Predictors of positive surgical margins after radical perineal prostatectomy

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Introduction/objective: *Margin positivity has been a well described adverse prognostic factor in patients undergoing radical prostatectomy. Previous studies with regards to predictors of margin positivity after prostatectomy have primarily focused on the retropubic or robotic approach. We sought to examine the predictors of margin positivity in a contemporary series of men undergoing radical perineal prostatectomy (RPP).*

Materials and methods: *We reviewed the records of 103 patients who underwent RPP at our institution from July 1998 until May 2008. A positive surgical margin (PSM) was defined as the presence of cancer cells at the inked margin of the surgical specimen. Records were reviewed for the following preoperative parameters: age at operation, body mass index (BMI), preoperative PSA, clinical stage and biopsy Gleason sum score. Pathological data included prostate weight (PW) and tumor volume.*

Results: *Mean age was 60.9 (range 45-76). Mean BMI was 31.4 kg/m2 (20.9-51.6). The preoperative prevalence of palpable disease was 50.5%. A PSM was found in 23.3%. Age, BMI, clinical stage, biopsy Gleason sum score and preoperative PSA were not found to be independent predictors of a PSM after RPP. Only prostate weight was found to be a significant preoperative predictor of a PSM after RPP with men with smaller prostates at higher risk.*

Conclusions: *Prostate weight was found to be significantly and inversely related to the PSM rate in this cohort of RPP patients. Patients with smaller volume prostates should be counseled preoperatively that they are at higher risk for a PSM when undergoing a RPP.*

Key Words: prostate cancer, perineal prostatectomy, positive margin, predictors

Introduction

In men with clinically localized prostate cancer, radical prostatectomy offers the potential for long term cancer control. Despite improved surgical techniques, however, positive surgical margins (PSM) occur in approximately 25% of men undergoing radical prostatectomy.[1] PSMs are an adverse prognostic factor and men with PSMs have been shown to be at greater risk for biochemical recurrence, local recurrence and distant metastatic disease.[2] Men with PSMs are also more anxious and fearful of cancer recurrence than those with negative margins.[3] Therefore, the ability to predict which patients might be at risk for PSM is important in preoperative counseling.

In previous studies, preoperative PSA, clinical stage and Gleason sum score have been shown to predict PSM and pathological stage in a group of men undergoing radical retropubic prostatectomy (RRP) for localized prostate cancer.[4] More recently, investigators have focused on predictors of PSMs in men undergoing

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robotic-assisted laparoscopic prostatectomy (RALP).[5] Radical perineal prostatectomy (RPP) also offers select patients a more minimally invasive approach to surgical treatment of localized prostate cancer and therefore there has been renewed interest in RPP at some centers.[6] In an effort to provide better preoperative counseling to patients, we sought to examine the preoperative predictors of PSMs in a contemporary series of men undergoing RPP.

Patients and methods

All patients who underwent RPP at our institution between July 1998 and May 2008 were reviewed. Procedures were performed by a single surgeon. A pelvic lymphadenectomy was not performed at the time of operation. After obtaining institutional review board (IRB) approval, all preoperative and operative data were recorded in our institutional database. Patients who underwent a salvage perineal prostatectomy after radiation therapy were excluded. The technique for RPP at our institution has been previously described.[7]

Data were analyzed according to age, preoperative PSA, body mass index (< 30, > 30 kg/m^2), biopsy Gleason sum score (2 to 6, 7, 8 to 10), clinical stage (nonpalpable T1 or palpable T2 or greater), margin status, prostate weight (< 40 g, > 40 g) and pathological stage. Clinical staging was performed as described by the 2002 American Joint Committee on Cancer Staging, 6th Edition. Complete fresh specimen weight was calculated for prostate weight. A PSM was defined as the presence of cancer cells at the inked margin of the surgical specimen.

Statistical analysis

Factors associated with positive surgical margins were explored. The associations between the subject's BMI (≥ 30), PSA(≥ 10), preoperative Gleason sum scores, clinical stage, tumor volume (> 10%) and pathological stage were analyzed with a Chi-square test or Fishers Exact test depending on percent of cells that had an expected counts less than five. These variables and prostate weight were concurrently analyzed continuously with ANOVA to illustrate potential group difference by subject's surgical margin status. Salient factors identified from these analyses were entered into a stepwise logistic analysis. These effects were then modeled with a criterion for entry into the model was set at $p < .1$ with a retention criterion $p < .05$. All analyses were conducted with SAS 9.1 software (SAS Institute Inc., Cary, NC, USA). A type I error rate of 5% was used to determine statistical significance.

