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Positive surgical margins during robotic radical prostatectomy: a contemporary analysis of risk factors

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Abstract

Objective—To determine the risk factors (clinical, pathological and technical) for positive surgical margins (PSMs) after robotically assisted radical prostatectomy (RARP), as a PSM is associated with an increased risk of biochemical recurrence and often responsible for significant patient anxiety.

Patients and Methods—Between November 2003 and March 2007, 216 consecutive patients had an RARP by one fellowship-trained urological oncologist. The surgical pathological specimens were fixed and processed using standard techniques, and assessed by a pathologist at the same institution. A PSM was defined as the presence of cancer adjacent to the inked margin. The clinical charts were reviewed retrospectively under an approved institutional review board protocol. Univariable and multivariable methods, including logistic regression models, were used to analyse the clinical, pathological and technical risk factors for PSM.

Results—The overall prevalence of PSM was 14.8% (32/216), and 5.4% (8/149) for pT2 cancers. The only preoperative factor that was associated with a greater risk of a PSM was the serum prostate-specific antigen (PSA) level ($P = 0.012$) and PSA density ($P = 0.005$). Age, clinical stage and clinical Gleason grade were not predictors of a PSM. The overall and pT2 PSM rate remained constant throughout the series of 216 patients ($P = 0.371$), indicating that the initial experience for RARP was not associated with a significantly greater risk of a PSM. However, there was a small independent ‘learning curve’ effect, with a lower rate of PSM associated with each increment of 25 patients (odds ratio 0.8, 95% confidence interval 0.6–1.0), supported by the significantly decreasing trend in PSM for pT3 cancers over time ($P = 0.031$). Although there was no significant increase over time in PSM with the use of an endostapler to control the dorsal venous complex (DVC), there was a significant learning effect, with a decrease in the PSM rate specifically in pT3 cancers using the suture technique ($P = 0.005$). A nerve-sparing procedure

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increased the risk of PSM in multivariable analysis ($P = 0.03$). As expected, pathological stage and pathological Gleason grade were the strongest predictors of PSM ($P < 0.001$).

Conclusion—The most important risk factors for a PSM after RARP are the preoperative PSA level, PSA density, pathological stage and Gleason grade. PSM rates for a surgeon in their initial experience can be comparable to that of a surgeon experienced in RARP. Using a stapling device to control the DVC does not appear to increase the risk of a PSM, although nerve-sparing increases the rates of PSM in extraprostatic prostate cancer.

Keywords

prostate cancer; surgical margins; robotic; PSA

Introduction

A positive surgical margin (PSM) after radical prostatectomy (RP) is associated with a greater risk of biochemical recurrence and often is the cause of significant patient anxiety [1]. The introduction of PSA testing, a better understanding of prostatic anatomy, and improvements in surgical technique have dramatically reduced the risk of PSMs [2]. Despite this, a PSM remains a significant clinical problem, as it has been reported to be up to 12–43% in contemporary series of open RP [2–4]. The popularity of robotic radical prostatectomy (RARP) has been growing exponentially, and it was suggested that the use of the DaVinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA) can reduce the incidence of PSMs [5–7]. Enhanced visualization and reduced blood loss associated with RARP have been cited as theoretical factors that could reduce PSM. Ahlering *et al.* [8] suggested that dissecting the periprostatic fat to expose the prostatic apex, and the use of a vascular stapler to control the dorsal venous complex (DVC) are specific surgical manoeuvres in RARP responsible for reducing the risk of PSM. The risk of PSM appears to be inversely proportional to the surgeon's experience, but the exact relationship and number of cases to achieve stability is unknown.

In addition to technical aspects, the risk of a PSM probably depends on clinical and pathological factors, e.g. stage, serum PSA level and Gleason sum [9,10]. The objective of the present study was to determine the risk factors for PSM in a contemporary series of RARP, assessing specifically the effect of surgeon experience, surgical technique (method used to control the DVC), stage (clinical and pathological), PSA levels, PSA density, Gleason score and prostate volume on PSMs.

