Biochemical recurrence rate in patients with positive surgical margins at radical prostatectomy with further negative resected tissue

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Accepted for publication 5 June 2009

OBJECTIVE

To determine the biochemical recurrence (BCR) rate in patients with positive surgical margins (PSMs) on the prostate specimen who have additional negative tissue resected from that site (M−−), compared to patients with negative margins (M−) and those with persistent PSM (M+), as those with PSM at radical prostatectomy (RP) are at greater risk of BCR, and in some instances where suspicious tissue is noted in the prostate bed or when frozen-section analysis shows PSM, additional tissue is resected from the suspect site of the PSM.

RESULTS

Pathological organ-confined (OC) cancer was present in 2901 men, of whom 2659 had M−, 216 had M+, and 26 had M−−. Extracapsular extension (ECE) alone with no seminal vesicle involvement was present in 843 men, of whom 657 had M−, 174 had M+ and 12 had M−−. For patients with OC cancer, the 36-month actuarial BCR-free probability was 97.9% (95% confidence interval 97.3–98.5) for M−, vs 89.0 (84.1–93.9)% for M+ vs 100% for M−−. For patients with ECE, the 36-month actuarial BCR-free probability was 83.7 (80.0–87.4)% for M− vs 73.7 (66.1–81.3)% for M+ vs 90.0 (71.4–100)% for M−−. The main limitation of the study was its retrospective nature, with the reason for resection of additional tissue not always well documented.

CONCLUSIONS

While the few patients with PSMs and further negative resected tissue limited the statistical analysis, it would appear that in these patients the disease behaves as in those with negative margins.

KEYWORDS

pathology, prostatectomy, prostatic neoplasms, frozen sections, margin
have a decreased BCR rate, more consistent with those patients with NSMs.

**PATIENTS AND METHODS**

Between January 1999 and June 2007, 4600 consecutive patients underwent RP (open retropubic, RRP, or laparoscopic, LRP) at our institution. We excluded 383 patients who had previous radiotherapy (104), chemotherapy (51) or hormonal therapy (264) or in whom no pathological Gleason score was assigned due to treatment effects seen on the RP specimen or stage pT0 (174). The remaining 4217 patients are the subject of this study. Institutional Review Board approval was obtained for the study. The pathology and operative reports of all patients with PSMs were reviewed. In 98 patients who had PSMs on the specimen, further periprostatic tissue was resected from the prostatic bed due to concern about residual cancer on visual inspection of the prostate specimen or prostatic bed, or in cases where FSA of the prostate specimen during RP revealed a positive or close margin.

All surgical specimens were processed with 3–5 mm step-sectioning, with the entire prostate submitted. A PSM was defined as tumour cells present at the inked margin. NSMs are designated M−, PSMs as M+, and PSMs on the prostate specimen with the final resected periprostatic tissue being reseated from the prostatic bed due to concern about residual cancer on visual inspection of the prostate specimen or prostatic bed, or in cases where FSA of the prostate specimen during RP revealed a positive or close margin.

The statistical significance of differences in proportions was tested using the chi-square test or Fisher’s exact test where appropriate. Kaplan-Meier analysis with the log rank test was used to compare BCR-free probability in those with M− vs M+ vs M+−, stratifying for pathological stage (organ-confined, OC) vs extracapsular extension alone (ECE) without seminal vesicle or lymph node involvement. The BCR-recurrence free probability was calculated at 36 months with 95% CI calculated using Greenwood’s formula.

**RESULTS**

Table 1 summarizes the clinical characteristics of the 4217 patients; the median (interquartile range, IQR) patient age was 59.1 (54.5–64.1) years. Table 1 also summarizes the intraoperative and pathological characteristics of the 4217 patients. Pathological OC cancer was present in 2901 men, of whom 2659 had M−, 216 had M+ and 26 had M+−. BCR was defined as a PSA level of ≥0.10 ng/mL after RP and a confirmatory increase, or a PSA level of ≥0.10 ng/mL and receiving salvage treatment (e.g. radiotherapy, hormonal manipulation, chemotherapy).

A greater proportion of patients with OC disease and M+− had tissue sent for FSA vs.
routine analysis than had patients with persistent PSMs despite further resected tissue (M+), i.e. 24/26 for OC M+− vs 18/29 for OC M+ (P = 0.008, chi-square test) and 10 of 12 for ECE M+− vs 22/31 for ECE M+ (P = 0.34, Fisher’s exact test). In the 29 patients with OC disease with persistent PSMs, 18 had additional tissue sent for FSA, while 11 had tissue sent for routine pathology analysis. Fifteen of the 18 OC M+− patients having FSA had tissue sent from a site other than the PSM, while in three the final tissue sent was not negative (one with final tissue sent as routine, one sent as FSA and one negative on FSA that was positive on permanent section). Nine of the 11 OC M+− patients who had further tissue sent as a routine section had tissue sent from a site other than the PSM, while in one the final tissue sent was not negative.

