Impact of margin status at 37 months after robot assisted radical prostatectomy

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Introduction: *We evaluate the impact of margin length, location, and pathologic stage on biochemical recurrence (BCR) after robot assisted radical prostatectomy (RARP) at 37 months of follow up.*

Materials and methods: *A total of 1420 patients underwent a robot assisted radical prostatectomy between March 2004 and May 2010. Patients who received adjuvant therapy, those who never achieved an undetectable prostate-specific antigen (PSA), and those who had less than 18 months of follow up were excluded. Patients were then divided and evaluated based on margin status.*

Results: *In total, 419 patients were included in the analysis. Eighty-three had a positive surgical margin (PSM) (19.8%), 336 had a negative surgical margin (NSM) (80.2%). The overall mean follow up was 37 months. On multivariate analysis the Gleason sum and PSM were independent predictors of BCR. Margin length and location had no significant difference on the rate of BCR. Patients with a PSM and pT2 disease had an increased rate of BCR compared to pT2 and NSM. The relative risk of BCR was 2.03 and 3.21 for patients who have a PSM versus a NSM, overall and in those with pT2 disease respectively. No different BCR is seen in pT2 PSM versus ≥ pT3 NSM; or ≥ pT3 PSM versus NSM.*

Conclusion: *With 37 months follow up; positive surgical margin and postoperative Gleason sum impact the rate of BCR. Location and length of the PSM do not appear to have an impact on BCR. There was an increased risk of BCR with PSM, especially in pT2 disease.*

Key Words: prostatectomy, recurrence, positive surgical margin, margin length, margin location

Introduction

The impact of positive surgical margins (PSMs) on prostate specific antigen (PSA) biochemical recurrence (BCR) has been evaluated for both open radical prostatectomy (ORP) and robot assisted radical prostatectomy (RARP). While PSMs have been shown to be an independent predictor of BCR in most ORP series,[1-16] there are examples where there is no correlation.[17] The role of PSM in RARP is also controversial. Shikanov et al[18] have shown that a PSM in RARP is an independent predictor of BCR while Menon et al[19] found no significant association. Increasing length of PSMs have been associated with increased risk of BCR. Focal margins[20] and those less than 1 mm have been shown to have risk equal to

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negative surgical margins (NSMs);[18] whereas extensive PSMs[20] and PSMs greater than 3 mm have an increased risk of BCR compared to those with less than 3 mm margin involvement.[11] Specific location of a PSM has also been implicated in BCR. Posterolateral,[4] base,[1] and bladder neck[21] have been shown to portend a higher likelihood of BCR, while apical margins have various prognoses.[1,7,15,17,22-24] However, some authors have shown no significant difference in outcome (survival and BCR) based on location.[18,20] Controversy abounds in current literature regarding the importance of PSMs and BCR, particularly in RARP. Herein, we investigate the impact of margin status, the length of PSM, and location of PSM on biochemical recurrence in our robot assisted radical prostatectomy series of 431 patients.

Materials and methods

With IRB approval, a retrospective analysis was performed of a prospectively collected database of 1420 patients undergoing transperitoneal RARP from March 2004 to May 2010. We selected to evaluate only those patients with a minimum follow up of 18 months. Follow up data was available on 431 of these patients with clinically localized adenocarcinoma of the prostate. To fully evaluate biochemical recurrence; we elected to exclude patients who never achieved an undetectable PSA. Also, patients who received immediate adjuvant radiation or hormonal therapies were excluded. We collected demographic and perioperative data, as well as pathologic data. The patients were divided into two groups: Group 1 included those with PSMs, and Group 2 included those with NSMs.

Patient demographics, preoperative PSA, biopsy Gleason sum, clinical stage, pathologic stage and Gleason sum were compared between the two groups. In those with a PSM, the location and length of margin was further analyzed in relation to BCR. Statistical analysis was performed using SPSS Version 10.0, statistical package. The student t test was used for numerical variables; chi-squared test was performed for the categorical variables; univariate and a step-wise multivariate analyses was also performed. In all tests a p value < 0.05 was considered to be statistically significant. Kaplan Meier survival curves were generated using JMP Version 8.0; log rank test was used to determine significance.

