Original article

The association between nerve sparing and a positive surgical margin during radical prostatectomy

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Received 20 June 2014; received in revised form 5 September 2014; accepted 7 September 2014

Abstract

Purpose: A positive surgical margin (SM) during radical prostatectomy (RP) increases risk of biochemical recurrence. We evaluated the effect of nerve-sparing procedures on risk of positive SM for pT2- and pT3-category tumors. We hypothesized that nerve sparing would increase rates of pT2 positive margins.

Methods: We evaluated a historical cohort of 9,915 consecutive RP patients treated at The Ottawa Hospital or Memorial Sloan-Kettering Cancer Center from 2000 to 2010. Patients underwent open, laparoscopic, or robotic RP. The primary outcome was presence of a positive SM stratified by pathologic pT2 and pT3 categories. The association between nerve sparing and positive margin was adjusted for prostate-specific antigen, RP Gleason sum, surgical modality, surgical date, and location in the multivariable model.

Results: Of 6,120 eligible patients, 3,958 (64.7%) had open RP, 1,566 (25.6%) had laparoscopic RP, and 596 (9.7%) had robotic RP. Approximately 8.6% (363/4,199) of patients with pT2-category disease and 25.2% (485/1,921) of patients with pT3-category disease had a positive margin. Patients with pT2-category disease who underwent a bilateral nerve-sparing procedure were more likely to have a positive margin when compared with those who underwent nerve resection on multivariable analysis (relative risk \((RR) = 1.52, 95\% \text{ CI: } 0.97–2.39\)) after adjusting for confounders. Patients with pT3-category disease who underwent a bilateral nerve-sparing procedure had no associated increase in risk of positive margin after adjustment for other variables \((RR = 0.96, 95\% \text{ CI: } 0.80–1.12)\). Prostate incision into tumor \((pT2R1)\) was significantly more likely in patients treated with robotic surgery \((RR = 1.76, 95\% \text{ CI: } 1.25–2.48)\) than in those with open surgery. There was no difference between laparoscopic and open RP \((RR = 0.86, 95\% \text{ CI: } 0.65–1.12)\).

Conclusions: Bilateral nerve sparing is associated with increased risk of positive SMs in patients with pathologic T2-category disease during RP. © 2014 Elsevier Inc. All rights reserved.

Keywords: Prostate; Carcinoma; Prostatectomy; Nerves

1. Introduction

Radical prostatectomy (RP) is a well-established treatment for men with clinically localized prostate cancer. The goals of this procedure are to achieve oncologic control while preserving urinary continence and erectile function, if possible. A nerve-sparing RP preserves the neurovascular bundles adjacent to the posterior-lateral prostate. It is associated with maintenance of erectile function and urinary continence [1–4]. However, a concern with nerve-sparing RP is that the closer dissection plane results in a higher risk of positive surgical margins (SMs). Previous studies
evaluating the relationship between nerve sparing and positive SMs have produced conflicting results, possibly owing to small sample size, incomplete information about potential confounders, lack of pathologic tumor stage stratification, or being performed in a noncontemporary era [5–11].

Positive SMs can occur in patients who have extraprostatic disease (pT3) and in patients with organ-confined (pT2) disease [12]. Prostate incision into organ-confined tumor can occur when the plane of surgical dissection is carried into the prostate. Pathologically, it is defined as tumor extension to the inked margin in the same plane where benign prostatic acini also extend to the inked margin [13,14]. Prostate incision into tumor (pT2R1) during RP increases the risk of biochemical recurrence and may decrease cancer-specific survival [14,15]. A positive SM has important implications for adjuvant treatment and is possibly an indication of poor surgical quality [16–18].

Our objective was to evaluate the effect of nerve sparing on risk of positive margins in patients with pT2- and pT3-category disease using a large multisurgeon prospective cohort of contemporary RP patients. We hypothesized that the close prostate dissection required for neurovascular bundle preservation would increase the risk of positive SMs.

2. Materials and methods

2.1. Patient selection

After receiving institutional review board approval, we evaluated a historical cohort of 9,915 consecutive RP patients treated at The Ottawa Hospital (n = 866) or Memorial Sloan-Kettering Cancer Center (MSKCC, n = 9,049) between 2000 and 2010 for clinically localized prostate adenocarcinoma. Patients who received preoperative androgen deprivation, who underwent preoperative prostate radiation therapy, who were operated on before 2000, or who had incomplete data were excluded. Data were combined to enhance generalizability through inclusion of a broader range of surgeons and settings.

