Predictive preoperative factors for positive surgical margins in robotic radical prostatectomy in low-risk prostate cancer

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ABSTRACT

Objective: Positive surgical margins after radical prostatectomy for localized prostate cancer is a powerful predictor of PSA recurrence. Clinical stage, Gleason score and preoperative PSA are predictive factors for positive surgical margin after radical prostatectomy. In this study, we aimed to identify preoperative factors affecting surgical margin positivity in low-risk prostate cancer after robotic radical prostatectomy (RARP).

Material and methods: Between 2008 and 2011 (<cT2b, PSA <10, Gleason <7), data from 112 patients with low-risk (<cT2b, PSA <10, Gleason <7), prostate cancer who had undergone RARP were examined prospectively. The effects of PSA, body mass index, surgery time after biopsy, percentage of positive cores, tumor length and prostate weight on positive surgical margin were evaluated. For statistical analyses, Mann-Whitney U, Pearson *chi-square* and logistic regression tests were used.

Results: It was observed that mean age and body mass index had no effect on positive surgical margins ($p=0.2$ and 0.6). According to univariate analysis, it was found that an elapsed time of less than six weeks from biopsy to surgery ($p=0.07$), tumor percentage of more than 5% in a biopsy specimen ($p=0.003$), a positive core percentage of more than 20% ($p=0.045$) and a prostate volume below 50 cc ($p=0.037$) increased the rate of positive surgical margins. Based on multivariate analysis, PSA levels above 5 ng/mL (OR: 8.006, $p=0.012$) and an elapsed time of less than 6 weeks between biopsy and surgery (OR: 10.814, $p=0.029$) increased the risk of positive surgical margins.

Conclusion: In low-risk prostate cancer, a waiting time of less than six weeks between biopsy and surgery and PSA levels above 5 ng/mL are predictive of high surgical margin positivity after robotic radical prostatectomy.

Key words: Prostatectomy; robotic; surgical margin.

Introduction

Radical prostatectomy is the standard treatment of the patients with localized prostate cancer with a life expectancy of 10 years. Positive surgical margins after radical prostatectomy is an indicator of disease recurrence.

^[1] Whatever the technique might be, patients in the lower risk group benefit mostly from radical surgery. In the field of urologic surgery, robotic surgery is mostly applied with optimal outcomes in radical prostatectomy.^[2] Surgical margin positivity has been reported as 10.7% for robot-assisted radical prostatectomy (RARP) in the localized prostate cancer.^[3] PSA, Gleason score, and clinical stage are known to effect post-radical prostatectomy surgical margin positivity.^[4] Since in low-risk localized prostate cancer these parameters are similar, other preoperative factors influential on surgical margin positivity are not known.

For more effective control of the disease, risk factors other than those known may decrease the risk of surgical margin positivity. In this study we aimed to analyze parameters influential on post-RARP surgical margin positivity in low-risk prostate cancer.

Material and methods

RARP was performed on a total of 282 prostate cancer patients diagnosed between 2008, and 2012, after the patients gave their informed consent forms. Diagnosis of prostate cancer was made after ultrasound-guided 10 core prostate biopsies performed with the indication of abnormal digital rectal examination findings and/or higher PSA levels. All patients enrolled in the study underwent RARP using Montsouris technique^[5] defined in the year 2000. On postoperative 7. day, cystograms were obtained, and urethral catheters of the

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patients were removed if any urine leakage was not observed. Biochemical recurrence was defined as increase in PSA at least 2 times above 0.2 ng/mL.

The study population consisted of a total of 112 patients with clinically localized prostate cancer in the lower risk group (clinical stage <T2b, PSA <10 ng/mL, Gleason score <7) whose biopsies, and histopathological examinations were performed in the same center. Age, PSA values, body mass index, previous abdominal surgery (if any), the time interval between biopsy, and the operation, percentage of positive core biopsies (ratio of positive cores to total number of cores), prostate volume, percentage of total tumor length (the ratio of total tumor length to total length of the biopsy material), and parameters related to the nerve-sparing surgery were recorded. The impact of these parameters on surgical margin positivity was investigated.