The specimens were grossly and microscopically evaluated with a standard protocol including gross sectioning from apex to base and extensive sampling (> 50%) of the peripheral zone from apex to base. Urethral and bladder neck margins were separately evaluated. A PSM was defined as any tumor at the inked (peripheral zone, apical, or bladder neck) margin(s) of the specimen, as read by our pathologists. The ink simply needed to abut (touch) the tumor for it to be deemed a PSM and did not require transection of tumor. In order to standardize the findings, we had one pathologist evaluate the slides for PSM length. Reported length equals the total length of all positive margins if there were multiple sites in a given specimen with a positive margin.

Results

Of the 1420 patients treated with RARP, 18 months of follow up information was available for 431 patients. Seven of these patients never had an undetectable PSA, two had undergone immediate adjuvant radiation therapy and one was started on immediate hormone ablation, all were excluded from the analysis. In addition, two patients in the negative margin group were found to have pT0 disease, and were also excluded. Of the 419 patients analyzed, 83 had a PSM (19.8%), while 336 had a NSM (80.2%). The comparison of the patient characteristics and pathologic information between the two groups is summarized in Table 1, and characteristics of those with PSMs are summarized in Table 2. The overall mean follow up was 37 months (18-71). Those with PSMs had a mean follow up of 38 months (20-71), while the NSM group had a follow up of 36 (18-69). They were similar in age, BMI, preop clinical stage and preop Gleason sum. The preoperative PSA, the pathologic stage, and the BCR rate were significantly higher in those with PSMs. In addition, on univariate analysis, the PSA, pathologic stage, postoperative Gleason sum, and positive margin were all independent predictors of biochemical recurrence (p = 0.016, 0.001, 0.001, 0.001 respectively). On multivariate analysis only the Gleason sum and margin status were the only variables to retain their significant explanatory power in predicting BCR (p = 0.012, 0.001 respectively). Overall BCR rate was 9.79% (41/419). The rate of BCR in those with a PSM was significantly higher at 18.1% (15/83) compared to those with a NSM which was 7.74% (26/336) (p = 0.007).

The apex was the most common location (p = <0.001), followed by multiple sites, Table 2. No location was found to be an independent risk factor for BCR (p = 0.309). Comparing apical to non-apical, base to non-base, and single to multiple, no significance was found (p = 0.575, 1.000, and 0.208 respectively), Table 3.

When evaluating PSMs for focal (defined as 1 mm or less) versus extensive disease there was no difference

TABLE 1. **Comparison of positive surgical margin (PSM) and negative surgical margin (NSM)**

	PSM	NSM	p value
No. of patients (%)	83/419 (19.8)	336/419 (80.2)	
Age	64.2 (42-75)	65.0 (41-82)	0.394
Body mass index	27.4 (21.0-42.6)	27.6 (20.1-41.3)	0.731
Preop PSA	6.63 (0.43-50.0)	5.77 (0.5-19.0)	0.038
Biopsy Gleason sum	6.39 (5-9)	6.42 (5-9)	0.961
5	2 (2.4)	3 (0.9)	
6	50 (60.2)	218 (64.9)	
7	28 (33.7)	93 (27.7)	
8	1 (1.2)	17 (5.1)	
9	2 (2.4)	5 (1.5)	
Nerve sparing			0.763
Bilateral	60 (72.3)	250 (74.4)	
Unilateral	7 (8.9)	33 (9.8)	
None	16 (19.3)	53 (15.8)	
Node dissection	9/83	51/336	0.381
Positive nodes	1	1	
Path Gleason sum	0.200		
5	0 (0)	2 (0.6%)	
6	33 (39.8)	155 (46.1)	
7	44 (53.0)	164 (48.8)	
8	5 (6.0)	10 (3.0)	
9	1 (1.2)	5 (1.5)	
Path stage			< 0.001
T2	36 (43.4)	288 (85.7)	
T3a	39 (47.0)	38 (11.3)	
T3b	87 (8.4)	9 (2.7)	
T4	1 (1.2)	1 (0.3)	
Follow up (mo.)	38 (20-71)	36 (18-69)	0.386
Number of biochemical recurrence	15 (18.1)	26 (7.74)	0.007
Time to recurrence (mo.)	17.9 (5.6-39.2)	22.2 (4.4-57.2)	0.270

in BCR (p = .724). When using 3 mm or 10 mm as the cutoff, again no significant difference was found in BCR (p value 1.000 and 1.000 respectively), Table 3. The Kaplan Meier survival curve confirms no significant difference based on the log rank test comparing the focal versus multifocal PSM and the length of PSM, Table 5 and Figure 1; Table 5 and Figure 2 respectively).

