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Biochemical Recurrence Rates after Minimally Invasive Radical Prostatectomy and Positive Surgical Margins in Localized Prostate Cancer.

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Abstract

Objective: To retrospectively evaluate biochemical recurrence rates of the patients who underwent minimally invasive radical prostatectomy and positive margins in localized prostate cancer. Treatment in men with positive surgical margins after radical prostatectomy is controversial. Immediate adjuvant therapy reduces the risk of biochemical recurrence at the cost of increased toxicity. Providing the appropriate treatment should be based on an understanding of the risk of recurrence without treatment.

Materials and Methods: We performed a retrospective analysis of the records of 944 men who underwent minimally invasive radical prostatectomy (laparoscopic or robotic assisted laparoscopic radical prostatectomy) in Siriraj hospital between December 2005 to July 2009. Patient age at surgery, clinical stage, preoperative PSA, operative time, estimated blood loss, surgical specimen pathology(specimen weight, tumor grade, tumor volume, stage and surgical margin status) and follow up PSA were recorded. All specimens were reviewed by one pathologist. Of 944 patients, 122 met criteria for analysis.

Results: Mean follow up was 21.4 months (3.2-58.3). The positive margin rate was 12.9% (122 of 944 patients). The overall PSA biochemical recurrence rate was 13.9% (17 of 122, 95%CI: 8.9%-21.2%). Mean PSA was

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slightly higher in patients with biochemical recurrence (11.9 vs 11.5, p = 0.864). The recurrence rate was higher in patients with multiple positive margins compared to those with a solitary positive margin (17.2% vs 12.9%, p = 0.549). However, these differences failed to attain statistical significance. Mean interval to biochemical recurrence (n=17) was 10.9±8.4 months (2.8-29.1). No statistically significant risk factors for recurrence in patients with a positive margin on univariated analysis were found.

Conclusions: A low biochemical recurrence rate, (13.9%) was found in patients with a positive surgical margin following minimally invasive radical prostatectomy. If adjuvant radiation is given to every patient with a positive surgical margin, more than 86% of patients will receive unnecessary adjuvant radiation and/or hormonal therapy.

Key Words: prostate cancer, laparoscopic and robotic radical prostatectomy, positive margins, biochemical recurrence.

Introduction

Prostate cancer is one of the most important medical problem in the male. In Europe, prostate cancer is the most common solid neoplasm, outnumbering lung and colorectal cancer.[1] The incidence of prostate cancer increased 2.0% annually from 1995 to 2001. An estimated 186,320 new cases were diagnosed in 2008 and prostate cancer is expected to account for 25% of new cases in men in 2008.2 Furthermore, prostate cancer is currently the second most common cause of cancer death in men.[2]

Radical prostatectomy is one of the most accepted and widely practiced management strategies for localized prostate cancer. At present day minimally invasive radical prostatectomy (laparoscopic radical prostatectomy: LRP; extraperitoneal laparoscopic radical prostatectomy: ELRP; robotic assisted laparoscopic radical prostatectomy: RALRP, and extraperitoneal robotic assisted laparoscopic radical prostatectomy: ERALRP) provided good outcome and accepted for standard treatment.[3,4] The incidence of positive margins varies widely in radical prostatectomy series. A review from Memorial Sloan-Kettering Cancer Center and Baylor College of Medicine demonstrated a positive margin rate among 26 surgeons of 10% to 48%. The wide range likely has many causes, include surgical technique and experience.[5] The risk factors associated with a positive margin, include clinical stage T2b, T2c or T3 cancer, preoperative PSA 10 ng/ml or higher, biopsy Gleason score 7 or greater, and multiple positive biopsy cores.[6-8]

It is acknowledged that cases of organ confined cancer are least likely to recur, while those of seminal vesical invasion or lymph node metastases are at highest risk for recurrence. However, most studies indicate that a positive margin after radical prostatectomy is a significant risk factor for biochemical recurrence.[6,9,10] In contrast, some studies suggest otherwise. Salomon et al reported that of 137 patients with prostate cancer invading the seminal vesicle a positive surgical margin was not an additional risk factor for recurrence.[11] In recent study of 350 patients after radical retropubic prostatectomy with positive margins, PSA recurrence rate was low (19%).[12]

