The Actual Value of the Surgical Margin Status as a Predictor of Disease Progression in Men with Early Prostate Cancer

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Abstract

Objectives: The surgical margin status after radical prostatectomy for prostate cancer has long been considered a powerful prognostic factor, as well as an important risk factor for local recurrent disease after radical prostatectomy. In this study, a critical analysis of the predictive value of the surgical margin status was performed.

Methods: A well-described cohort of 281 participants of a population-based randomized screening trial who underwent radical prostatectomy between 1994 and 2000 was analyzed. Besides pathologic tumor stage, Gleason score, percentage of high-grade cancer, and tumor volume, the prognostic value of the surgical margin status for disease outcome (prostate-specific antigen [PSA] relapse, local recurrence) was statistically evaluated. Specifically, site ('apical' or 'circumferential') and extent of surgical margin negativity ('negative', or 'close') or positivity ('focal' or 'extensive') was assessed.

Results: At a median follow-up of 7 yr (range, 5–120 mo), 39 (13.9%) and 7 (2.5%) men had biochemical failure (PSA >0.1 ng/ml), and local relapse, respectively. The surgical margin status was positive in 66 (23.5%), with 26 (9.3%) at the prostatic apex. The margin status was an independent statistically significant risk factor for biochemical relapse, though not for local recurrence. Of those with positive margins, 22 (33.3%) had PSA relapse and 4 (6.1%) had local recurrence, whereas these figures were 17 (7.9%) and 3 (1.4%) for those with a negative surgical margin, respectively. The extent of margin positivity was not predictive of PSA relapse nor was the site of the surgical margin.

Conclusions: In surgically treated prostate cancer, the surgical margin status has, although being a statistically significant prognostic factor, only limited predictive value for PSA relapse and local recurrent disease. The majority of men with (extensive) positive surgical margins will not experience PSA relapse nor local disease progression, even in absence of adjuvant radiotherapy. So, cases with a positive margin of resection may still be cured, although the procedure in itself was not ‘radical’.

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1. Introduction

Radical prostatectomy has become a reliable means of curative treatment for men with early detected prostate cancer compared to no treatment [1,2]. For prostate cancer, powerful prognostic factors for biochemical and clinical outcome have been identified such as serum prostate-specific antigen (PSA) level, pathologic tumor stage, Gleason score, and surgical margin status. Whereas tumor stage and histologic grade are inherent to the biologic aggressiveness of disease, the surgical margin status has a multifactorial cause. Tumor features (extraprostatic extension, tumor volume), anatomic and patient factors (the location of the prostate deep within the lesser pelvis), the method of pathologic tissue processing, and the surgical technique itself (the inadvertent surgical entry into the prostatic capsule, laparoscopic versus open radical prostatectomy) may influence the rate of margin positivity.

Positive surgical margin rates between 10% and 30% have been reported in recent series [3–5]. Intuitively, a positive surgical margin is associated with biochemical failure and local disease progression at the site of incomplete tumor removal. Controversy exists on the prognostic impact of a positive margin at the apex of the prostate gland compared to other sites of the prostate. By some, a statistically adverse prognostic outcome was reported in those with positive apical margins [6–9]. Others reported that an apical positive margin did not affect the progression rate of disease compared to those with negative surgical margins [10–12]. So, opposed to other solid tumors, a positive surgical margin of resection might not imply an adverse prognostic outcome, nor a need for adjuvant treatment, in all patients.

To investigate more thoroughly the prognostic value of the surgical margin status for biochemical and local recurrence of disease, a well-described cohort of 281 screened men who underwent radical prostatectomy with long follow-up was studied. The extent of surgical margin positivity or negativity and the site of positive margins were related to biochemical and local disease progression. Not only the statistical prognostic value of the margin status was evaluated, but also the actual predictive value for PSA relapse, and more importantly, the predictive value for local relapse.