2.2. Surgical technique

All patients underwent a RP performed by 1 of 19 surgeons at MSKCC or by 1 of 3 surgeons at the Ottawa Hospital. The approach was not standardized and procedures were performed by open, laparoscopic, or robotic technique. Patients underwent nerve resection, unilateral nerve sparing, or bilateral nerve sparing. The decision to spare or resect nerves was at the discretion of the surgeon and patient based on preoperative sexual function and extent of disease. No information was available on intrafascial or interfascial periprostatic dissection. Furthermore, no information was available for the extent of “wide dissection” during non–nerve-sparing procedures.

2.3. Pathologic technique

Dedicated genitourinary pathologists reviewed all pathology specimens at both centers. Intact RP specimens were fixed in formalin, inked to determine SMs in the fresh state, serially sectioned, and entirely submitted for histologic examination. The inked apical margin was assessed via the perpendicular coned technique. The most apical 3-mm portion of the gland is sectioned from apex to base at approximately 3-mm intervals and entirely submitted. Pathologists assessed prostate specimens for grade, category, SM status, and the presence of extraprostatic extension. A positive SM was consistently defined as tumor extending to the inked surface of the prostatectomy specimen. Prostate incision into tumor (pT2R1) was defined as tumor at the inked margin in the same plane where benign prostatic acini are at the inked margin. The location and extent of prostate incision into tumor was not available.

2.4. Statistical analysis

Descriptive statistics were used to characterize the study subjects. The primary outcome was the presence of a positive SM on the prostatectomy specimen. This was evaluated a priori in the overall cohort and in category-stratified cohorts (pT2 and pT3). The association between nerve sparing and a positive margin was assessed using univariable and multivariable logistic regression analyses. Adjustments for prostate-specific antigen (PSA; continuous), pathologic Gleason sum (categorical <7, 7, and >7), pathologic category (pT2 and pT3; only in the overall model), RP modality (categorical open, pure laparoscopic, and robotic-assisted laparoscopic), year of prostatectomy (continuous), and location (The Ottawa Hospital or MSKCC) were made in the multivariable model. The tests were 2-sided with P < 0.05 considered statistically significant. Confidence intervals are 95% when reported. Statistical analyses were conducted using SAS v9.2 (SAS Institute Inc, Cary, NC).

3. Results

Patients who received preoperative androgen deprivation (n = 369), who underwent preoperative prostate radiation therapy (n = 5), who were operated on before 2000 (n = 178), or who had incomplete data on nerve sparing (n = 2,621), pathologic category (n = 298), preoperative PSA (n = 238), or surgical modality (n = 86) were excluded, leaving 6,120 patients included in the analysis. Of the eligible patients, most had clinical T1c-category (3,814/5,872, 65.0%) and Gleason 6 disease on biopsy (3,086/5,877, 52.5%). Detailed patient and disease characteristics are presented in Table 1. Patients underwent open...
patients who underwent bilateral nerve sparing were more likely to have prostate incision into tumor (RR = 1.33; 95% CI: 0.84–2.10) than those with nerve resection were (Table 4). After adjusting for available potential confounders (PSA level, RP Gleason sum, RP modality, RP year, and institution) patients with bilateral nerve sparing remained more likely to have a positive SM (RR = 1.52; 95% CI: 0.97–2.39; P = 0.069) than those who had nerve resection (Table 4).

Prostate incision into tumor (pT2R1) occurred in approximately 4.6% (72/1,566) of laparoscopic cases, 6.1% (242/3,958) of open cases, and 8.2% (49/596) of robotic cases. Prostate incision into tumor was significantly more likely to occur in patients treated with robotic surgery (RR = 1.76; 95% CI: 1.25–2.48; P = 0.001) vs. those with open surgery. There was no difference between those undergoing laparoscopic and open RP (RR = 0.86; 95% CI: 0.65–1.12; P = 0.266). The risk of prostate incision into tumor has decreased over time (RR = 0.93 per y; 95% CI: 0.90–0.97; P = 0.001). Preoperative PSA level and pathologic Gleason score were significantly associated with prostate incision into tumor (Table 4).

3. Pathologic pT3-category cohort

Among patients with pT3-category tumors, bilateral nerve sparing was not associated with a significantly altered risk of a positive SM on univariable analysis (RR = 0.94; 95% CI: 0.78–1.13) or multivariable analysis after adjusting for available potential confounders (RR = 0.96; 95% CI: 0.80–1.16; P = 0.698). Preoperative PSA, RP year, and location (Ottawa vs. MSKCC) were significantly associated with risk of a positive SM (Table 5).