To date, optimal treatment in patients with a positive surgical margin after radical prostatectomy remains unclear. Options include observation with salvage treatment if there is biochemical or clinical recurrence, adjuvant radiation therapy, and adjuvant hormonal therapy. Some groups recommend adjuvant radiation therapy prior to an increase in PSA, while others observe and treat if there is recurrence. Recently 2 large, randomized prospective clinical trials investigated the role of immediate adjuvant RT in men with extracapsular disease or a positive surgical margin following radical prostatectomy.[13,14] Both studies showed that adjuvant therapy decreased the risk of PSA recurrence but at the cost of increased toxicity. However, no metastasis-free or overall survival benefit was seen in either study. Making the appropriate choice should be based on an understanding of the risk of recurrence without treatment in patients with a positive margin after radical prostatectomy. Herein, we reviewed our series at our institution with specific attention to recurrence rates and associated variables.

Materials and methods

We retrospectively reviewed the outcome in 944 patients with prostate cancer who underwent minimally invasive radical prostatectomy (laparoscopic or robotic assisted laparoscopic radical prostatectomy) at the department of surgery, faculty of

medicine Siriraj hospital between December 2005 to July 2009. The patients with localized prostate adenocarcinoma (T1 and T2, stage according to the 2002 TNM classification) with positive surgical margins were enrolled in this study. This database includes information on patient age at surgery, clinical stage, preoperative PSA, operative time, estimated blood loss, surgical specimen pathology (specimen weight, tumor grade, tumor volume, stage and surgical margin status) and follow-up PSA. Prostate specimens were sectioned according to the protocol at our institution. A positive surgical margin was defined as extension of tumor to the inked surface of resected specimen. Margins were categorized as positive or negative at each anatomical location, ie the apex, base, anterior, posterior and right/left lateral periphery. All specimens were reviewed by 1 pathologist. PSA was first analyzed about 1 month and at followup every 1-3 months postoperatively. Biochemical recurrence was defined as a single PSA of greater than 0.2 ng/mL or two consecutive values of 0.2 ng/ml15. Patients treated with preoperative androgen deprivation or radiation therapy, immediate adjuvant hormonal or radiation therapy before biochemical recurrence were excluded. Patients with insufficient follow-up of less than 3 months were also excluded. We excluded men with locally advanced disease and negative surgical margins, leaving 124 cases for organ-confined prostate cancer. After pathology review, 2 out of 124 patients were withdrawn because of false positive margins. 944 patients, 122 met criteria for analysis.

Statistical analysis

A previous study of Simon et al reported biochemical recurrence rates of 19% in localized prostate cancer after radical prostatectomy with positive margins.[12] Thus, a minimum sample size of 106 patients with localized prostate cancer with positive margin was estimated at 95% confidence interval for a biochemical recurrence of patients with localized prostate cancer with a positive margin of 19±7.5%.

SPSS for Windows statistical software program version 10 was used to analyze the data. Descriptive characteristics of clinical and pathological data are presented as the mean±SD, median (range) and frequency distribution. Differences in descriptive characteristics were assessed by Student's t test on quantitative data and the chi-square test on qualitative data. Patient age at surgery, operative time, estimated blood loss, prostate size, tumor volume, clinical stage (T1 to T2), total PSA (less than 10, 10 to 20 and greater than 20 ng/ml), nerve sparing procedure (none, unilateral and bilateral), positive margin status (solitary and multiple), radical prostatectomy Gleason score (2 to 6, 7 and 8 to 10), followup in months and time to biochemical recurrence in months were analyzed. Univariate analysis using Cox proportional hazards regression was performed to determine the risk of biochemical recurrence in patients with positive margins.