Patients and Methods

Between November 2003 and March 2007, 216 consecutive patients underwent RARP by one fellowship-trained urologist oncologist (D.K.O.); their clinical characteristics (age, preoperative PSA level, biopsy and pathological Gleason sum, and prostate volume) are shown in Table 1. Clinical charts were reviewed retrospectively under a protocol approved by the institutional review board.

The RARP specimens were cut into 5 mm axial sections, formalin-fixed and routinely processed for paraffin embedding. Subsequently the embedded specimens were cut into 5 µm sections and stained with haematoxylin and eosin. A PSM was defined as the presence of ink on prostate cancer cells in the primary specimens. The pathological findings were determined by one of five fulltime faculty pathologists at the authors' institution.

All patients had RARP via a transperitoneal approach; when indicated, a nerve-sparing procedure and/or standard obturator lymph node dissection was done robotically. The DVC was controlled with a 45-mm EndoGIA® (Ethicon, Somerville, NG, USA) stapler in the first 82 patients and then by suture ligation in the subsequent 134. In both approaches the anterior prostatic surface, puboprostatic ligaments and DVC were de-fatted for better visualization before stapling or suturing. The ligation was done with two 0 polyglactin sutures (one 'back bleeder' suture placed to help define the prostatic apex) before the bladder neck dissection, but the DVC was not divided until after the bladder neck had been divided and the seminal vesicle dissection had been completed.

Univariable and multivariable statistical methods, including logistic regression models, were used to analyse the clinical, pathological and technical risk factors for PSM. independent variables entered into the regression analysis included age, preoperative PSA level, clinical stage and Gleason score from the biopsy.

Results

The overall prevalence of PSM was 14.8% (32/216) and 5.4% (eight/149) for pT2 cancers (Table 2). There was no association between age and PSM (Table 1, $P = 0.361$), but after adjusting for pathological stage men aged >70 years had a lower rate of PSM (Table 1; Mantel-Haenszel chi-square, $P = 0.014$). The rate of PSM increased with increasing preoperative PSA level (Table 1 $P = 0.012$, Cochran's test for linear trend). PSM increased from one of 16 when the preoperative PSA level was 2.5 ng/mL, to eight of 29 (14%) when it was 10 ng/mL. Age-adjusted odds ratios for PSA level increased from ≈ 2 for a PSA level of 6 ng/mL to 16.2 for levels of >10 ng/mL. After adjusting for pathological stage, a higher PSA density was associated with an increased relative odds for PSM of 3.9 (Table 1; Mantel-Haenszel chi-square, $P = 0.005$). In the multivariable logistic regression analysis of preoperative variables only, increasing PSA level was associated with a greater risk of PSM after adjusting for age and prostate volume. For a PSA level of 10 ng/mL, the adjusted odds ratio suggests a 16-fold increase in the probability of PSM (odds ratio 16.2, 95% CI 1.6–161.1). Clinical stage and biopsy Gleason grade were also examined but did not predict PSM in univariable or multivariable analysis.

The overall and pT2 PSM rate remained fairly constant throughout the 216 patients and showed no significant change ($P = 0.371$). However, there was an effect of experience detected in the multivariable analysis controlling for nerve-sparing, pathological Gleason score, pathological stage, age and PSA density ($P = 0.025$; Table 3). In addition, there was a small independent 'learning curve' effect representing a lower rate for PSM associated with each increase in 25 patients (odds ratio 0.8, 0.6–1.0) favoured by the significantly decreasing trend in PSM for pT3 cancers over time ($P = 0.031$; Table 1). This trend paralleled a change

in surgical method to control the DVC. Although there was no significant increase over time in PSM with the use of the EndoGIA stapler to control the DVC ($P = 0.177$, linear trend) there was a significant 'learning effect' with a decrease in the PSM rate specifically in pT3 cancers using the suture technique ($P = 0.005$; Table 1). For pT2 tumours, the PSM rate for the nerve-sparing technique was 5.9%, vs 3.3% for no nerve-sparing, and for pT3 tumours, 39.5% vs 21.7%, respectively. Neither of these differences was statistically significant in the univariable analysis. However, in the multivariable logistic regression analysis, nerve-sparing surgery was associated with a significant increase in PSM ($P = 0.030$; odds ratio 5.5, 1.17–26.46) after adjusting for stage, age and pathological Gleason score (Table 3).