4. Discussion

The benefits of nerve-sparing RP on erectile function and urinary continence have been shown in multiple observational studies [1–4]. However, our study reveals that patients with organ-confined cancer (pT2) who undergo a nerve-sparing RP

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**Table 1**

Demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Bilateral (n = 5,429)</th>
<th>Nerve sparing (n = 441)</th>
<th>Resection (n = 250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>59.2 ± 7.1</td>
<td>60.6 ± 6.9</td>
<td>62.3 ± 7.5</td>
</tr>
<tr>
<td>Mean PSA, ng/ml (SD)</td>
<td>6.3 ± 5.8</td>
<td>8.3 ± 8.5</td>
<td>9.4 ± 10.2</td>
</tr>
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Clinical category (*) (%)

- T1: 3,559 (68.3)
- T2: 1,571 (30.1)
- T3: 83 (1.5)

Pathologic category (%)

- T2: 3,927 (72.3)
- T3: 1,502 (27.7)

Biopsy Gleason sum (%)

- 0–6: 2,928 (56.2)
- 7: 1,957 (37.5)
- >7: 329 (6.3)

RP Gleason sum (%)

- 0–6: 1,846 (34.2)
- 7: 3,274 (60.6)
- >7: 286 (5.3)

RP year (%)

- 2000–2005: 2,709 (49.9)
- 2006–2010: 2,720 (50.1)

Surgical modality (%)

- Open: 3,491 (64.3)
- Laparoscopic: 1,392 (25.6)
- Robotic: 556 (10.1)

Note: Bold indicates those with a positive surgical margin for emphasis.
are at an increased risk (RR = 1.52, 95% CI: 0.97–2.39) of a positive SM compared with patients undergoing either unilateral or bilateral nerve resection. Although not statistically significant (P = 0.069), the lower bound of the confidence interval bordering 1.0 suggests an increased risk of a positive margin in patients with pT2-category disease who undergo nerve-sparing RP. The point estimate increases from univariable to multivariable analysis (RR = 1.33 to RR = 1.52) suggesting that significance might be attained with a larger sample size or if additional variables such as tumor volume or margin length were included in the model.

In this study, the overall risk of a prostate incision into tumor (pT2R1) was low (5.9%), and within the range of other reported studies (1.3–33%) [13,19–24]. Prostate incision into tumor (pT2R1) has been shown to have a detrimental effect on biochemical recurrence-free survival and potentially, cancer-specific survival [13,14,19–21, 25,26]. In a prior analysis, we found that patients with pT2R1 had a higher risk of PSA recurrence (recurrence-free survival = 0.77, CI: 0.72–0.83) compared with those with pT2R0 (recurrence-free survival = 0.94, CI: 0.93–0.95) and those with completely resected, extraprostatic disease (recurrence-free survival = 0.86, CI: 0.84–0.87) [14]. In addition to worse cancer outcomes, positive SMs may result in adjuvant or salvage radiotherapy [16–18]. This additional local therapy, while possibly beneficial from an oncologic perspective, has adverse effects on sexual, urinary, and bowel function [16–18].

The pathologic category pT3 analysis found no association between nerve sparing and risk of positive SM (RR = 0.96; 95% CI: 0.80–1.16; P = 0.698). Preoperative PSA, year of surgery, and institution were also significantly associated with positive SM among patients with pT3-category disease. Unfortunately, we did not have information on the extent of extraprostatic extension, tumor volume, or extent of positive margin. All of these factors could be important considerations when interpreting these results. It is likely that patients with pT3 disease who underwent nerve resection had more extensive tumor than those who underwent a nerve-sparing procedure. The effect of this potential selection bias is unknown, but may underestimate the beneficial effects of wide dissection for patients with pT3-category tumors.

These results do not suggest that nerve-sparing RP should not be performed. In fact, nerve sparing should be performed, and encouraged, in men with acceptable risk of extraprostatic extension and good sexual function [27]. However, these results do have implications on operative planning for patients with poor preoperative erectile function where unilateral/bilateral nerve resection or interfascial dissection may be most appropriate. Individual surgeon experience and surgical technique likely affect risk of positive SMs and should also be taken into consideration [28–30].
Previous studies have also observed an association between nerve sparing and risk of positive SM [7,10]. Although Palisaar et al. [7] found a pT2 positive margin rate of 10.6% and no overall association between nerve-sparing procedures (bilateral and unilateral sparing vs. nerve resection) and PSA failure, they did note a significant 5-fold increase in positive margins at the lateral aspect of the prostate in patients with organ-confined cancer who underwent a nerve-sparing procedure compared with those who underwent a non–nerve-sparing procedure (26/843 [3%] vs. 4/669 [0.6%]; P = 0.001). The comparison group for the non–nerve-sparing procedure came predominantly from an older cohort (1992–1995) before PSA screening was commonly performed and, subsequently, had more advanced disease.