TABLE 1. **Demographic and pathologic data**

No. pts	103
Mean ± SD age (range)	60.9 ± 7.8 (45-76)
Mean ± SD PSA (range)	6.1 ± 3.2 (0.4-20.3)
Mean ± SD BMI (range)	31.4 ± 7.5 (20.9-51.6)
No. BMI (%)	
< 30 kg/m^2	50 (48.5)
> 30 kg/m^2	51 (49.5)
Unknown	2 (2)
No. biopsy Gleason score (%)	
2-6	67 (65)
7	30 (29)
8-10	6 (6)
No. clinical stage (%)	
T1	51 (49.5)
T2 or higher	52 (50.5)
No. margin status (%)	
Negative	79 (76.7)
Positive	24 (23.3)
Mean ± SD prostate weight (g) (range)	34.6 ± 12.3 (13-67)
No. prostate weight (%)	
< 40 g	70 (68)
> 40 g	27 (26.2)
Unknown	6 (5.8)
No. tumor volume (%)	
> 10%	57 (55)
< 10%	38 (37)
Unknown	8 (8)

Results

Our study group consisted of 103 men who underwent RPP during the study period and met the criteria for inclusion. Patient demographics are shown in Table 1. The mean age of the RPP cohort was 60.9 ± 7.8 years

TABLE 2. **Location of positive margins**

Site	**No. pts (%)**
Multifocal	7 (30.4)
Posterior	5 (21.7)
Apical	5 (21.7)
Anterior	3 (13)
Unknown	2 (8.7)
Bladder neck	1 (4.4)

TABLE 3. **Factors associated with surgical margins**

	Negative margin	Positive margin	F	χ^2	p
Age (mean ± SD)	60.66 + 7.81	61.83 + 7.78	.42		.519
PSA (mean ± SD)	5.91 + 2.84	6.79 + 4.25	1.39		.241
Prostate weight (mean ± SD)	36.10 + 12.34	29.65 + 10.83	5.06		.027*
BMI (mean ± SD)	31.55 + 7.50	1.09 + 7.85	.07		.795
Biopsy Gleason score ≥ 7 No. patients (% of each group)	29 (36.7)	7 (29.2)		.46	.497
Clinical stage ≥ T2 No. patients (% of each group)	40 (50.6)	12 (50)		.003	.957
Path stage ≥ T2c No. patients (% of each group)	70 (88.6)	16 (66.7)		6.43	.011*
Tumor volume > 10% No. patients (% of each group)	42 (56.7)	15 (71.4)		1.48	.226

(range 45-76). The mean BMI of the cohort was 31.4 ± 7.5 kg/m^2. Fifty-one patients (50%) were considered obese with BMI > 30 kg/m^2. Mean preoperative PSA was 6.1 ± 3.2 ng/dl (range 0.4-20.3). Sixty-seven patients (65%) had a Gleason sum score of 6 or less on prostate biopsy, 30 patients (29.1%) were Gleason 7 and 6 patients (5.8%) had Gleason 8 or higher. Fifty-one patients (50%) had nonpalpable clinical T1 disease. Twenty-four patients (23.3%) had either a single positive margin or multiple positive margins. The locations of the positive margins is shown in Table 2. Eighty-six patients (83.5%) had organ confined disease (pT2) on final pathology. Of these pT2 patients, 16 (18.6%) had a PSM. Fifty-seven patients (55%) had pathological tumor volumes > 10%.

The univariate analysis is shown in Table 3. Both prostate weight and pathological stage were associated with PSMs. Prostate weight was inversely related to PSM (F (1,95) = 5.06, p = .027). Pathological stage (T3 or higher) was also predictive of PSM ($\chi^2(1) = 6.43$, p = 0.011). Tumor volume (> 10%) was not associated with a PSM. A multivariable analysis of these factors predicting positive surgical margins is shown in Table 4. From the table, pathological staging above T2c increases the odds of positive surgical margins ≈ approximately 5.4 times. Concurrently, decreasing prostate weight increases the same odds ≈ approximately 1.06 times. No interaction between these factors was noted (Wald $\chi^2 = 1.508$, p = .219).

Discussion

PSMs are a risk factor for progression after radical prostatectomy. In order to improve preoperative counseling, multiple studies have looked at predictors of PSMs after radical prostatectomy. These studies have focused on the more popular retropubic and robotic approaches to prostatectomy. RPP in contrast to RRP offers select patients quicker recovery, less blood loss, lower transfusion rates and shorter hospital stays.[6] More specifically, RPP might be the surgical choice for obese men and those who have had prior abdominal or inguinal surgery in which postoperative adhesions might make either RRP or RALP difficult. In an effort

TABLE 4. **Stepwise logistic model for positive margins**

Factor	DF	Parameter	Error	χ^2	p	Adj. odds ratio	Confidence interval
Pathological stage > T2c	1	-.8469	.0310	7.46	.006	5.43	1.61-18.5
Prostate weight	1	-.0592	.0255	5.40	. 02	1.06	1.01-.1.61

to help counsel these patients, our study evaluated risk factors for PSMs in patients undergoing RPP. We found that BMI was not a predictor of PSMs in RPP patients, but that prostates of lower weight were predictive of PSMs. Not surprisingly, patients with T3 disease were also more likely to have positive margins.