2. Patients and methods

2.1. Patient selection

The study group consisted of 281 consecutive men who underwent retropubic radical prostatectomy at the Erasmus Medical Center Rotterdam between June 1994 and December 1999. Their mean age was 64 yr (range, 55–73 yr), and the median PSA level at the time of biopsy was 5.2 ng/ml (range, 0.8–29.5 ng/ml). All men were participants of the screen arm of the European Randomized study of Screening for Prostate Cancer (ERSPC), section Rotterdam [13]. In short, a cancer diagnosis was made after the evaluation of an elevated PSA level (ie, PSA ≥3.0 ng/ml) or a digital rectal examination (DRE) or transrectal ultrasound (TRUS) finding suspicious for cancer at low PSA values (0.0–2.9 ng/ml). In case of an elevated PSA level or a suspicious rectal examination, a diagnostic biopsy was performed to obtain prostatic tissue. The biopsy procedure consisted of a systematic lateralized sextant biopsy [14]. One or two additional biopsies were taken from hypoechogenic lesions when present. The decision to perform radical prostatectomy was made by the patient and his treating urologist, considering the patient’s age, comorbidities, biopsy tumor features, and personal preferences. All patients underwent bilateral pelvic lymph node dissection prior to radical prostatectomy, and none received (hormonal) treatment prior to operation. Unfortunately, we were not able to obtain complete data on whether nerve-sparing radical prostatectomy was performed nor whether the neurovascular bundle was sacrificed for tumor control.

2.2. Patient follow-up

All patients were followed with serial PSA measurements at intervals of 3 mo for the first year after radical prostatectomy, semiannually for the second year, and yearly thereafter. Two definitions for PSA relapse were used. The first definition was stringent at the finding of two sequential detectable PSA levels of 0.1 ng/ml and higher, whereas the second definition demanded that serum PSA had to reach a level of 1.0 ng/ml at least. This latter definition was chosen to identify the patients who are believed to be at risk (or already had evidence) of local disease progression. Time to biochemical progression was defined as the time from radical prostatectomy to the time of (first) recurrence of serum PSA of ≥0.1 ng/ml or until last follow-up, if the patient did not experience PSA relapse. For those with PSA relapse after radical prostatectomy, DRE was performed to assess whether there was clinical evidence of local recurrent disease. Local disease progression was defined as recurrence of disease as proven by a positive for cancer histology near the vesicourethral anastomosis. Patients with a histologically proven local recurrence of disease underwent external radiotherapy to the prostatic bed. In our hospital, it is not general policy to offer external radiotherapy in those with (extensive) positive surgical margins. Time to local recurrence of disease was defined as the time from radical prostatectomy to the time of first recording of local relapse, or to date of last follow-up if the subject did not have evidence of progression.

2.3. Conventional pathology

All radical prostatectomy specimens were fixed, totally embedded, and processed according to well-established protocols [15,16]. The specimens were fixed in 10% buffered formalin for 24 h and subsequently inked. The apex of the
prostate was removed and sectioned at 4-mm intervals along the sagittal plane. The remainder of the prostate was cut at 4-mm intervals, perpendicular to the rectal surface. A global radical prostatectomy Gleason score was determined, and the tumor was staged according to the fifth UICC/TNM'97 classification by a single genitourinary pathologist (T.vdK.). Considering the proportion of high-grade cancer (Gleason growth pattern 4/5), three categories were distinguished: no high-grade cancer; >0–50%, and ≥50% high-grade cancer. All tumor areas were traced and outlined on the slides, and subsequent morphometric analysis was performed to determine the tumor volume [17].

Presence of tumor cells at the inked margin of resection was considered a positive surgical margin. Specific attention was made to assess the anatomic site of the positive margin using prostate mappings, whether ‘apical’, or ‘circumferential’ (the lateral prostatic borders). An effort was made to categorize negative surgical margins according to distance to resection, whether ‘negative’ (no proximity of tumor cells to any of the inked surgical margins) or ‘close’ (tumor cells in close proximity to the ink), as well as the positive surgical margins, whether ‘focal’ (only few tumor cells touching the specimen ink), or ‘extensive’ (larger tumor area in contact with the specimen ink).

2.4. Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS 12.0; SPSS, Chicago, IL). The \( \chi^2 \) test and Cox proportional regression analysis was used to assess the relationship between variables, and PSA or local relapse after radical prostatectomy. Pathologic stage, Gleason score, proportion of high-grade cancer, tumor volume, and surgical margins were categorized as shown in Tables 1–3. Kaplan-Meier curves were constructed to show the probability of remaining free of PSA and local relapse as a function of time after radical prostatectomy (Fig. 1). The assumption that no predictive value (H0) existed for the variable evaluated was rejected if \( p < 0.05 \). To identify independent prognostic factors, forward stepwise Cox multiple regression analysis was performed by removing variables from the model that were not statistically significant at the univariate level, while controlling for other variables. Backward stepwise elimination was performed to verify that the same parameters remained of prognostic significance in the final models.

