



Can We Predict the Surgical Margin Positivity in Patients Treated with Radical Prostatectomy? A Multicenter Cohort of Turkish Association of Uro-Oncology

Radikal Prostatektomi Uygulanan Hastalarda Cerrahi Sınır Pozitifliğini Ön Görebilir miyiz? Çok Merkezli Üroonkoloji Derneği Çalışması

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Abstract of this study was presented in 10th Urooncology Congress (26-30th October 2011, Antalya).

What's known on the subject? and What does the study add?

Positive surgical margins after radical prostatectomy are associated with an increased hazard of biochemical recurrence, local recurrence, and the development of distant metastasis as well as the need for secondary cancer treatments. This is the first and single study that is analyzing the surgical margin positivity after radical prostatectomy and predictive factors from Turkey. Also, this study presents significant contribution to the literature with a high patient volume.

ABSTRACT

Objective

To analyze the parameters that predict the surgical margin positivity after radical prostatectomy for localized prostate cancer.

Materials and Methods

In this multicenter study, the data of 1607 consecutive patients undergoing radical prostatectomy for localized prostate cancer in 12 different clinics in Turkey between 1993-2011 were assessed. Patients who had neoadjuvant treatment were excluded. We assessed the relationship between potential predictive factors and surgical margin status after radical prostatectomy such as age, cancer characteristics, history of transurethral prostate resection, surgical experience and nerve-sparing technique by using univariate and multivariate Cox regression analyses and t test.

Results

The overall surgical margin positivity rate was 22.6% (359 patients). In univariate analyses, preoperative prostate specific antigen level, clinical stage, biopsy Gleason score, percentage of tumor involvement per biopsy specimen, transurethral prostate resection history, surgical experience and nerve-sparing technique were significantly associated with positive surgical margin rate. In multivariate analyses, preoperative prostate specific antigen level (OR: 1.03, p=0.06), percentage of tumor involvement per biopsy specimen (OR: 7.14, p<0.001), surgical experience (OR: 2.35, p=0.011) and unilateral nerve-sparing technique (OR: 1.81, p=0.018) were independent predictive factors for surgical margin positivity.

Conclusion

Preoperative prostate specific antigen level, percentage of tumor involvement per biopsy specimen, surgical experience and nerve-sparing technique are the most important predictive factors of surgical margin positivity in patients undergoing radical prostatectomy for localized prostate cancer.

Key Words

Prostate cancer, radical prostatectomy, surgical margin, PSA, percentage of tumor involvement, surgical experience, nerve sparing technique

ÖZET

Amaç

Localize prostat kanseri nedeniyle radikal prostatektomi yapılan hastalarda cerrahi sınır pozitifliğini öngörecek parametreleri analiz etmek.

Gereç ve Yöntem

Bu çok merkezli çalışmada, 1993-2011 yılları arasında Türkiye'deki 12 farklı klinikte lokalize prostat kanseri nedeniyle radikal prostatektomi uygulanan 1607 hastanın verileri değerlendirildi. Neoadjuvan tedavi alan hastalar çalışmaya dahil edilmedi. Radikal prostatektomi sonrası cerrahi sınır durumu ile ilişkili olabilecek yaş, kanser özellikleri, transüretral prostat rezeksiyonu öyküsü, cerrahi deneyim ve sinir koruyucu teknik gibi potansiyel öngörücü faktörler arasındaki ilişki tekli ve çoklu Cox regresyon analizi ve T-test kullanılarak değerlendirildi.

Bulgular

Tüm cerrahi sınır pozitiflik oranı %22,6 (359 hasta) olarak bulunmuştur. Tekli analizlerde, preoperatif prostat spesifik antijen seviyesi, klinik evre, biyopsideki Gleason skoru, biyopsi spesmenindeki kanser yüzdesi, transüretral prostat rezeksiyonu öyküsü, cerrahi deneyim ve sinir koruyucu teknik uygulaması pozitif cerrahi sınır oranı ile anlamlı olarak ilişkili bulunmuştur. Çoklu analizlerde ise preoperatif prostat spesifik antijen seviyesi (OR: 1,03, p=0,06), biyopsi spesmenindeki kanser yüzdesi (OR: 7,14, p<0,001), cerrahi deneyim (OR: 2,35, p=0,011) ve tek taraflı sinir koruyucu teknik uygulanması (OR: 1,81, p=0,018) cerrahi sınır pozitifliği için bağımsız öngörüşel faktörler olarak tespit edilmiştir.

