

Assessment of Preoperative Predictive Factors for Positive Surgical Margins in Patients with Low or Intermediate Risk Prostate Cancer Who Underwent Retropubic Radical Prostatectomy

Radikal Prostatektomi Uygulanan
Düşük ya da Orta Riskli Hastalarda Operasyon Öncesi
Prediktif Faktörlerin Pozitif Cerrahi Sinir Gelişmesi
Açısından Değerlendirilmesi

 Burhan COŞKUN^a,
 Erbil ERGENEKON^b

^aDepartment of Urology,
Bursa Uludağ University
Faculty of Medicine,
Bursa, TURKEY
^bDepartment of Urology,
Şişli Hamidiye Etial Training and
Research Hospital,
İstanbul, TURKEY

Received: 26 Nov 2019

Received in revised form: 10 Dec 2019

Accepted: 12 Dec 2019

Available online: 13 Dec 2019

Correspondence:
Burhan COŞKUN
Bursa Uludağ University
Faculty of Medicine,
Department of Urology, Bursa,
TURKEY/TÜRKİYE
burhanc@uludag.edu.tr

ABSTRACT Objective: Positive surgical margins after radical prostatectomy is important due to increased risk of biochemical recurrence. Preoperative clinical stage, prostate specific antigen (PSA) value and the Gleason Score are the predictors of surgical margin status. In this study we aimed to assess the effects of preoperative variables on surgical margin positivity in patients with low or intermediate risk. **Material and Methods:** Preoperative clinical stage, PSA value, prostate volume and variables obtained from prostate biopsies of 73 patients who were grouped in low or intermediate risk according to D'Amico criteria (Clinical stage≤ T2b, PSA<10 ng/dl, Gleason Score ≤ 7) were compared with regard to surgical margin positivity status retrospectively. **Results:** The rate of the patients with positive surgical margins was 23.3%. The mean prostate volume was 84.91 ml±21.43 and 56.05 ml±18.42 in negative and positive surgical margin groups, respectively ($p=0.001$). While 14.6% of the patients with a PSA level <10 ng/dl had positive surgical margins, this rate was 34.4% in the patients with a PSA level of 10-20 ng/dl. ($p=0.05$). Increased numbers of positive cores in prostate biopsy were related with positive surgical margins ($p=0.001$). In multivariate analysis, only, prostate volumes less than 70 ml was found to be statistically significant ($p=0.023$). **Conclusion:** Smaller prostate volumes less than 70 ml. increase the risk of positive surgical margins in patients with low or intermediate risk.

Keywords: Margins of excision; prostatic cancer

ÖZET Amaç: Radikal prostatektomi sonrası cerrahi sınırların pozitif olması biyokimyasal rekürrens riskini artırması nedeniyle önemlidir. Operasyon öncesi klinik evre, PSA değeri ve Gleason Skoru pozitif cerrahi sınırlar açısından belirleyici özelliktedir. Bu çalışmada, düşük ve orta risk özelliklerile radikal prostatektomi uygulanan hastalarda operasyon öncesi verilerin cerrahi sınır pozitifliği üzerine olan etkisini araştırmayı amaçladık. **Gereç ve Yöntemler:** Retrospektif olarak D'Amico kriterlerine göre düşük ve orta risk grubunda (klinik evre ≤ T2b, PSA<10 ng/dl, Gleason Skoru ≤ 7) olan 73 hastanın ameliyat öncesi klinik evre, PSA değeri, prostat hacmi ve prostat biyopsisinden elde edilen verileri pozitif cerrahi sınır saptanmasına göre karşılaştırıldı. **Bulgular:** Pozitif cerrahi sınır saptanan hastaların oranı %23,3 idi. Ortalama prostat hacmi negatif cerrahi sınır grubunda 84,91 ml±21,43 ve pozitif cerrahi sınır grubunda 56,05 ml±18,42 olarak bulundu ($p=0,001$). PSA seviyesi 10 ng/dl'den düşük olan hastalarda cerrahi sınır pozitifliği oranı %14,6 bulunurken, PSA seviyesi 10-20 ng/dl arasında olan hastalarda bu oran %34,4 olarak bulundu ($p=0,05$). Prostat biyopsisinde artmış pozitif kor sayıları pozitif cerrahi sınır ile ilişkili bulundu ($p=0,001$). Çoklu değişken analizinde ise sadece prostat hacminin 70 ml'den az olması istatistiksel olarak anlamlı bulundu ($p=0,023$). **Sonuç:** Düşük veya orta risk grubunda olan 70 ml'den küçük prostat hacimli hastalarda cerrahi sınır pozitifliği riski artmıştır.