Statistical analysis

For statistical analysis IBM SPSS v.20 software package program was used. A ROC curve was constructed to evaluate the effects of PSA, percentage of tumor-positive cores, and total tumor length on surgical margin positivity. Cut-off values for percentage of positive cores (20%), percentage of total tumor length (5%), and PSA (5 ng/mL) were also determined. In a univariate analysis, parameters effective on surgical margin positivity were included in the multivariate analysis. For statistical analyses Mann-Whitney U, Pearson chi-square, and logistic regression analyses were used. Confidence interval of 95% was accepted. A $p < 0.05$ was considered as the level of statistical significance.

Results

Data of the patients included in the study are summarized in Table 1. Histopathological examination of the biopsy specimens revealed surgical margin positivity in 14, and negativity in 98 patients. In a univariate analysis, the effects of age ($p=0.2$), body mass index ($p=0.6$), previous abdominal surgery ($p=0.8$), application of nerve-sparing surgery ($p=0.63$), clinical stage ($p=0.51$), and perineural invasion ($p=0.86$) on surgical margin positivity were not found to be statistically significant.

In a univariate analysis, prostate volume of <50 cc ($p=0.037$), increased PSA values (>5 ng/mL) ($p=0.02$), percentage of positive core biopsies (>20%) ($p=0.005$), total tumor length (>5%) ($p=0.003$) increased the risk of surgical margin positivity.

Results of a multivariate analysis of the effective factors on surgical margin positivity are summarized in Table 2. Prostate volume ($p=0.095$), and percentage of tumor-positive cores ($p=0.136$) did not effect surgical margin positivity. PSA over 5 ng/mL (OR=8.006, $p=0.012$), and the time interval less than 6

weeks between the time of biopsy to the operation (OR=10.814, $p=0.029$) were found to be independent predictive factors influential on surgical margin positivity.

Discussion

Nomograms predictive of recurrences, and oncological outcomes after radical prostatectomy in prostate carcinoma encompass preoperative PSA, Gleason score, and clinical stage.^[6,7] However, surgical margin positivity is an important factor for disease recurrence. To decrease the incidence of surgical margin positivity, preoperative risk factors should be defined precisely. Coelho et al.^[8] reported that only clinical stage is predictive of surgical margin positivity (OR: 10.7; $p < 0.0002$). Ficarra et al.^[9] also reported that clinical stage was an independent predictive factor for surgical margin positivity (HR: 2.2; $p < 0.008$). However in a study performed by Liss et al.^[10] the authors emphasized that only PSA levels among preoperative factors are influential on surgical margin. However in a study by Obek et al.^[11], the researchers did not find combined use of digital rectal examination, and biopsy sufficient for the evaluation of location, and positive surgical margins. They asserted that only presence of tumor both in the right, and left lobes can be useful for clinical staging. In our study any impact of clinical stage on surgical margins could not be demonstrated. The reason for this similar finding is that clinical characteristics of our group resembled to those of the abovementioned study. Since clinical staging is determined based on digital rectal examination findings, it is a subjective evaluation, and thus it can create a significant difference in a series consisting of moderate and high risk patients.

In a study performed by Ahyai et al.^[12] the impact of tumour volume on biochemical recurrence, and positive surgical margins was investigated. In this study, tumor volume has been reported as an independent risk factor for surgical margin positivity, and biochemical recurrence. However this evaluation could be made only during postoperative histopathological examination. In a study by Freedland et al.^[13] percentage of positive cores, and serum PSA value were reported as independent predictive factors for surgical margin positivity. Percentage of positive cores in biopsy specimen can be an indicator of a preoperative tumor burden. In our study, percentage of positive cores above 20% was significant in univariate analysis, but it had no effect on surgical margin positivity in multivariate analysis.

A consensus does not exist on the waiting period for the operation after the biopsy. An average of 4–6 weeks of waiting period after the biopsy has been usually recommended for the patients who will undergo open surgery.^[14] Martin et al.^[15] reported that robotic radical surgery performed after a minimum of 6 weeks after biopsy decreased complication rates without any effect

Table 1. The impact of preoperative data on surgical margin positivity in univariate analysis