Sonuç

Localize prostat kanseri nedeniyle radikal prostatektomi uygulanan hastalarda, preoperatif prostat spesifik antijen seviyesi, biyopsi spesmenindeki kanser yüzdesi, cerrahi deneyim ve sinir koruyucu teknik uygulaması cerrahi sınır pozitifliği öngören en önemli faktörlerdir.

Anahtar Kelimeler

Prostat kanseri, radikal prostatektomi, cerrahi sınır, PSA, tümör tutulum yüzdesi, cerrahi deneyim, sinir koruyucu teknik

Introduction

The pathologic definition of positive surgical margins (PSMs) seems straight forward which is considered as-"a tumor extending to the inked surface of the prostatectomy specimen that the surgeon has cut across"(1). Surgical margin status is independent of the pathological stage and a positive margin is not evidence of extraprostatic extension (2).

Positive margins have been reported in 7.6% to 41.6% of patients undergoing open RP in contemporary series and have been associated with an increased hazard of biochemical recurrence (BCR), local recurrence, and the development of distant metastasis as well as the need for secondary cancer treatment (3,4,5).

With the widespread diffusion of prostate-specific antigen (PSA) testing and improvements in surgical technique, the risk of PSMs has been reduced considerably (6). Even so, PSM rates are associated with the cancer properties, surgical technique and experiences of the surgeon and/or pathologist.

The aim of this multicenter study was to analyse the preoperative and peroperative factors predicting for PSM of 1607 patients who underwent radical prostatectomy (RP).

Materials and Methods

This multicenter study was performed by the Prostate Cancer Study Group of Turkish Association of Urooncology. Respective clinical and pathological findings of 1607 patients who underwent RP in 12 clinics in Turkey between 1993 and 2011 were assessed. All of the patients had clinically localized disease and thus were candidates for RP. The data about the age of the patient, preoperative PSA value, Gleason score of transrectal prostate needle biopsy, number of positive biopsy cores, percentage of cancer in biopsy specimens, history of transurethral resection of prostate (TURP), experience of the surgeon (number of procedures), type of surgical procedure (open, laparoscopic or robot-assisted), utilization of nerve-sparing (NS) technique, clinical stage, Gleason score of RP specimen, pathological stage, status of surgical margin and extracapsular extension, seminal vesicle invasion, and lymph node metastasis, follow up time and clinical progression status

were recorded in a common database. Those with missing information of the preoperative serum PSA level, Gleason score, clinical stage and patients who had neoadjuvant treatment were excluded from analysis. All biopsy specimens were graded histologically using the Gleason scoring system (7). For the purposes of this study all participating centers agreed to record capsular penetration, status of surgical margins, seminal vesicle invasion and lymph node status of the patients according to the 1992 TNM staging system (8). Cancer was considered as organ confined if the capsule was not penetrated. The clinical staging was also done by the aid of the same staging system. Preoperative characteristics and the pathological findings in our patients were compared to a published-Johns Hopkins cohort as well as other validation study groups.

Statistics

All statistical evaluations were 2-sided and performed by Statistical Package for Social Sciences (SPSS) Version 11.0 package program. The impact of possible predictive factors (age, preoperative PSA value, clinical stage, preoperative Gleason score, positive biopsy core ratio, history of TURP, surgical experience, NS status) on surgical margin positivity after RP were assessed by univariate and multivariate Cox regression analysis and t test.

Results

Median age of the patients was 63 years (range, 40 to 84 years). Preoperative serum PSA levels ranged from 0.4 to 100 ng/ml (median, 7.6 ng/ml). The median follow-up time was 24 months (range, 1 to 177 months). The patient characteristics were shown in Table 1.

| Table 1. Patient characteristics | |
|--|-----------------|
| Characteristics | n=1607 |
| Age, year, median (range) | 63 (40-84) |
| Preoperative serum PSA [‡] level, ng/ml, median (range) | 7.6 (0.4-100) |
| Biopsy Gleason score, % | |
| <7 | 73.4 |
| 3+4 | 15.5 |
| 4+3 | 6.1 |
| >7 | 5.0 |
| Clinical stage, % | |
| T1a | 0.4 |
| T1b | 1.1 |
| T1c | 55.5 |
| T2a | 28.8 |
| T2b | 9.1 |
| T2c | 3.9 |
| T3 | 1.4 |
| Percentage of cancer in biopsy specimens,% median (range) | 0.33 (0.04-1.0) |
| TURP [§] history, % | 6.7 |

‡: Prostate-specific antigen, §: Transurethral resection of prostate

All patients underwent RP. A total of 1585 patients (98.6%) underwent open RP. Characteristics of RP were shown in Table 2. NS technique utilized in 656/1607 (40.8%) of the patients. Previous case loads of surgeons were as shown in Table 2.