As expected, there was also a significant effect for pathological stage, with a higher PSM rate for pT3 vs pT2 (Table 1, $P < 0.001$; unadjusted odds ratio 9.5, 3.9–22.8). There was a significant increase in PSM rate with increasing pathological Gleason Score ($P < 0.001$; unadjusted odds ratio 3.6, 1.9–6.8).

In multivariable analysis including all factors before during and after RARP, pathological stage was the most important predictor of PSM, with an adjusted odds ratio for stage T3 vs T2 of 9.2 (3.0–28.3) (Table 3). PSA density was the second most important predictor of PSM after pathological stage (3.4, 1.2–9.6 for PSA density > 0.15). Pathological Gleason score was associated with a greater risk of PSM independent of stage and PSA density; relative to a Gleason score of 6, the odds for a PSM were increased 2.4 times (1.1–5.5) for Gleason score 7 and 5.8 times (2.5–13.2) for scores of 8–9 after adjusting for covariates.

Discussion

A PSM after open RP is an established factor for biochemical recurrence and can be affected by preoperative factors, surgical technique and pathological factors. Although the association of a PSM after RARP with recurrence remains to be shown, probably it would be similar to that of open RP. In the present study of RARP the overall incidence of a PSM of 14.8% (32/216) and the pT2 PSM rate of 5.4% (eight/149; Table 2) is comparable to values reported elsewhere for both RARP and open RP, and compares favourably with that of laparoscopic RP [2–8,11–14].

In contemporary practice, clinical stage, serum PSA level and biopsy-determined Gleason score are the most commonly used factors to assess an individual patient's risk of having extraprostatic disease and a PSM [10]. Among the present men undergoing RARP, the only preoperative factors predictive of PSM were serum PSA level ($P = 0.012$) and PSAD ($P = 0.005$), which concurs with several previous studies [9,10]. When PSA was examined as a continuous variable, a PSA level of >10 ng/mL had a PSM rate 16 times higher than lower PSA levels. However, when the PSA values were divided into ranges, the risk increased by about half with a PSA level of 2.6–6 ng/mL, by about three times for 6–10 ng/mL and nearly eight times for >10 ng/mL category (Table 2).

PSA density was proposed as a method to improve the accuracy of PSA testing [15]. In the present study, multivariable analysis showed that the preoperative PSA density was one of the most significant factors for predicting the risk of PSM (Table 3). A PSA density of

>0.150 was significant for predicting PSM ($P = 0.005$). A PSA density of >0.150 corrected for age >70 years was associated with an increased odds ratio for PSM of 6.5 (Table 2). One caveat to the present study is that the pathological volume was used for the analysis rather than the TRUS-determined volume, as this information was not available for many of the patients who had had a prostate biopsy at another facility.

Surprisingly, clinical stage and the biopsy-determined Gleason grade did not predict PSM. Gao *et al.* [16] used a multivariable analysis in a low-risk population (PSA < 10 ng/mL, Gleason <7, and clinical stage T1c-T2b) and concluded that in these patients the biopsy Gleason score, PSA level and clinical stage did not correlate with extraprostatic extension or PSM. In the present patients we did not exclude the higher risk patients, which might explain the differences in our findings. Watson *et al.* [17] reported a significant trend suggesting that the prostate biopsy could be used to predict PSM status, in that 43% of those with a biopsy Gleason sum of ≥ 7 had a PSM, vs 30% of those with a Gleason sum of <7. That the present patients were from a heavily screened population could explain why there was no correlation between Gleason sum with PSM in the present study.