For patients with OC cancer, the mean (95% CI) 36-month actuarial BCR-free probability was 97.9 (97.3–98.5)% for M− vs 89.0% for M+.

**TABLE 2** The site of further tissue resection by pathological stage

<table>
<thead>
<tr>
<th>Group</th>
<th>Site</th>
<th>Bladder neck</th>
<th>NVB/PL margin</th>
<th>Apex/urethra</th>
<th>DVC/anterior margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC (55)</td>
<td>With further tissue resection, N</td>
<td>13</td>
<td>25</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Rendered ‘M−’ by further resection, n(%) or n/N</td>
<td>1/13 (52)</td>
<td>13</td>
<td>10 (48)</td>
<td>3/11</td>
</tr>
<tr>
<td>ECE alone (43)</td>
<td>With further tissue resection</td>
<td>12</td>
<td>18</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Rendered ‘M−’ by further resection</td>
<td>0</td>
<td>9 (50)</td>
<td>3/13</td>
<td>0</td>
</tr>
</tbody>
</table>

DVC, dorsal vein complex; PL, posterolateral.
(84.1–93.9)% for M vs 70.0–87.4)% for M– (Fig. 2A). For patients with ECE, the 36-month actuarial BCR-free probability was 83.7 (80.0–87.4)% for M vs 73.7 (66.1–81.3)% for M– vs 90.0 (71.4–100)% for M+– (Fig. 2B).

**DISCUSSION**

Given the adverse prognostic significance of PSMs [1], surgeons strive to achieve NSMs while maximizing sparing of the neurovascular bundles (NVBs) at RP where possible, to achieve the ‘trifecta’ [15]. Despite the availability of preoperative nomograms to predict ECE [16], surgeons are sometimes confronted with significant desmoplastic reaction around the NVBs at the time of RP, which might be attributed to ECE of cancer [9], leading to NVB resection or a capsular incision in cases of attempts at nerve sparing. BCR rates in patients with capsular incision are higher than in those with OC margin-negative disease or focal ECE with NSMs, and comparable to those in patients with focal ECE with PSM or established ECE with NSMs [17]. As such, in cases of capsular incision into the prostate that are recognized during RP, surgeons often resect additional tissue to achieve a NSM. While several investigators have reported on use of intraoperative FSA to render surgical margins negative [11–14,18–25], there is a paucity of data on the prognostic implications of this approach, with few studies evaluating BCR rates in those with PSMs that have been rendered negative [13,21].

An early study on the use of FSA during RP to evaluate SM status and render otherwise PSMs negative by further resection reported lowering of PSA levels in those whose margins had been made negative [11]. However, this was a small study with 66 patients, in which six of eight patients with a PSM on FSA who had further tissue resected until the margin was rendered ‘negative’, while the two others did not undergo RP; the assessment of postoperative PSA level was confounded by use of adjuvant radiotherapy in seven of the eight patients, as well as an unquoted duration of follow-up. Cangiano et al. [13] reported no cases of BCR in nine patients having a positive posterolateral FSA with subsequent wide resection of the NVB, compared to five of 39 with negative PSA (P = 0.94). Lepor and Kaci [21] reported that all 16 patients with <5% cancer on the final apical margin had an undetectable serum PSA level at a mean follow-up of 19.1 months, compared to one of five of patients having a final apical margin biopsy showing ≥5% cancer developing BCR at a mean follow-up of 24 months. Kübler et al. [26], reporting on 77 patients undergoing perineal RP with documented invasion of the prostatic apex, found a mean (±SD) 36-month BCR-free survival rate of 55.9 (14.9)% for patients with positive apical biopsies compared to 78.7 (6.3)% for those with negative biopsies (P = 0.023). These studies are consistent with the present study that suggests that the BCR rate is lower in those with PSM that have been rendered negative than in patients with PSM. As such, while these patients with PSM who have been rendered negative are coded as having PSM in RP databases for the purposes of quality assurance and refining the technique of RP, for the purposes of adjuvant therapy, perhaps these patients with PSM rendered negative should be considered to have NSMs.