When evaluating only those patients with pT2 disease, 36 of 324 (11.1%) had a PSM, and in those with pT3 disease 46 of 92 (50.0%) had a positive margin. Lastly, there were two patients with pT4 disease, and one had a PSM (50%). Next, these groups were subcategorized and compared based on margin status, Table 4. When patients with a positive margin and pT2 disease were compared to patients with a negative surgical margin and pT2 disease, the rate of BCR was significantly higher in those with a PSM (16.7% verses 4.5% respectively, p = 0.015). Interestingly, those with PSM and pT2 disease did not have a statistically significant different rate of BCR compared to those with a NSM and ≥ pT3 disease (16.7% verses 27.1% respectively, p = 0.302). In those with a PSM and ≥pT3 disease, there was no difference in the rate of BCR compared to those with NSM and ≥ pT3 disease (19.1% verses 27.1%, p = 0.467). The relative risk of BCR was 2.03 (95% CI 1.28-3.21) for patients who have a PSM versus a NSM, and in those with T2 disease the relative risk of BCR is 3.21 (95% CI 1.52-6.76) when there is a PSM versus a NSM.

TABLE 2. **Characteristics of patients with positive surgical margin (PSM)**

No. of patients with PSM (%)	83/419 (19.8)
No. with pT2 in PSM group	36/83 (43.4)
No. with ≥ pT3 in PSM group	47/83 (56.6)
Length data	
Mean length of PSM (mm)	4.40 (0.5-18.0)
No. with 1 mm or less total length	16/83 (19.3)
No. with > 1 to 3 mm	28/83 (33.7)
> 3 mm	39/83 (47.0)
Location data	
Apex only	38/83 (45.8)
Base only	8/83 (9.6)
Mid only	10/83 (12.1)
Bladder neck only	5/83 (6.0)
Multiple sites	22/83 (26.5)

Discussion

PSM rates have been shown to be similar between RARP and open RP,[25,26] and even lower in RARP versus ORP in one series.[27] The role of PSM has been a point of debate; however most studies in ORP,[1-16] and a recent RARP[18] analysis have shown PSM to be related to BCR. This has not been a unanimous finding, however, as both ORP[17] and an RARP[19] series have reported no correlation of PSM with BCR. In our analysis PSM conferred a significantly increased risk for BCR. Studies with further follow up may more accurately reflect the true influence of BCR in PSM. For instance, the longest published follow up in RARP relating to BCR was 36 month, and no significance was found,[19]

TABLE 3. **Characteristics of patients with biochemical recurrence (BCR) and positive surgical margin (PSM)**

Location of PSM and BCR	**%/p value**
Total patients with PSM and BCR	15
Location[1]	
Apical (8/15)	53.3%
Mid (1/15)	6.7%
Multiple (6/15)	40.0%
Apical (8/38) vs. non-apical (7/45) PSM	p = 0.575
Base[2] (3/15) vs. non-base (12/68) PSM	p = 1.000
Single (9/61) vs. multiple (6/22) PSM	p = 0.208
Length of PSM and BCR	
≤ 1 mm 12.5% (2/16) vs. > 1 mm 19.4% (13/67)	p = 0.724
≤ 3 mm 17.7% (8/45) vs. > 3 mm 18.4% (7/38)	p = 1.000
≤ 10 mm 18.2% (14/77) vs. > 10 mm 16.7% (1/6)	p = 1.000

[1]BCR in the base and bladder position as a sole
[2]Including those with a base in a multiple PSM

TABLE 4. **Comparing biochemical recurrence (BCR) at different pathological stages**

Overall BCR		p = 0.007
NSM vs. PSM	7.74% (26/336) 18.1% (15/83)	
pT2 with BCR		p = 0.015
NSM vs. PSM	4.51% (13/288) 16.7% (6/36)	
≥ pT3 with BCR		p = 0.467
NSM vs. PSM	27.1% (13/48) 19.1% (9/47)	
BCR in:		p = 0.302
≥ pT3 NSM vs. pT2 PSM	27.1% (13/48) 16.7% (6/36)	
BCR in:		p = 1.000
pT2 PSM vs. ≥ pT3 PSM	16.7% (6/36) 19.1% (9/47)	
BCR in:		p = < 0.001
pT2 NSM vs. ≥ pT3 NSM	4.51% (13/288) 27.1% (13/48)	