Surgical technique can clearly affect PSM and it has been suggested that the use of robotics in RP is one method to reduce PSM, particularly in patients with pT2 disease [2,8]. The present study does not directly evaluate the effect of robotic surgery on PSMs but provides evidence that an acceptable PSM rate can be achieved with RARP even among a surgeon's initial case experience. The learning effect was not shown in the univariable analysis, although there was an effect on PSM in the multivariable analysis adjusting for covariants (Table 3; $P = 0.020$). Several studies reported PSM rates in a surgeon's early experience, and suggested a 'learning curve' of 20–50 cases [5,18,19]. In the present series, >100 RARPs had been completed at our institution before assessing those in the present study. Our findings show a difference between an institutional and an individual surgeon's 'learning curve', and suggest that once an active RARP programme is established at an institution, other surgeons should be able to learn the procedure without compromising oncology efficacy during their early experience. The overall PSM was 14.8% (32/216) and 5.4% (eight/149) for pT2 cancers, and remained constant. The risk of PSM was comparable to that reported by other high-volume RARP surgeons [6,19].

Since Walsh's first description of the anatomical RP it has been widely accepted that among men with organ-confined disease (pT2) the use of a proper nerve-sparing procedure does not increase the risk of PSM or compromise cure rates. The present data are in conflict with this conclusion, as PSM rates increased in men having a nerve-sparing procedure, as shown in the multivariable logistic regression adjusting for stage, age and pathological Gleason score (Table 3). The increased risk of PSM was most pronounced for patients with pT3 disease, highlighting the need to find better preoperative predictors of pathological stage. The explanation for the increased risk of PSM for men having a nerve-sparing procedure is not clear, but might be the result of our robotic nerve-sparing technique. We have altered our nerve-sparing techniques to better replicate the anatomical procedure described by Walsh. Specifically, we now release the neurovascular bundles before dividing the pedicles, and do the posterior apical dissection retrogradely. The effect on PSM rates of this change is currently being evaluated.

It was suggested the method used to divide the DVC can affect the PSM rate; indeed, Ahlering *et al.* [8] suggested that using the EndoGIA stapler was a critical factor in reducing their rates of PSM. In our experience we did not find that stapling the DVC helped to reduce the PSM rate, as the rate did not increase when we began to control the DVC with suture ligation rather than the stapler. One explanation for the reduction in PSM rate is that the improved visualization of the apex that resulted from removing the peri-prostatic fat was responsible for reducing the PSM, rather than the method of controlling the DVC. Our current method to control the DVC includes placing a ‘back bleeder’ suture, which we think helps to define the prostatic apex. There is a significant ‘learning effect’ when using the suture technique, which takes the novice about 25 cases to decrease the PSM rate in pT3 prostate cancer, yet in the present study the overall and pT2 PSM rate did not increase with the change in technique. We agree with Ahlering *et al.*, that despite the technique used, a key factor in reducing the PSM rate during RARP is a meticulous dissection of the prostatic apex and the removal of peri-prostatic fat [8]. Following this strategy we had no positive apical margins among men with T2 disease.

As expected, the most important factors in predicting PSM were pathological stage and pathological Gleason sum. This suggests that the biology of the cancer is more important in determining the oncological outcome than surgical technique. It is our hope that improvements in imaging and molecular characterization of prostate cancer will ultimately lead to the elimination of PSMs.

In conclusion, the risk of a PSM during RARP is comparable or better than during open RP. The most important risk factors for a PSM during RARP are preoperative PSA density, pathological stage and Gleason grade. PSM rates for a surgeon in their initial ‘learning curve’ can be comparable to that of an experienced RARP surgeon. The technique of controlling the DVC does not affect PSM, but using a nerve-sparing procedure increases the risk of a PSM, particularly for those men with extraprostatic disease. As RARP can produce PSM rates comparable to open RP it is likely that cancer control rates will also be comparable. A longer follow-up is needed to confirm this assertion.