Copyright © 2019 by Türkiye Klinikleri

Anahtar Kelimeler: Eksizyon sınırı; prostatik kanser

Prostate cancer is the second most common cancer in men in Turkey.¹ Widespread use of prostate specific antigen (PSA) screening resulted in more patients diagnosed with localized prostate cancer which is crucial for survival advantage in these patients.²

Radical prostatectomy is the preferred treatment option in patients with localized prostate cancer.³ The 15 years cancer specific survival rates are reported between 82%-90% in large series for localized prostate cancer.^{4,5}

A negative surgical margin status is one of the most desired outcomes after retropubic radical prostatectomy (RRP) as well as the pathological stage. A positive surgical margin (PSM) is found to be related with biochemical recurrence which indicates a local recurrence or metastasis following the surgery.⁶

Despite the improvements in imaging methods and investigation for better markers, it is still challenging to identify the patients with localized disease before the definitive treatment. D'Amico criteria has long been used for the risk stratification for patients undergoing RRP.⁷ Serum PSA levels, clinical staging and preoperative Gleason score are the predictive factors for desirable oncological outcomes following the surgery according to this stratification system. The patients are grouped into low, intermediate or high risk according to these variables. There are several studies searching the role of other preoperative factors such as prostate volume, the number of positive cores, the rate of involvement in each core in low or intermediate group.⁸

In this study, it was aimed to review the pre-operative predictive factors for PSM in patients with low or intermediate risk prostate cancer who underwent retropubic radical prostatectomy in our institution.

MATERIAL AND METHODS

The present study was conducted according to the principles of 2008 Helsinki Declaration. The patients who underwent open RRP in a single tertiary referral center were reviewed retrospectively.

The search in database revealed 126 entries for RRP. A total of 26 patients with insufficient records were excluded from the study. Among 100 patients, 73 patients who were classified to have low or intermediate risk according to D'Amico risk stratification were included in the study (Figure 1). While low D'Amico risk group was defined as clinical stage <T2b, PSA<10 ng/dl and Gleason score <7 the intermediate group was defined as clinical stage of T2b, PSA>10-20 ng/dl and a Gleason Score of 7.

All patients had a detailed physical examination, PSA assessment and a trans-rectal ultrasound-guided biopsy (8-10 core). TNM 2002 for prostate cancer was used for staging of the patients. The relation between mean age, body mass index, serum PSA level, preoperative Gleason score, perineural invasion, clinical stage, the number of positive cores on biopsy, prostate volume and PSM after RP were evaluated.

The statistical analysis was performed by using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, U.S.). ROC curves were studied for PSA, prostate volume and the number of positive cores. The cut off values for PSA and prostate volume were determined as 10 ng/dl and 70 ml, respectively. Independent t-test, Pearson Chi-Square test and binary logistic regression test were used for comparison of the variables.

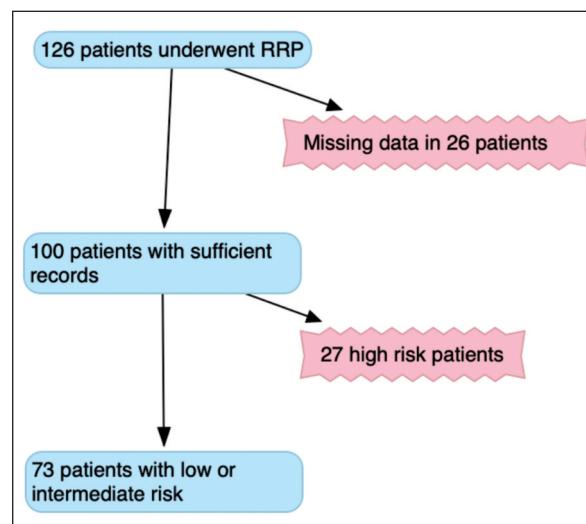


FIGURE 1: Flowchart of the included patients.

RESULTS

The mean age of 73 patients was 62.20 ± 5.68 years, the mean body mass index was $29.94 \pm 4.41 \text{ kg/m}^2$, mean PSA value was $9.32 \pm 4.58 \text{ ng/dl}$ and the mean prostate volume was $78.19 \pm 24.02 \text{ ml}$. The rate of Gleason 3+3, 3+4 and 4+3 scores were 78.1%, 16.4% and 6.8%, respectively. The rate of positive perineural invasion was 47.9%. Clinical staging revealed T1c, T2a and T2b in 67.1% 23.3% and 8.2% of the patients, respectively.