TABLE 5. **Estimated 5 year biochemical recurrence free (BRF) survival for positive margin (PSM) patients**

Pathologic subgroup log-rank	**No. patients (%)**	**5 yr BRF (%)**
Overall	83	81
Multifocal PSM (Figure 1)		
Present	43 (51.8)	76
Absent	40 (48.2)	88
p value		0.25
Margin length (mm) (Figure 2)		
< 1	4 (4.8)	75
1-3	33 (39.7)	82
> 3	46 (55.4)	82
p value		0.93

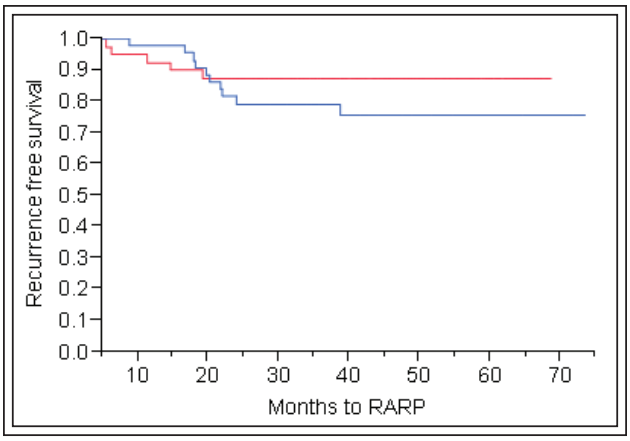

Figure 1. Kaplan Meier curve. Focal versus multifocal. Blue multifocal, red unifocal.

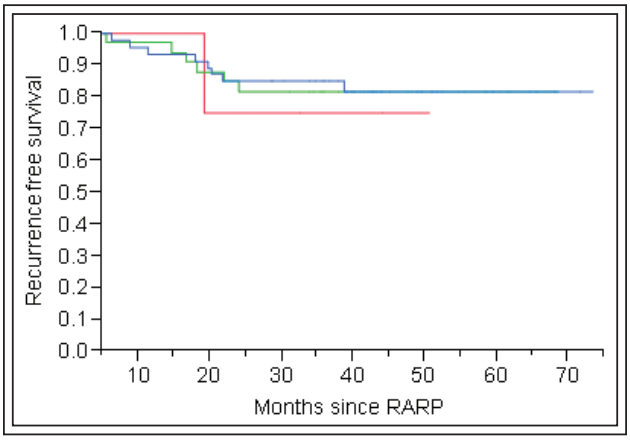

Figure 2. Kaplan Meier curve. Margin length. Red < 1 mm, green 1-3 mm, and blue > 3 mm margin length.

however no information was given about the use adjuvant radiotherapy of the patient population with PSM. Shikanov et al[18] had a follow up of 12 months, and found that PSM had a significant impact on BCR. Here we are reporting 38 months of follow up and we also identified a statistically significant impact on BCR.

When evaluating the rate of PSM, Ficcara et al showed rates range from 2%-59% in large RARP series, 6%-12% for T2 and 27%-50% for T3.[28] Compared to an overall rate of PSM of 11%-38%; 3%-18% for T2, and 22%-53% for T3 in ORP.[16] Our overall rate of 19.8% (11.1% for T2 and 50.0% for T3) is comparable to published rates for large volume academic centers.[29] We utilize a very strict definition of PSM, as described earlier, which may explain why the rate of PSM for T3 tumors is on the upper limit of those reported.