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Abbreviations

PSM	positive surgical margin
(RA)RP	(robotically assisted) radical prostatectomy
DVC	dorsal venous complex

Table 1
The characteristics of the 216 patients treated with RARP

Characteristic	Mean (SD)
Age, years	62.4
Preoperative PSA level, ng/mL	6.98
Biopsy Gleason score	6.5
Nerve-sparing procedure, % (unilateral or bilateral)	71
Pathological Gleason score	6.72
Prostate weight after RARP, g	53.2

Table 2
The frequency of PSM vs increasing age, preoperative PSA level, PSA density in pT2 vs pT3 prostate cancer, pT3 with suture technique (used in cases 83–216 to control the DVC, but only pT3 was assessed to show the effect on PSM status), with case number (divided into groups of 25), and with nerve-sparing procedure in pT2 and pT3 disease

	n (%)		
Variable	Negative	Positive	Total
Age, years ($P^* = 0.361$)			
<55	24 (80)	6 (20)	30
55–59	36 (88)	5 (12)	41
60–64	54 (88)	8 (12)	62
65–69	42 (81)	10 (19)	52
70	26 (96)	1 (4)	27
Total	182 (86)	30 (14)	212
PSA, ng/mL ($P^* = 0.012$)			
2.5	15 (94)	1 (6)	16
2.6–4.0	20 (91)	2 (9)	22
4.1–6.0	69 (91)	7 (9)	76
6.1–10.0	57 (83)	12 (28)	69
>10	21 (72)	8 (14)	29
Total	182	30	212
PSA density, ng/mL/mL ($P^{\ddagger} = 0.005$)			
pT2 ($P^{\ddagger} = 0.112$)			
0.015–0.150	104 (96)	4 (11)	108
>0.150	34 (90)	4 (4)	38
Total	138 (95)	8 (6)	146
pT3 ($P^{\ddagger} = 0.009$)			
0.015–0.150	25 (81)	6 (19)	31
>0.150	14 (48)	15 (52)	29
Total	39 (65)	21 (35)	60
Adjusted odds ratio			3.9
pT3 and suture technique (case series no.) ($P^* = 0.005$)			
83–107	2	5	7
108–132	5	3	8
>133	26 (81)	6 (19)	32
Total	33	14	47
Case number ($P^{\ddagger} = 0.7$)			
1–25	19 (83)	4 (17)	23
26–50	20 (80)	5 (20)	25
51–75	21 (91)	2 (9)	23

Variable	<i>n</i> (%)		
	Negative	Positive	Total
76–100	21 (84)	4 (16)	25
101–125	20 (80)	5 (20)	25
126–150	23 (92)	2 (8)	25
151–175	19 (83)	4 (17)	23
176–190	14	0	14
>191	25 (86)	4 (14)	29
Total	182 (85.8)	30 (14.2)	212
Nerve-sparing			
pT2 ($P^* = 0.574$)			
No	29 (97)	1 (3)	30
Yes	111 (94)	7 (6)	118
Total	140 (94.6)	8 (5.4)	148
pT3 ($P^* = 0.153$)			
No	18 (78)	5 (22)	23
Yes	23 (60)	15 (40)	38
Total	41 (67.2)	20 (33)	61
$P^\ddagger$ (adjusted for stage)			0.206

* Cochrane's linear trend;

† Pearson chi-square;

‡ Mantel-Haenszel chi-square.

Table 3
The multivariable model for the risk of PSM; McFadden's $p^2 = 0.277$

Variable	Estimate (SEM)	<i>P</i>	Odds ratio (95% CI)
Constant	−5.39 (1.23)	<0.001	
pT stage (pT2 vs pT3)	2.22 (0.576)	<0.001	9.16 (28.4–2.96)
PSA density (0.15 vs >0.15)	1.23 (0.527)	0.020	3.43 (9.63–1.22)
Age, years (<70 vs 70)	−2.12 (1.18)	0.072	0.120 (1.20–0.012)
Pathological Gleason score (4–6 vs 7 vs 8–9)	0.876 (0.422)	0.038	2.40 (5.50–1.05)
Case order* (1–9)	−0.258 (0.115)	0.025	0.773 (0.968–0.617)
Nerve-sparing (no vs yes)	1.719 (0.794)	0.030	5.58 (26.46–1.176)

* Case order = 1 for first 25, 2 for next 25, etc.