The overall PSM rate was 22.6% (359/1607 of the patients). In univariate analysis, preoperative PSA level (p=0.000), clinical stage (p<0.001), biopsy Gleason score (p<0.001), percentage of cancer in the biopsy specimens (p<0.001), history of TUR surgery (p=0.032), surgical experience (p<0.001) and NS technique (p=0.006) were all associated with PSM status in RP (Table 3). PSM rates increased with increasing PSA levels, biopsy Gleason score and percentage of cancer in biopsy specimens (Table 3). Nevertheless, same was true for the clinical stage. Interestingly, patients with cT1b disease had a significantly higher rate of PSM (47.1%). PSM status was significantly lower in surgeons with an experience of >300 procedures. Bilateral NS technique had lower (16.6%) PSM rate compared to non or unilateral NS techniques.

In multivariate analysis, preoperative PSA level (p=0.006), percentage of cancer in the biopsy specimens (p<0.001), surgical experience (p=0.011) and NS technique (p=0.021) were significant independent predictor factors of PSM in RP (Table 4).

Discussion

PSM after RP for prostate cancer has been shown to be associated with an increased risk of PSA recurrence, local recurrence, and the development of distant metastasis (5). Accordingly, preoperative prediction of surgical margin status is crucial to decide the proper surgical technique or necessity of neoadjuvant therapy. PSM depends on surgeon and his experience, surgical technique, cancer characteristics as well as pathological evaluation.

| Table 2. Characteristics of radical prostatectomy | |
|---|--------|
| Characteristics | n=1607 |
| Operation type, % | |
| Open | 98.6 |
| Laparoscopic | 1.2 |
| Robot-assisted | 0.2 |
| Nerve-sparing, % | |
| No | 59.2 |
| Unilateral | 12.0 |
| Bilateral | 28.8 |
| Surgeon experience, % | |
| 0-20 cases | 3.3 |
| 21-50 cases | 11.9 |
| 51-100 cases | 18.5 |
| 101-150 cases | 12.0 |
| 151-200 cases | 29.4 |
| 201-250 cases | 5.6 |
| 301-400 cases | 10.9 |
| >500 cases | 7.5 |

Table 3. Univariate analysis of risk factors that predict surgical margin status

| Risk Factors | Margin Status | | |
|---|---------------|------------|---------|
| | Negative | Positive | p value |
| Preoperative PSA [¥] level (ng/ml) | 1160 (77.5) | 337 (22.5) | 0.000 |
| 0-4 | 81 (85.3) | 14 (14.7) | |
| 4.1-10 | 768 (84.0) | 146 (16.0) | |
| 10.1-20 | 237 (65.5) | 125 (34.5) | |
| >20.1 | 74 (58.7) | 52 (41.3) | |
| Clinical stage | 1229 (77.4) | 358 (22.6) | <0.001 |
| T1a | 4 (80.0) | 1 (20.0) | |
| T1b | 9 (52.9) | 8 (47.1) | |
| T1c | 722 (82.0) | 158 (18.0) | |
| T2a | 344 (75.6) | 111 (24.4) | |
| T2b | 84 (64.4) | 52 (35.6) | |
| T2c | 44 (71.0) | 18 (29.0) | |
| T3 | 12 (54.5) | 10 (45.5) | |
| Biopsy Gleason score | 1231 (77.5) | 358 (22.5) | 0.004 |
| <7 | 928 (79.7) | 237 (20.3) | |
| 3+4 | 181 (73.3) | 66 (25.7) | |
| 4+3 | 69 (70.4) | 29 (29.6) | |
| >7 | 53 (67.1) | 26 (32.9) | |
| Percentage of cancer in biopsy specimens | 789 (80.6) | 190 (19.4) | <0.001 |
| 0-20 | 291 (90.4) | 31 (9.5) | |
| 21-40 | 286 (83.9) | 55 (16.1) | |
| 41-100 | 212 (67.1) | 104 (32.9) | |
| TURP [§] history | 1066 (78.3) | 296 (21.7) | 0.032 |
| No | 1003 (78.9) | 268 (21.1) | |
| Yes | 63 (69.2) | 28 (30.8) | |
| Surgical experience | 1078 (78.3) | 299 (21.7) | <0.001 |
| 0-20 | 36 (78.3) | 10 (21.7) | |
| 21-50 | 129 (78.7) | 35 (21.3) | |
| 51-100 | 178 (70.1) | 76 (29.9) | |
| 101-150 | 138 (84.7) | 25 (15.3) | |
| 151-200 | 295 (72.7) | 111 (27.3) | |
| 201-250 | 65 (72.2) | 25 (27.8) | |
| 301-400 | 142 (94.0) | 9 (6.0) | |
| >500 | 95 (92.2) | 8 (7.8) | |
| Nerve-sparing | 1097 (75.8) | 350 (24.2) | 0.006 |
| No | 531 (73.9) | 223 (26.1) | |
| Unilateral | 125 (71.8) | 49 (28.2) | |
| Bilateral | 341 (81.4) | 78 (18.6) | |