3. Results

3.1. Patient characteristics

The median follow-up for the cohort of 281 patients was 81 mo (range, 5–120 mo). Within the overall follow-up period, 18 (6.4%) patients died of causes unrelated to prostate cancer after a median of 48 mo (range, 5–108 mo) after radical prostatectomy. Fifteen (5.3%) men had a follow-up of <60 mo, and no PSA measurements in the last 2 yr before this analysis, and were assumed lost to follow-up. Of these, 2 (0.7%) had evidence of PSA relapse, though no evidence of local relapse at their last visit to the outpatient department at 44 and 49 mo of follow-up, respectively.

PSA relapse (ie, ≥0.1 ng/ml) occurred in 39 (13.9%) patients after a median follow-up of 21.0 mo (range, 1–97 mo) after radical prostatectomy. Local relapse was found in 7 (2.5%) patients after a median follow-up of 64 mo (range, 17–112 mo). All locally progressing
patients had PSA levels ≥1.0 ng/ml (and rising) after treatment.

3.2. The association between postoperative tumor features and surgical margins

Table 1 shows the distribution of postoperative tumor features and their correlation to the surgical margin status. The surgical margins were positive in 66 cases (23.5%), with 26 (9.3%) having a positive margin at the apex only. For organ-confined disease, 18.0% of cases (38 of 211) had positive surgical margins in any location, whereas this figure was 36.7% (18 of 49) for tumors with extraprostatic extension (pT3a). For tumors invading the seminal vesicles (pT3b), bladder neck, or external sphincter musculature (pT4), 52.4% (11 of 21) were still confined to the specimen.

3.3. The association between surgical margins and outcome

Of those with positive margins, 22 (33.3%) had PSA relapse and 4 (6.1%) had local relapse; these figures were 17 (7.9%) and 3 (1.4%) for those with negative surgical margins, respectively (both: \( \chi^2, p < 0.05 \)). For those with positive margins, the median time to PSA progression was 26 mo (range, 2–74 mo), and this figure was 12 mo (range, 1–97 mo) for those with negative margins. For pT2 tumors with positive margins, 11 of 38 (28.9%) had PSA relapse, and these figures were 6 of 18 (33.3%) and 5 of 10 (50.0%) for pT3a and pT3b-pT4 tumors, respectively. No statistically significant difference was seen between pT2 and pT3a tumors and positive margins with respect to PSA relapse. Of those with a positive apical and circumferential margin, 8 (30.8%) and 14 (35.0%) experienced PSA relapse, respectively (\( \chi^2, p = 0.65 \)). In cases with extensive positive margins, biochemical progression occurred in 36.0% (18 of 40), and local relapse in 8.0% (4 of 50). In other words, 64% of men with an extensive positive surgical margin had undetectable PSA levels after radical prostatectomy. There was no statistically significant difference between men with a focal positive margin (4 of 17), and those with extensive positive margins (18 of 50) with respect to PSA relapse (\( \chi^2, p = 0.49 \)).

Of those with a negative margin of resection, 7 of 173 (4.0%) with pT2, 4 of 31 (12.9%) with pT3a, and 6 of 11 (54.5%) with pT3b-pT4 had biochemical relapse after radical prostatectomy (\( \chi^2, p < 0.05 \)). These figures were 3 of 97 (3.1%) for tumors with no high-grade cancer, 6 of 64 (9.4%) for >0–50%, and 8 of 18 (44.4%) with ≥50% high-grade cancer (\( \chi^2, p < 0.05 \)). Also, tumor volume and Gleason score were statistically significant markers for biochemical progression when categorized according to Table 1 (\( \chi^2, p < 0.05 \)).

