31].

In many areas of surgical oncology, PSMs are frequently used as a measure of surgical quality based on their association with cancer recurrence and mortality. Eastham et al. reported that the individual surgeon’s technique is a major risk factor for PSM in RP specimens, suggesting that technical errors leading to PSM may subject a man to an increased risk of BCR [6]. This has led some to propose using variations in PSM rates among surgeons and/or techniques
to measure quality of surgery. In an analysis of 7765 patients treated by RP by 1 of 72 surgeons of varying experience, Vickers et al. demonstrated that PSM and BCR rates were associated with surgeon experience, although the correlation between the two outcomes was poor [34]. They concluded that surgical margin status is not a strong surrogate for cancer control and is of questionable relevance to evaluate the quality of surgery. The lack of association between PSM and CSM in our study further undermines the relevance of PSM rates as a measure of surgical proficiency. It should be emphasized that surgeons performed RP in these patients with the intent to achieve NSMs. Despite the lack of association between PSM and CSM, surgeons should continue to strive to achieve NSMs. We do not know if PSM occurring in the setting of RP performed without the intent to achieve NSMs would not increase a man’s risk of CSM. As PSM is a frequent indication for postoperative radiotherapy and/or androgen deprivation therapy, avoiding PSMs may reduce the need for (and side effects of) secondary therapy.

The association of postoperative radiotherapy with increased CSM (particularly when administered late) is likely related to its correlation with BCR, as virtually all patients received postoperative radiotherapy for a rising PSA level. The lack of association of early postoperative radiotherapy with CSM may be due to the protective effect of adjuvant and early salvage radiotherapy and/or the indolent natural history of BCR in patients with PSA levels <0.5 ng/ml [7,13,25]. The increased risk of CSM among men receiving late salvage radiotherapy is unlikely to be causative, but likely is attributable to the fact that most men with postprostatectomy PSA levels >0.5 ng/ml have coexisting systemic disease and thus are unlikely to benefit from salvage radiotherapy; this cohort also had worse features in terms of Gleason score, preoperative PSA levels, and year of diagnosis [19].

5. Conclusions

In summary, PSMs do not appear to increase a man’s risk of dying of PCa within 10–15 yr of RP. These results have important implications for the use of adjuvant radiotherapy and the relevance of PSM rates to measure quality of surgery. Nevertheless, PSM does matter as it increases a man’s risk of BCR and need for secondary therapy, and may be a source of considerable patient anxiety given the perception that it implies an incomplete cancer resection. Thus, urologists should continue to strive to reduce PSM rates.

Author contributions: Andrew J. Stephenson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stephenson, Klein, Kattan, Eggener, Scardino, Eastham, Wood, Rabah.

Acquisition of data: Stephenson, Klein, Wood, Scardino, Eastham.

Analysis and interpretation of data: Stephenson, Klein, Kattan, Eggener, Scardino, Eastham, Wood, Rabah, Hernandez.

Drafting of the manuscript: Stephenson.

Critical revision of the manuscript for important intellectual content: Stephenson, Klein, Kattan, Eggener, Scardino, Eastham, Wood, Rabah, Hernandez.

Statistical analysis: Stephenson, Hernandez, Kattan.

Obtaining funding: Klein, Stephenson, Scardino, Wood, Eastham.

Administrative, technical, or material support: Stephenson.

Supervision: None.

Other (specify): None.

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