The overall rate of PSM was 23.3%. The final pathological examination resulted in Gleason 3+3, 3+4, 4+3, 4+4 and 4+5 in 56.1%, 30.1%, 9.6% 2.7% and 1.4% of the patients, respectively. The total rate of capsular invasion was 31.5%. A total rate of pT2 tumors was 67.2%. The rate of pT3a and pT3b tumors were 21.9% and 11% respectively.

The univariate comparison of the pre-clinical

variables according to the surgical margin status was presented in **Table 1**. The preoperative serum PSA levels of more than 10 ng/dl, the number of positive cores and prostate volumes of less than 70 gr were found to be statistically significant in dichotomous comparisons ($p=0.05$, $p=0.001$ and $p=0.004$, respectively). The comparison of the mean volumes in positive and negative surgical margins revealed a statistically significant difference ($p=0.001$). The patients with smaller prostate volumes were found to have more PSM.

The results of binary multivariate analysis were presented in **Table 2**. This analysis showed a statistically significant difference only for prostate volumes less than 70 gr ($p=0.023$, OR: 9.601).

DISCUSSION

Preoperative PSA value, biopsy Gleason score, and clinical staging were found to be correlated with

TABLE 1: The univariate comparison of the pre-clinical variables according to the surgical margin status.

	NSM	PSM	P value
Mean age (years)	65.12 ± 5.81	65.47 ± 5.36	0.82
Body mass index (kg/m^2)	30.08 ± 4.49	29.47 ± 4.24	0.616
Serum PSA (ng/ml)	8.86 ± 4.33	10.85 ± 5.08	0.116
Serum PSA <10 (n)	35 (85.4%)	6 (14.6%)	0.05
>10-20 (n)	21 (65.6%)	11 (34.4%)	
Prostate volume (ml)	84.91 ± 21.43	56.05 ± 8.42	0.001
Gleason 3+3	47 (82.5%)	17.5 (10%)	0.44
Perineural invasion	28 (80%)	7 (20%)	0.588
Clinical staging T1c	39 (79.6%)	10 (20.4%)	0.556
Prostate volume <70 ml	16 (57.1%)	12 (49.2%)	0.002
Number of positive cores			0.001
1	19 (100%)	0 (0%)	
2	10 (83.3%)	2 (16.7%)	
3	11 (61.1%)	7 (38.9%)	
4	16 (76.2%)	5 (23.8%)	
6	0 (0%)	3 (100%)	

PSA: Prostate specific antigen, NSM: Negative surgical margin, PSM: Positive surgical margin.

TABLE 2: The effect of preoperative variables on positive surgical margins in multivariate analysis.

	P values	Odds Ratio	%95 CI
Serum PSA >10 g/dl	0.373	3.91	0.124 - 2.187
Prostate volume <70 gr	0.023	9.601	1.249 - 20.124
Number of positive cores	0.991	21.315	None

PSA: Prostate specific antigen, CI: Confidence interval.

pathological stage, seminal vesicle and lymph node involvement and surgical margin status after RRP. Surgical experience can affect only surgical margin status among these variables.^{9,10} PSM is a relatively frequent condition due to the limited space in prostatic fossa. The distance between prostatic capsule and the surgical margin is just 2-3 mm. This close proximity can lead to PSM in case of non-favorable factors.^{9,11,12}

The overall PSM rate is ranging between 5-43% depending on patient selection criteria in different series.¹³ In our study, the PSM rate was 23.3% which is compatible with the other reports.

The preoperative clinical staging is the most important factor for inferior outcomes following radical prostatectomy. In a review, the rate of PSM was 17-22% for T1 and 27-40% for T2 stages after RRP.⁹ These results were confirmed with other studies with robot-assisted radical prostatectomy as an independent factor for PSM.^{14,15} Although the rate of PSM was higher in T2 group of our patients, we did not find a statistical significance. This can be related that our cohort was predominated by T1 patients (67.1%).

Serum PSA levels were found to be an important factor for PSM in the literature. In their study, Freeland et al. found the PSA levels as an independent risk factor for development of PSM.¹⁶ The rate of PSM in patients with a PSA level less than 10 was 8-30% and this rate was 25-43% for the patients with a PSA level more than 10 ng/dl.⁹ In our study, the rate of PSM was 14.6% and 34.4% in patients with a PSA level less than 10 ng/dl and PSA level between 10-20 ng/dl, respectively. Although this was statistically significant in univariate analysis, the multivariate analysis did not result in a significant relation.