Results

Descriptive analysis was performed in the 122 patients with localized prostate cancer with positive margin (table 1). Mean followup was 21.4 months (minimum 3.2). The positive margin rate was 12.9% (122 of 944 patients). The overall PSA biochemical recurrence rate was 13.9% (17 of 122). Mean operative time was higher in patients with biochemical recurrence (216.7 vs 197.6, p=0.238), as was the mean estimated blood loss (691.2 vs 543.5, p=0.206). The recurrence rate in patients with clinical stage T1 was 14% vs only 3% in patients with clinical stage T2. Mean PSA was higher in patients with biochemical recurrence (11.9 vs 11.5, p = 0.864). The recurrence

Table 1 *Patients characteristics*

	Biochemical Recurrence		
	No	**Yes**	**p-value**
No. cases (%)	105 (86.1)	17 (13.9)	
Age :			
Mean ± SD	66.9 ± 7.6	63.5 ± 9.8	0.094
Median (range)	68 (40 - 83)	64 (48 - 84)	
Op. time (min) :			
Mean ± SD	197.6 ± 60.4	216.7 ± 69.7	0.238
Median (range)	180 (89 - 400)	210 (90 - 330)	
EBL (ml.) :			
Mean ± SD	543.5 ± 406.7	691.2 ± 634.9	0.206
Median (range)	500 (50 - 2,500)	500 (100 - 2,300)	
Prostate Size (g) :			
Mean ± SD	39.9 ± 16.9	39.2 ± 14.1	0.874
Median (range)	35.9 (14 - 106)	36 (22 - 74)	
Tumor volume (%) :			
Mean ± SD	27.5 ± 19.9	26.5 ± 15.3	0.843
Median (range)	20 (5 - 80)	20 (5 - 70)	
No.clinical stage (%) :			
T1	84 (85.7)	14 (14.3)	1.000
T2	21 (87.5)	3 (12.5)	
PSA (ng/ml) :			
Mean ± SD	11.5 ± 10.0	11.9 ± 8.2	0.864
Median (range)	7.6 (1.5 - 54.0)	9.6 (5.2 - 34.4)	
No. less than 10 (%)	65 (86.7)	10 (13.3)	0.916
No. 10-20 (%)	26 (83.9)	5 (16.1)	
No. greater than 20 (%)	14 (87.5)	2 (12.5)	
No. nerve sparing procedure (%)			
None	62 (86.1)	10 (13.9)	0.986
Unilat or bilat	43 (86.0)	7 (14.0)	
No. positive margins (%)			
Solitary	81 (87.1)	12 (12.9)	0.549
Multiple	24 (82.8)	5 (17.2)	
RP Gleason:			
No. 2-7 (%)	90 (84.9)	16 (15.1)	0.466
No. 8-10 (%)	15 (93.8)	1 (6.3)	

rate was high in patients with multiple positive margins vs those with a solitary positive margin (17.2% vs 12.9%, p= 0.549). However, these differences failed to attain statistical significance.

Nerve sparing was performed in 41% of patients (50 of 122). The nerve sparing procedure and biochemical recurrence was analyzed (table 2). No significant differences existed between non-nerve sparing technique and nerve sparing procedure (p= 0.986).

The location of surgical margin in relation to biochemical recurrence was assessed (table 3). Of patients with a positive margin, 76.2% (93 of 122) had only 1 site that was positive. The most common surgical margin location was the apex (81%). The least common site was left-lateral in 1.6% of cases. Mean time to biochemical recurrence was 19.8±12.3 months. The relative risk of recurrence was also analyzed in the 122 patients with a positive margin using multivariate HR (table 4). No statistically significant risk factors were noted for recurrence in patients with positive margins.

Discussion

At present there is no consensus about optimal treatment in localized prostate cancer (pT1, pT2) with positive surgical margins. A positive margin after operation has been shown to have a poor prognosis for recurrence of disease.[9,10] Most series report a recurrence rate of approximately 50% in patients with a positive margin.[6,10] The National Comprehensive Cancer Network (NCCN) practice guidelines 2009, suggest adjuvant radiation therapy when positive surgical margins are diffuse(>10 mm margin involvement or ≥3 sites of positivity) or associated with persistent ser um PSA, but it still controversial when margin involvement is less, and especially when associated with an undetectable serum PSA level.16 Moul et al reported that early hormonal therapy administered for PSA only recurrence after radical