### Table 1 – Distribution of postoperative tumor features of screened participants of ERSPC, section Rotterdam (n = 281), and the number of men who had positive and negative surgical margins after radical prostatectomy

<table>
<thead>
<tr>
<th>Postoperative variable</th>
<th>Surgical margin status</th>
<th>Negative</th>
<th>Positive</th>
<th>Total no.</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathologic stage</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td></td>
<td>173</td>
<td>38</td>
<td>211</td>
<td>&lt;0.01</td>
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<tr>
<td>pT3a</td>
<td></td>
<td>31</td>
<td>18</td>
<td>49</td>
<td></td>
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<tr>
<td>pT3b-4</td>
<td></td>
<td>11</td>
<td>10</td>
<td>21</td>
<td></td>
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<tr>
<td><strong>Gleason score</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2-6</td>
<td></td>
<td>137</td>
<td>28</td>
<td>165</td>
<td>&lt;0.01</td>
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<tr>
<td>7</td>
<td></td>
<td>76</td>
<td>33</td>
<td>109</td>
<td>&lt;0.01</td>
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<tr>
<td>8–10</td>
<td></td>
<td>2</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>% Gleason growth pattern 4/5</strong></td>
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<td></td>
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<tr>
<td>0</td>
<td></td>
<td>97</td>
<td>16</td>
<td>113</td>
<td></td>
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<tr>
<td>&gt;0–50</td>
<td></td>
<td>100</td>
<td>42</td>
<td>142</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥50</td>
<td></td>
<td>18</td>
<td>8</td>
<td>26</td>
<td></td>
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<tr>
<td><strong>Tumor volume</strong></td>
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<tr>
<td>&lt;0.5 ml</td>
<td></td>
<td>97</td>
<td>12</td>
<td>109</td>
<td>&lt;0.01</td>
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<tr>
<td>0.5–1.0 ml</td>
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<td>57</td>
<td>14</td>
<td>71</td>
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<tr>
<td>≥1.0 ml</td>
<td></td>
<td>61</td>
<td>40</td>
<td>101</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>215</td>
<td>66</td>
<td>281</td>
<td></td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; ERSPC = European Randomized study of Screening for Prostate Cancer.

\( \chi^2 \) test.
The surgical margin status was an independent significant prognostic factor for biochemical relapse if the PSA ≥ 0.1 ng/ml criterion for PSA relapse was used but not for PSA ≥ 1.0 ng/ml or local relapse during follow-up (Tables 2 and 3). 

4. Discussion

The recurrence rate after surgical treatment for malignant disease is indicative of the aggressiveness of disease and of the radicality of the surgical
procedure. Those at risk of local recurrence at the vesicourethral anastomosis site after radical prostatectomy for prostate cancer are those with adverse prognostic tumor features, as well as those with positive surgical margins. Contrary to other malignancies such as those of the head and neck, the rectum, and uterine cervix, local disease progression in surgically treated prostate cancer patients will in most cases not lead to death from uncontrolled disease progression within the first 10 yr after surgery. Local disease progression can, however, lead to anxiety in the affected patient and the burden of local or systemic treatment. With the introduction of the serum PSA test in the late 1980s, biochemical relapse after radical prostatectomy has become a surrogate end point of clinical disease progression, with the potential of predicting either local recurrent or distant metastatic disease. A yet unresolved issue surrounding the availability of PSA determination after radical prostatectomy is if, when, and at what site (local versus distant) these asymptomatic men with biochemical failure are to experience clinical disease progression, and whether these men should be treated early or expectantly with the possibility of delayed treatment. Due to restricted follow-up, however, most recent series on surgically treated prostate cancer patients do not report on clinical progression rates after prior biochemical relapse, whereas many others do not report on population cohorts that were exclusively derived from the PSA era. The present series describes a cohort of 281 men who underwent radical prostatectomy with relatively long follow-up, a median of 7 yr. This patient series was well-defined and is typical of contemporary PSA-tested populations with respect to age, biopsy indication, and prognostic factors.

To illustrate the influence of patient selection on disease outcome, we compared a historical cohort of patients undergoing radical prostatectomy at our department to the present patient series. Between 1977 and 1991, 172 consecutive patients underwent radical prostatectomy for assumed localized prostate cancer at our department [11]. In this cohort derived from the pre-PSA era, 70.3% had pT3a or pT3b-pT4 disease, and positive margins were present in 32.6%. Local disease progression occurred in 11% after a mean follow-up of 43 mo. Biochemical failure was not yet reported in great detail. Since then, major changes have been implemented in the management of men with prostate cancer due to PSA-based screening, resulting in a substantial stage and grade migration. Despite this prognostically favorable shift, and a better understanding of the prostatic anatomy and improved surgical techni-ques since then, only a modest decrease in positive surgical margin rate (32.6% versus 23.5% in the present series) was seen. The rate of local disease progression, on the other hand, was found to be lower in our present series, which had substantially longer follow-up (11% versus 2.5%). Because the rate of surgical margins was comparable between the two patient series, factors other than the mere presence or absence of a positive surgical margin, or the surgical technique itself, must have explained the higher rate of local disease progression in the historical cohort of patients [18].