Likewise, the PSA levels, biopsy Gleason Scores were found to be related with PSM. The patients with a preoperative Gleason Score less than 7 was found to have a PSM rate ranging between 11-30% and this rate was 17-43% for a Gleason score of 7 or more. In our study, the rate of PSM was 10% for Gleason 3+3. The comparison of Gleason 3+3 scores with Gleason scores of 3+4 or 4+3

were not statistically significant. We believe the highly prevalent rate of patients with 3+3 (78.1%) may be responsible for insignificant results.

In the present study, the prostate volume less than 70 ml was significantly associated with higher rates of PSM. This inverse relationship was reported in several open, laparoscopic and robot-assisted laparoscopic prostatectomy series.^{14,17-19} This phenomenon can be explained by overproduction of PSA in larger prostates which in turn emerge as an indicative factor for prostate biopsy. Also, this can increase detection of an insignificant cancer in which PSM is unlikely.^{20,21}

Similar to the inverse correlation in small prostates for PSM; the higher numbers of positive cores in a biopsy report can be suggestive of a clinically important disease. This issue has been studied in various trials.^{22,23} Although univariate analysis resulted a significant relation, there was no significant relation between the number of positive cores and PSM in multivariate analysis in the present study.

Perineural invasion has been studied as an indicator for aggressive disease for several cancers.²⁴ The importance of a perineurial invasion detected in a prostate biopsy specimen is controversial.²⁵ In the present study, we did not find a relation between perineural invasion and PSM.

The percentage of tumoral involvement in each biopsy core can be another predictor of inferior outcomes.⁸ We were not able to assess this relationship in our study due to infrequent documentation of this variable.

Having smaller group of patients is the main limitation of the present study which is making difficult to interpret the results. Another important limitation is predomination of the patients with Gleason 3+3.

CONCLUSION

In conclusion, preoperative parameters are important factors to achieve adequate outcomes after RRP. Smaller prostate volumes less than 70 gr increase the risk of PSM in patients with low or intermediate risk.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, ex-

pertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Erbil Ergenekon; **Design:** Erbil Ergenekon, Burhan Coşkun; **Control/Supervision:** Erbil Ergenekon, Burhan Coşkun; **Data Collection and/or Processing:** Burhan Coşkun; **Analysis and/or Interpretation:** Burhan Coşkun; **Literature Review:** Burhan Coşkun; **Writing the Article:** Burhan Coşkun; **Critical Review:** Burhan Coşkun, Erbil Ergenekon; **References and Fundings:** Erbil Ergenekon; **Materials:** Erbil Ergenekon.