Location of PSM has not been consistently shown to influence BCR. A PSM at the base,[1] posteriolateral,[4] and bladder neck[21] has been associated with BCR in ORP. This is not a unanimous finding, as location is not always associated with a higher BCR rate in both open[9,20] and robot assisted series.[18] Apical PSMs have received significant attention as this is the most common location of PSM during both RP and RARP.[1,4,24,30,31] The impact of PSM at the apex and risk of BCR are mixed.[1,5,15,17,22-24] In our data there is no significant difference in the rate of BCR and location of PSM. One reason may the relatively few numbers of patients with PSM at the base, and posteriolateral portion of the gland. Blute et al[1] evaluated 2334 patients in their analysis, with 85 PSM at the base which was found to confer an increased risk for BCR. In our analysis we had no patients with a sole PSM at the base, however evaluating those with the base as part of multiple PSMs, no significant deference was seen compared to other sites. Duration of follow up could be another reason why no significance was seen regarding location and BCR, Blute et al[1] had 42 months of follow up compared to our 37 months of follow up. However the longest specific RARP series reporting on location data is 12 months, with 1398 patients total; 18 with PSM at the base, and 109 at the mid portion.[18] Here we have superior follow up time for an RARP series, however, fewer positive margins at these specific sites.

Length > 1 mm,[18] focal versus extensive[20] and multiple PSM[1,20,23,32] has also been implicated as an increased risk factor for BCR. Shikanov et al showed the total length of < 1 had similar rates of BCR as those with negative margins, PSM ≥ 1 mm was associated with an increased risk, and the highest risk was for those above 3 mm in their robot assisted series.[18] Once again, the length of follow up in their series was a limitation (12 months), and longer follow up may in fact neutralize the effects of these findings. A recent open series showed focal versus extensive PSM to be significant for BCR,[20] unfortunately there was no standardization for pathologic analysis, and no definition was given for focal versus extensive. We attempted to evaluate our data using multiple permutations for significant values, 1 mm, 3 mm, and 10 mm, but no significant association could be demonstrated. One reason is likely related to the longer margins that have yet to recur. Evaluating the PSM patients, 47% had greater than 3 mm positive margins. Eighteen were greater than 6 mm (22%), and only one of these had a BCR. Of the 18 patients > 6 mm, nine had pT3a disease, not including the one with BCR. These larger PSMs without BCR are clearly impacting the outcomes, which may be the reason we did not find a statistical relationship. It also is possible that not enough time has elapsed. The overall mean time to recurrence

was 20 months, which is relatively short compared to the mean time to failure in ORP of 35 to 48 months.[22] Further follow up is needed to fully understand the impact of length on BCR in RARP.

As found in other series, PSM in pT2 has an impact on BCR. Freedland et al[33] confirmed that there were no differences in BCR rates between men with a PSM in T2 disease, versus men with a NSM in T3, versus men with a PSM in T3 disease. Recently, Stephenson et al[20] agreed that a PSM in T2 placed patients at a similar risk of recurrence as those with NSM and T3 disease. They also showed that a PSM in a Gleason 7 had a similar risk of BCR in those with Gleason 8 and NSM. Herein we found that a BCR was not statistically different in patients with a PSM in pT2 versus a PSM pT3, and a PSM pT2 versus a NSM pT3. This suggests that the role of a PSM may elevate a T2 tumor to the same recurrence rate as those with T3 disease. The overall biochemical recurrence rate of 9.79% at 37 months is encouraging for patients undergoing a RARP. Even in patients with a PSM, the rate of BCR of 18.1% at 38 months is reassuring. However, with an overall relative risk of BCR of 2.03 (95% CI 1.28-3.21) for patients who have a PSM versus a NSM; and in particular those with T2 disease with a relative risk for BCR at 3.21 (95% CI 1.52-6.76) when there is a PSM versus a NSM, the importance of proper surgical technique is clearly emphasized.

Aside from the standard limits of a retrospective review, the main limitation of this study is related to few patients with PSM that met our criteria for inclusion (83/1420 patients). This is particularly limiting to the analysis regarding location of PSM, as each location has limited numbers of patients. It is possible with a larger sample size and increasing follow up, that a certain location will standout as it has in the ORP literature. Nevertheless, at 37 months, this is the longest reported follow up in the RARP literature with detailed analysis of both length and location.

Conclusions

With 37 months follow up, positive surgical margins have a clear impact on biochemical recurrence. In this RARP series, location and length do not appear to have an impact on recurrence. The impact of a PSM in a patient with pT2 disease confers a significant risk of BCR compared to a NSM pT2; emphasizing the role the surgeon has in disease control through proper technique. No difference is seen in the rate of BCR in those with ≥ pT3 PSM and NSM. Further follow up and patient accrual is needed to delineate the true role of PSM in RARP. □

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