Other studies have not have not found nerve sparing to be an independent predictor of positive SMs [6–8,11,12]. Most of these studies were performed before 2000, were performed by a single surgeon, were not stratified by category (pT2 vs. pT3), or had a sample size fewer than 1,000 men. The largest study, performed by Ward et al. [6], found that in patients who were operated on between 1990 and 2000, the risk of positive SMs in patients undergoing a nerve-sparing procedure was 0.86 (95% CI: 0.76–0.97, P = 0.012) when compared with those undergoing resection after incorporating age, clinical stage, biopsy grade, year of surgery, and PSA level in the analysis. The finding that nerve sparing prevented positive SMs seems to suggest the presence of an unmeasured confounder such as tumor volume. An alternative theory is that nerve sparing improves periprostatic anatomic dissection, thereby resulting in fewer positive margins.

In the present study, surgical modality was associated with risk of positive SM. Prostate incision into tumor was significantly more likely in patients treated with robotic surgery (RR = 1.76; 95% CI: 1.25–2.48; P = 0.001) vs. those treated with open surgery. There was no difference between patients undergoing laparoscopic and open RP (RR = 0.86; 95% CI: 0.65–1.12; P = 0.266). Williams et al. [30] reported a similar finding in their study comparing open radical retropubic prostatectomy with robotic-assisted laparoscopic prostatectomy, each performed by a single surgeon. They found that men undergoing robotic-assisted laparoscopic prostatectomy were significantly more likely to have a positive margin (adjusted odds ratio = 1.9; 95% CI: 1.2–3.1; \(P = 0.0095\)) when compared with those treated with radical retropubic prostatectomy. Whether this difference is because of the learning curve associated with the robotic procedure or potentially secondary to the benefit of magnification and improved optics of robotics leading to more intrafascial dissection is unclear.

Other factors found to be associated with positive SMs were institution and year of surgery. A positive SM was significantly associated with RP performed for pT3-category disease in Ottawa vs. MSKCC (RR = 1.66, 95% CI: 1.16–2.39). This may be because of the varied techniques or extent of wide local excision. Prostate incision into tumor (pT2R1) was less likely to occur in more recent years (RR = 0.93, 95% CI: 0.90–0.97). This may be the result of decreased tumor volume owing to PSA screening and the associated staging migration or to individual surgeons gaining expertise with additional cases performed.

The strengths of our study include the large sample size, pathologic category-stratified analysis, and multi-institutional nature incorporating many (22) surgeons at varied levels of experience. Furthermore, the inclusion of patients treated by open, laparoscopic, and robotic approaches is a unique feature and emphasizes the generalizability of our results.

Our study is limited because it is a historical cohort and is susceptible to bias and unadjusted confounding. There is clear patient selection bias in that surgeons and patients are more likely to choose a non–nerve-sparing procedure for larger or more extensive tumors. Furthermore, we were unable to adjust for the likely confounding effects of prostate volume, tumor volume, extent of extraprostatic extension, and periprostatic fascial dissection technique (intrafascial/interfascial). The clinical implications of a positive margin are also limited owing to the lack of information about margin size and location. This study took place in academic institutions and thus the results may not be directly transferable to nonacademic hospitals. However, given that rates of 30% have been reported in population-based studies with pT2R1 (with no significant difference between community and teaching hospitals), it is
probable that the association between nerve sparing and positive SMs exists similarly in both academic and non-academic centers [24].

Clinical nomograms for estimating the extent of disease, consideration of pre-existing erectile function, and use of prostate magnetic resonance imaging in cases with higher risk features may help patients and surgeons balance the benefits and risks of nerve-sparing RP. Future prospective studies and possibly a randomized trial of nerve sparing for patients with higher-risk disease may clarify the effect of nerve preservation on cancer-related and functional outcomes.

5. Conclusion

Bilateral nerve sparing during RP is associated with increased risk of positive SMs in patients with pathologic organ-confined prostate cancer. These data highlight the challenges of balancing oncologic and functional outcomes in RP in addition to the learning curve associated with technologic advancement.

References