Our present data indicate that a clear association existed between conventional prognostic factors as assessed in the radical prostatectomy specimen and disease outcome after radical prostatectomy. Surgically treated men with a positive margin in any location (apical, circumferential) and of any extent (focal, extensive) had a statistically higher chance of PSA relapse and local relapse compared to those with negative margins. Opposed to some other reports, those with a positive apical surgical margin only had an equal risk of progression compared to those with a positive margin in any other location of the prostate gland [6–9]. Although we found a statistically significant association between surgical margin status and (local) progression of disease, the actual risk of relapse was low. Overall, two thirds of men with a positive margin were free of disease (had undetectable PSA levels) during follow-up. This same figure holds true for those with positive margins and pT3a tumors. Local relapse in those with a positive surgical margin, and subsequent PSA relapse, occurred in only 18.2% of cases. Explanations for this observation can only be hypothesized, but apparently, tumor cells are not able to survive or otherwise grow to (clinically) detectable levels at the site of the positive surgical margin due to electrocoagulation effects during surgery, absence and disruption of tumor vasculature, or inflammatory reactions.

Recently, Bolla et al. showed that immediate postoperative radiation therapy improved biochemical progression-free survival in those at high-risk of progression (pT3 ± positive surgical margins) [19]. Because in our series the outcome of patients in whom the tumor proved to be irradically excised is favorable in most, we refrain from performing early adjuvant radiation therapy in all. Possibly, subgroups with adverse prognostic features might indeed benefit from adjuvant radiation treatment, but the exact characteristics of these subgroups need to be further defined, prospectively [20].

Furthermore, in specimen-confined disease (ie, those with negative surgical margins), there also was a clear association between pathologic tumor
stage, tumor volume, the amount of high-grade cancer, and PSA relapse. Evidently, inherent (aggressive) tumor features have a major impact on outcome as well. In our series, three men with negative margins experienced local relapse. An explanation for this finding might be that these men were, in fact, having a positive surgical margin, though that was not detected by the pathologist.

Some caveats may limit the interpretation of our results. First, the follow-up period may be too short for those with PSA relapse to experience clinical recurrence of disease. Johansson et al. reported that in a cohort of initially untreated patients with localized disease, local tumor progression and distant metastatic disease developed even after 15 yr of follow-up [21]. Pound et al. reported that in those with PSA relapse after radical prostatectomy, the median time to metastatic progression was 8 yr [22], that is, longer than our median follow-up period. In our series, the number of cases progressing clinically might thus increase with continued follow-up. On the other hand, it is likely that the majority of cases with PSA relapse have already been identified in our study, as it is recognized that over 90% of patients undergoing radical prostatectomy will have a relapse within 5 yr after surgery [21,23]. Furthermore, we have now 12 men in follow-up (10 with positive surgical margins) in whom the PSA level has risen above the 1.0 ng/ml threshold, and in whom we were not able to prove progression of disease clinically. In our series, clinical progression of disease never occurred without a prior PSA relapse, with postoperative PSA levels of at least 1.0 ng/ml. Because the interval between the documentation of biochemical progression and clinical recurrence of disease is long, particularly in those with late PSA relapse, search for clinical recurrence might well be restricted to those in whom the postoperative PSA level has risen above the 1.0 ng/ml threshold. Secondly, in our series the incidence of local recurrent disease might be underestimated due to the finding that DRE and TRUS are known to lack sensitivity in detecting local recurrence [24,25]. Whether other detection modalities such as ProstaScint® [26] or magnetic resonance imaging with an endorectal coil [27] will increase this sensitivity remains to be established.

5. Conclusion

Although we found a statistically significant association between the surgical margin status and disease recurrence after radical prostatectomy, the margin status has only limited impact on the actual risk of (biochemical) disease progression. In our series, most men with a positive surgical margin, whether focal or extensively, did not experience PSA relapse within 7 yr after radical prostatectomy. Moreover, the vast majority of men with a positive margin of resection, whether apical or circumferential, did not experience local relapse. Patients should be reassured that in most instances, cases with a positive margin of resection will still be cured, although the procedure in itself was not ‘radical’.

References