	Surgical margin		p value
	Negative (n=98)	Positive (n=14)	
Median age (years)	62.7	60.8	0.2
Median body mass index (kg/m ²)	26.9	26.4	0.6
Previous abdominal surgery (n)			
Yes	31	4	0.8
No	67	10	
PSA (ng/mL)			
<5	46	2	0.02
>5	52	12	
Time interval between biopsy, and operation (n)			
>6 weeks	44	1	0.07
<6 weeks	54	13	
Percentage of positive cores in biopsy specimens (n)			
<20%	49	3	0.045
>20%	49	11	
Total tumor length in biopsy specimen (n)			
<5%	58	3	0.003
>5%	33	11	
Prostate volume (mL)			
<50 mL	34	13	0.037
>50 mL	64	1	
Nerve-sparing surgery (n)			
Bilateral	86	13	0.63
Unilateral	6	0	
Unprotected	6	1	
Perineural invasion (n)			
Present	8	2	0.86
Absent	17	5	
Clinical stage (n)			
I	58	7	0.51
II	40	7	
Number of positive cores (n)	2.6	3.2	0.005

on surgical margin positivity. Similarly, Lee et al.^[16] indicated that shorter time interval between biopsy, and surgery had no effect on surgical margin positivity. However in our study, as multivariate analysis demonstrated, in cases who had undergone

Table 2. The impact of preoperative data on surgical margin positivity in multivariate analysis

	p	Odds Ratio	95% CI
PSA >5 ng/mL	0.012	8.006	1.568-40.876
Time interval between biopsy, and operation (<6 weeks)	0.029	10.814	1.273-91.869
Percentage of positive cores in biopsy specimens >20%	0.136	3.040	0.706-13.093
Prostate volume <50 mL	0.095	6.324	0.725-55.123

surgery within less than 6 weeks after biopsy, the risk of surgical margin positivity increased 10-fold (OR: 10.814, p=0.029). One possible explanation might be adhesions developed during early postoperative period because of local tissue reaction which may complicate clear exposure of the surgical plane. In open surgery, surgical planes can be determined with tactile perceptions, in robotic surgery surgical planes can be decided based on only images displayed on the monitor. Therefore, our outcomes can be quite different from those declared by Eggener et al.^[17] for their open radical prostatectomy series. In low-risk localized prostate cancer a waiting period of 6 weeks is an acceptable time interval.

In a study by Ficarra et al.^[9], prostate volume (HR=0.42 (CI 95%: 0.24-0.73; p=0.002), and clinical stage were reported as independent predictive factors for surgical margin positivity. Link et al.^[18] and Marchetti et al.^[19] indicated decrease in prostate volume as an independent predictive factor for surgical margin positivity. Link et al.^[18] performed robotic radical prostatectomy on 1847 patients, Then the patients were categorized according to their prostate volumes as 0-30 g, 30-50 g, 50-70 g, and ≥70 g, and the effect of prostate volumes on surgical margin positivity was investigated. Accordingly, they reported increased incidence of surgical margin positivity with increasing prostate volume. Also in our study, smaller prostate volumes (<50 mL) had an impact on surgical margin positivity in univariate analysis, however in multivariate analysis (OR=6.324; 95% CI 0.72-55.123; p=0.095) they didn't effect surgical margin positivity. The underlying reason can be inclusion of only low-risk patients in our study.

In a study performed by Zorn et al.^[20], the authors used preoperative risk factors in the planning of nerve-sparing method, and performed RARP employing 5 different techniques. These risk factors included clinical stage, biopsy Gleason score, percentage of positive cores, and maximum percentage of tumor cores. In low-risk patients with PSAs lower than 6 ng/mL bilateral nerve-sparing surgery, in patients with higher percentages of tumor positive cores unilateral nerve sparing surgery, and in

high-risk patients extended excisions were performed. Results of the patients were compared with those of the control group, and decreased rates of surgical margin positivity were reported with this planning strategy.^[20] In our series, we determined higher risk for surgical margin positivity in low-risk patients with PSAs lower than 5 ng/mL. However Coelho et al.^[8] indicated that nerve-sparing surgery had no effect on surgical margin positivity. Gümüş et al.^[21] reported decrease in the rates of surgical margin positivity with increasing experience. At the beginning of the learning curve, low-risk patients can be preferred to decrease surgical margin positivity. Surgical margin positivity is mostly seen in the prostate apex, and its posterolateral region. During dissections performed in prostate apex, and posterolateral region refraining from use of electrocautery to preserve continence, and erectile function, in addition to dissections performed very close to prostate might increase rates of surgical margin positivity.

In conclusion, time interval shorter than 6 weeks between biopsy, and operation, and a PSA value above 5 ng/mL increase the risk of surgical margin positivity in RARP in the low-risk prostate cancer patients.

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