Increased BMI has been shown to be an independent predictor of positive margins in a group of obese men undergoing RP.[8] Obese men with BMI > 35 kg/m^2 were more likely to have PSMs at the apex suggesting that this an iatrogenic PSM related to difficulty of an apical dissection in obese men.[8] In men undergoing RALP, there has been conflicting data regarding the impact of obesity on PSMs. Boorjian et al studied 400 consecutive men undergoing RALP and divided them into three groups based on BMI: < 25 kg/m^2, 25 kg/m^2-29 kg/m^2 and > 30 kg/m^2.[9] They found that increasing BMI was not significantly associated with an increased risk of PSMs. However, in another study of obese patients undergoing RALP, Herman et al demonstrated that both overweight (BMI 25 kg/m^2-29 kg/m^2) and obese men (BMI > 30 kg/m^2) had significantly higher rates of PSMs (20% and 21%, respectively) than did men with a normal BMI (11%).[10] They concluded that RALP was more technically challenging in these overweight and obese men.

In our study, increasing BMI was not a significant predictor of PSMs in patients undergoing RPP. This finding is particularly important in that RPP is frequently the surgery of choice for obese men. RPP avoids a potentially significant abdominal pannus and the dorsal venous complex and can be accomplished with acceptable perioperative morbidity in obese men.[11] In our study, the mean BMI was 31.4 kg/m^2 and about one half of patients in our series were obese based on their BMI. The fact that these obese men are not at higher risk for a PSMs is important for our preoperative counseling.

Our study also found that prostate weight was an independent predictor of a PSM with prostates of lower weight having a greater risk of having a PSM. To our knowledge, this is the first study to show this relationship in RPP patients, although other studies of RRP and RALP patients have shown a similar finding. Hsu et al calculated the prostate volume for patients undergoing RRP using the formula [π/6 (length x width x height)] and found that the margin status was significantly and inversely related to prostate volume.[12] The PSM rate was 1.8 times greater for men with prostates less than 25 cm^3 than for those with prostates greater than 51 cm^3. In a large series of men undergoing RALP, Msezane et al reported a 25.4% PSM rate in prostate weights < 50 g, 14.4% in 50 g-70 g, and 7.5% in > 70 g ($p < 0.001$).[13] In their multivariate analysis, lower prostate weight was a risk factor for PSM. In our study, we had an overall PSM rate of 23.3% after RPP. We divided PW into < 40 g and > 40 g and found that patients with PW < 40 g were significantly more likely to have a PSM. Thirty percent of patients with PW < 40 g had a PSM compared with 7% of patients with PW > 40 g ($p < 0.05$).

Previous studies using other surgical approaches have commented on likely explanations for this inverse relationship between PW and PSMs. The peripheral zone of the prostate is the most common location for prostate cancer. In a smaller gland, there is substantially decreased peripheral zone volume when compared to a patient with larger prostate. Therefore, it is more likely that a prostate tumor will be closer to the capsule thus increasing the chance for inadvertent excision into capsule with a resulting PSM.[13] Another explanation is that smaller prostates have higher tumor volumes thus increasing PSM. In order to assess if higher tumor volume could explain our findings, we analyzed tumor volumes < 10% and > 10% and did not find a significant association between tumor volume and PSM, Table 3.

Lead time bias has also been theorized to play a role in the inverse relationship between PW and PSM.[14] Larger prostates are associated with higher PSA primarily because of the presence of a large amount of benign hyperplastic tissue. Men with large prostates and a high PSA (chiefly driven by benign hyperplasia) are going to undergo a biopsy earlier when any cancer present is likely going to be at a lower clinical stage leading to less PSM.[14] Men with smaller prostates and a comparatively high PSA are going to be biopsied when their cancer is at a higher clinical stage thus making them at higher risk for a PSM.

There are several limitations to our study. Our study is retrospective and limited to the experience of one surgeon at one institution. Sectioning of the prostate specimens was done by several different pathologists which may have led to different interpretations of margin status. Similar to other studies, we used specimen weight and not preoperative tumor volume based on transrectal ultrasonography (TRUS).[13] As a tertiary referral center, many of these patients were sent to our institution by community urologists specifically for a RPP. Some patients did not have a TRUS volume calculated. Even for those patients that did have a volume calculated, the wide array of urologists performing the preoperative TRUS precluded any meaningful way to standardize these measurements. Therefore, we used the postoperative specimen weight. Previous studies have shown

that TRUS underestimates prostate volume when compared with specimen weight after prostatectomy.[15] In our preoperative counseling we feel confident in letting patients know that if they have a heavy volume prostate gland calculated on TRUS, then they most likely will have a heavy prostate gland when weighed after prostatectomy. We also do not have long term follow up on many of these patients to see if a PSM after RPP impacts biochemical recurrence or survival.

Conclusion

Predictors of PSM can be helpful during preoperative counseling of patients undergoing radical prostatectomy. We found that increased BMI did not predict PSM in patients undergoing RPP and therefore this surgical approach can be safely offered to obese men. Preoperative counseling of RPP patients should also include prostate weight as men with smaller prostates were at increased risk of PSMs. Further studies are needed to assess predictors of recurrence free and overall survival in RPP patients. □

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