REFERENCES

- Zorlu F, Zorlu R, Divrik RT, Eser S, Yorukoglu K. Prostate cancer incidence in Turkey: an epidemiological study. *Asian Pac J Cancer Prev.* 2014;15(21):9125-30. [\[Crossref\]](#) [\[PubMed\]](#)
- Scattoni V, Sangalli M, Roscigno M, Raber M, Gallina A, Fabbri F, et al. Detection and diagnosis of prostate cancer: what's new. *Arch Ital Urol Androl.* 2005;77(3):173-9. [\[PubMed\]](#)
- Montorsi F, Wilson TG, Rosen RC, Ahlering TE, Artibani W, Carroll PR, et al. Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. *Eur Urol.* 2012;62(3):368-81. [\[PubMed\]](#)
- Walsh PC. The status of radical prostatectomy in the United States in 1993: where do we go from here? *J Urol.* 1994;152(5 Pt 2):1816. [\[Crossref\]](#) [\[PubMed\]](#)
- Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol.* 2003;169(2):517-23. [\[Crossref\]](#) [\[PubMed\]](#)
- Meeks JJ, Eastham JA. Radical prostatectomy: positive surgical margins matter. *Urol Oncol.* 2013;31(7):974-9. [\[Crossref\]](#) [\[PubMed\]](#)
- D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol.* 2003;21(11):2163-72. [\[Crossref\]](#) [\[PubMed\]](#)
- Turan T, Boylu U, Başataç C, Gümüş E. Predictive preoperative factors for positive surgical margins in robotic radical prostatectomy in low-risk prostate cancer. *Turk J Urol.* 2013;39(2):69-73. [\[Crossref\]](#) [\[PubMed\]](#) [\[PMC\]](#)
- Wieder JA, Soloway MS. Incidence, etiology, location, prevention and treatment of positive surgical margins after radical prostatectomy for prostate cancer. *J Urol.* 1998;160(2):299-315. [\[Crossref\]](#) [\[PubMed\]](#)
- Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol.* 2005;174(3):903-7. [\[Crossref\]](#) [\[PubMed\]](#)
- Obek C, Sadek S, Lai S, Civantos F, Rubinowicz D, Soloway MS. Positive surgical margins with radical retropubic prostatectomy: anatomic site-specific pathologic analysis and impact on prognosis. *Urology.* 1999;54(4):682-8. [\[Crossref\]](#) [\[PubMed\]](#)
- Bong GW, Ritenour CW, Osunkoya AO, Smith MT, Keane TE. Evaluation of modern pathological criteria for positive margins in radical prostatectomy specimens and their use for predicting biochemical recurrence. *BJU Int.* 2009;103(3):327-31. [\[Crossref\]](#) [\[PubMed\]](#)
- Graefen M. The positive surgical margin after radical prostatectomy--why do we still not really know what it means? *Eur Urol.* 2006;50(2):199-201. [\[Crossref\]](#) [\[PubMed\]](#)
- Ficarra V, Novara G, Secco S, D'Elia C, Boscolo-Berto R, Gardiman M, et al. Predictors of positive surgical margins after laparoscopic robot assisted radical prostatectomy. *J Urol.* 2009;182(6):2682-8. [\[Crossref\]](#) [\[PubMed\]](#)
- Coelho RF, Chauhan S, Orvieto MA, Palmer KJ, Rocco B, Patel VR. Predictive factors for positive surgical margins and their locations after robot-assisted laparoscopic radical prostatectomy. *Eur Urol.* 2010;57(6):1022-9. [\[Crossref\]](#) [\[PubMed\]](#)
- Freedland SJ, Aronson WJ, Terris MK, Kane CJ, Amling CL, Dorey F, et al. Percent of prostate needle biopsy cores with cancer is significant independent predictor of prostate specific antigen recurrence following radical prostatectomy: results from SEARCH database. *J Urol.* 2003;169(6):2136-41. [\[Crossref\]](#) [\[PubMed\]](#)
- Marchetti PE, Shikanov S, Razmaria AA, Zagaja GP, Shalhav AL. Impact of prostate weight on probability of positive surgical margins in patients with low-risk prostate cancer after robotic-assisted laparoscopic radical prostatectomy. *Urology.* 2011;77(3):677-81. [\[Crossref\]](#) [\[PubMed\]](#)
- Link BA, Nelson R, Josephson DY, Yoshida JS, Crocitto LE, Kawachi MH, et al. The impact of prostate gland weight in robot assisted laparoscopic radical prostatectomy. *J Urol.* 2008;180(3):928-32. [\[Crossref\]](#) [\[PubMed\]](#)
- Chan RC, Barocas DA, Chang SS, Herrell SD, Clark PE, Baumgartner R, et al. Effect of a large prostate gland on open and robotically assisted laparoscopic radical prostatectomy. *BJU Int.* 2008;101(9):1140-4. [\[Crossref\]](#) [\[PubMed\]](#)
- Foley CL, Bott SR, Thomas K, Parkinson MC, Kirby RS. A large prostate at radical retropubic prostatectomy does not adversely affect cancer control, continence or potency rates. *BJU Int.* 2003;92(4):370-4. [\[Crossref\]](#) [\[PubMed\]](#)
- D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Tomaszewski JE, Wein A. A prostate gland volume of more than 75 cm³ predicts for a favorable outcome after radical prostatectomy for localized prostate cancer. *Urology.* 1998;52(4):631-6. [\[Crossref\]](#) [\[PubMed\]](#)

22. Zorn KC, Gofrit ON, Steinberg GP, Taxy JB, Zagaja GP, Shalhav AL. Planned nerve preservation to reduce positive surgical margins during robot-assisted laparoscopic radical prostatectomy. *J Endourol.* 2008;22(6):1303-9. [\[Crossref\]](#) [\[PubMed\]](#)
23. Tuliao PH, Koo KC, Komninos C, Chang CH, Choi YD, Chung BH, et al. Number of positive preoperative biopsy cores is a predictor of positive surgical margins (PSM) in small prostates after robot-assisted radical prostatectomy (RARP). *BJU Int.* 2015;116(6):897-904. [\[Crossref\]](#) [\[PubMed\]](#)
24. Chen SH, Zhang BY, Zhou B, Zhu CZ, Sun LQ, Feng YJ. Perineural invasion of cancer: a complex crosstalk between cells and molecules in the perineural niche. *Am J Cancer Res.* 2019;9(1):1-21. [\[PubMed\]](#)
25. Zhang LJ, Wu B, Zha ZL, Qu W, Zhao H, Yuan J, et al. Perineural invasion as an independent predictor of biochemical recurrence in prostate cancer following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. *BMC Urol.* 2018;18(1):5. [\[Crossref\]](#) [\[PubMed\]](#) [\[PMC\]](#)