Table 2 *Nerve sparing procedure by Biochemical recurrence (%).*

Nerve sparing	No. pts	No. Recurrence
None	72	10 (13.9)
Unilat.	11	0 (0)
Bilat.	39	7 (17.9)

Table 3 *Solitary margin locations and biochemical recurrence rates (%).*

Site	No. pts	No. Recurrence
Apex	99	13 (13.1)
Bare	36	5 (13.9)
Anterior	12	3 (25)
Posterior	2	1 (50)
Right-lateral	3	1 (33.3)
Left-lateral	2	0

Table 4 *Risk of biochemical recurrence in patients with surgical margins.*

	Univariate HR	95 % CI	p-value
Age	0.94	0.88 - 0.99	0.043
Op. time	1.00	0.99 - 1.01	0.692
EBL	1.00	0.99 - 1.00	0.674
Prostate size	1.00	0.97 - 1.03	0.995
Tumor volume	0.99	0.97 - 1.02	0.671
Clinical stage :			
T1	Referent		
T2	0.94	0.22 - 3.94	0.933
PSA (ng/ml) :			
Less than 10	Referent		
10 - 20	1.30	0.43 - 3.92	0.647
Greater than 20	0.85	0.16 - 4.53	0.845
Nerve sparing procedure			
None	Referent		
Unilat or bilat	1.11	0.42 - 2.94	0.833
No. positive margins :			
Solitary	Referent		
Multiple	1.35	0.40 - 4.56	0.626
RP Gleason :			
2- 7	Referent		
8 - 10	0.41	0.05 - 3.23	0.398
Site :			
Non -Apex	Referent		
Apex	0.60	0.20-1.89	0.375

prostatectomy was an independent delayed clinical metastasis signal for high risk cases.[17] Our data suggest otherwise. We studied localized prostate cancer and found that of the 122 patients with 1 or more positive margins the overall recurrence rate following laparoscopic or robotic radical prostatectomy in our series is low (13.9%). Therefore, if all patients with a positive margin were treated in adjuvant fashion, approximate 86% would be treated unnecessarily and subjected to potentially damaging side effects and loss of quality of life. Death from prostate cancer is rare after radical prostatectomy. There has been no mortality in our series.

The positive margins in localized prostate cancer (pT2) in this study is 12.9% which is not different from a world series reported at 7-16% in LRP and 5.7-15.1% in RALRP.[7,18,19,20] There are many possible causes of a positive margin, including surgical technique and experience.[5] Like other series, we found that the most common location of positive margins is at the apex (99 cases). This may be because the prostate capsule is not well defined at

the apex and thus it is difficult to expose because it is the deepest location and when a surgeon attempts to keep maximized urethral length for maintain continence it may lead to positive surgical margins.[21] Nerve sparing procedure does not increase risk of biochemical recurrence in our study and this is in accord with the previous report of Sofer et al.[22]

There are several factors that increase the possibility of recurrence in patients found to have a positive margin, including PSA greater than 20 ng/ml, Gleason score 8 to 10 and seminal vesicle invasion.[23] All of these factors should be considered when making decisions about treatment for the patients. In our series we failed to attain statistical significant difference for identification the risk factors of biochemical recurrence. This may be due to a too short followup time (21.4 months) as compared to another previous study about 45.8 months[12]. The small sample size in this study may reflect the non-significance relationship of those risk factors to biochemical recurrence. As analyzed by Cox proportional hazards regression, the optimal amount of sample size should be approximate 526 patients, far larged than the 122 patients in this study. However, this study reveals some possible risk factors, such as that apical location of positive surgical margin, multiple sites of positive margins and a Gleason score of more than 8 may be related to biochemical recurrence. A better outcome should be forthcoming after prospective study in the near future. Until that time the result of our study may be helpful for medical decision making.

Conclusion

In localized prostate cancer, patients with a positive surgical margin following minimally invasive radical prostatectomy have a relatively low recurrence rate. It was only 13.9%. If we treated every patient with adjuvant radiation or hormonal therapy with a positive margin, approximately 86% of our patients would have been treated unnecessarily. The cost of radiotherapy and hormone therapy is high and also impairs the quality of life for the patient.

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