In the present series, 98 patients who had a PSM on the specimen had further tissue resected; 38 of the 98 (39%) had no cancer in the final tissue resected, with no other site of PSM, with the margins thus being rendered negative with resection of additional tissue. The 98 patients having further tissue resected represent only 2.3% of the entire cohort treated during the period of the study; thus the 38 margins rendered negative represent 0.9% of the entire cohort, effectively reducing the PSM rate in the entire series from 13.9% to 13.0%. The studies reporting on the effect of resection of additional tissue on PSM are summarized in Table 3 [11–14,18–25]. The rate of PSMs rendered negative in the reported studies range from 0.9% in the present series to 21%, with the relative reduction in PSM of 6.5–66.7%. Given that the present study suggests an improvement in BCR in those in whom the PSM is rendered negative, there is a potentially significant reduction in ‘biologically active’ PSM and secondarily of BCR with a strategy of resection of additional tissue in cases where there is concern about a capsular incision or residual prostate tissue, or in cases where nerve-sparing has been used and FSA of the prostate specimen reveals cancer at the margin.

It has been reported that the yield of FSA is too low to justify its routine practice [21,25]. Tsuobi et al. [25] reported that the sensitivity of FSA is 41.8%; only 23 of 55 patients with PSM on the permanent section had the PSM identified on FSA. In the 23 patients with the PSM identified on FSA, 17 (74%) were rendered margin-negative with resection of additional tissue, while in the 32 with a PSM, only 14 (44%) were rendered margin-negative with resection of additional tissue, as the remaining 18 had a PSM at a different site from that of the FSA. In their 760 patients, 259 had FSA, to render 31 men margin-negative. Nevertheless, this represents a 29.5% relative reduction in the PSM rate, from 13.8% to 9.7%. In the present series, as seen in Fig. 1, 34 of 74 (46%) patients who had tissue sent for FSA were rendered margin-negative with the resection of additional tissue, compared to four of 24 (17%) who had the tissue sent for routine permanent section (P = 0.011, chi-square test). While this difference is statistically significant, our study only evaluated the effect of resection of further tissue on those with a PSM, rather than a prospective evaluation of the effect on all patients.
(including those with NSMs) who had undergone resection of additional tissue. Including the patients with NSMs would reduce the percentage of patients who potentially benefit from a strategy of intraoperative FSA. Indeed, Lepor and Kaci [21] reported that the yield of intraoperative biopsy of the bladder neck and NVB/lateral pedicle is too low to justify it in routine practice. In the present study, about half of the subset of patients with PSM with either OC cancer or ECE alone having further tissue resection in the region of the NVB/posterolateral margin were rendered margin-negative, as were about half of the subset of patients with PSM and OC cancer having further tissue resection at the apex/urethra. In cases of capsular violation or where there is concern about gross residual tissue, resection of additional tissue might be beneficial, as the BCR rate is improved in patients where the final resected tissue is negative for cancer.

Our study has several limitations. As it is a retrospective evaluation, the reason for resection of additional tissue was not always well documented in the operative notes. Second, the study evaluates only patients who had a PSM on the specimen who had resection of additional tissue, and as such is not designed to evaluate the yield or adverse consequences of a strategy of FSA, which is best done prospectively. Thus, while most patients rendered margin-negative had further resection from the NVB/posterolateral margin, or in the case of OC cancer, from the apex/urethra, the denominator of all patients (including those with NSMs on the specimen) was not evaluated in this study to determine the yield of further tissue resection at the various sites, or the consequences in terms of erectile function or incontinence. The relatively few patients who had a PSM and had additional tissue resection limits the statistical analysis, so that while statistical significance was not achieved for the difference in BCR between those with PSM and those with PSM rendered negative, the Kaplan–Meier curves suggested a trend that might be able to be confirmed with a larger study. Insofar as a PSM is used to designate those who have residual cancer in the prostate bed, our study suggests that those with PSMs that have been rendered negative might have disease that behaves like that with NSMs, and perhaps should be considered as such when considering potential adjuvant therapy.

The BCR rate in patients with a PSM that has been rendered negative with resection of additional tissue is comparable to that in patients with NSMs and lower than that in patients with persistent PSMs, suggesting a potential benefit to resection of additional tissue in cases where there is a concern of PSM on the RP specimen.

**ACKNOWLEDGEMENTS**

Supported by the Sidney Kimmel Center for Prostate and Urologic Cancers.

**CONFLICT OF INTEREST**

None declared.

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Abbreviations: BCR, biochemical recurrence; (L)(R)RP, (laparoscopic) [retropubic open] radical prostatectomy; (P)(N)SM, (positive) [negative] surgical margin; NVB, neurovascular bundle; OC, organ-confined; ECE, extracapsular extension; FSA, frozen-section analysis; IQR, interquartile range.