¥: Prostate-specific antigen, §: Transurethral resection of prostate

Table 4. Multivariate analysis of the preoperative predictor factors of surgical margin status

| Risk Factors | Multivariate | | |
|--|-----------------|---------------------|---------|
| | OR [¶] | 95% CI [†] | p value |
| Preoperative PSA [¥] level | 1.03 | 1.01-1.05 | 0.006 |
| Percentage of cancer in biopsy specimens | 15.56 | 7.14-33.90 | <0.001 |
| Surgical experience | 2.35 | 1.22-4.54 | 0.011 |
| Nerve-sparing | | | 0.021 |
| Unilateral | 1.81 | 1.11-2.97 | 0.018 |
| Bilateral | 0.81 | 0.51-1.30 | 0.386 |

¶: Odds ratio, †: Confidence interval, ¥: Prostate-specific antigen

PSM rates were reported between 7.6% and 41.6% in the literature (3,4,9,10,11). Overall PSM rate in our cohort was 22.6%, which was in line with previous publications.

Freedland et al. examined the association between preoperative PSA and risk of adverse pathologic features and biochemical progression on 925 men with prostate cancer treated by RP within the Shared Equal Access Regional Cancer Hospital (SEARCH) database (12). They showed that higher preoperative PSA values were associated with increased odds of extraprostatic extension, PSM, and seminal vesicle invasion and increased risk of biochemical progression. Cheng et al. also showed that preoperative serum PSA level was independently associated with surgical margin status in patients who underwent RP for prostate cancer (13). Similarly, PSM rates had been increased with increasing serum PSA levels in our study. Both in univariate and multivariate analysis indicated, a positive association with PSA levels and PSM.

Wieder and Soloway reported that patients with higher preoperative PSA levels, biopsy Gleason score 7 and clinical stage T2b, T2c or T3 cancer have a higher risk of positive margin (6). Ramos et al. showed lower PSM rates in T1c tumors compared to T2b in 1620 patients who underwent open RP by a single surgeon (14). Terakawa et al. showed that biopsy Gleason score and clinical T stage were significantly associated with the presence of PSM in 220 patient who underwent RP (15). Coelho et al. showed that the only preoperative factor predicting the PSM in 876 patients who underwent robot-assisted laparoscopic RP was clinical stage, with a higher PSM rate for T3 versus T1c and T2 versus T1c (16). In their study biopsy Gleason grade was not correlated with PSM in the multivariate analysis. In our study, PSM rates increased with clinical stages with the-only exception of cT1b group (47.1%). The reason for abovementioned high PSM rate could be preoperative understaging and technical difficulties in the operation due to a former TURP. Therefore, a detailed preoperative staging possibly with 3T multiparametric magnetic resonans imaging (MRI), an extended repeat prostate biopsy-as well as very selective use of nerve sparing procedure cases in this group of patients. detailed prostate biopsy) and do nevre sparing in selected cases in this group of patients.

In the present study, PSM rates had been increased with the increasing biopsy Gleason score-in the univariate analysis, however did not predict the margin status in multivariate analysis.

Cheng et al. showed that percentage of cancer in the biopsy specimens was independently associated with surgical margin status in patients who underwent RP for prostate cancer (13). Ahyai et al. also reported tumor volume is significantly larger in patients with a PSM than in those with no PSM in pT2 disease (17). In our study, PSM rate increased with the increasing percentage of cancer in biopsy specimens. The PSM rate had been increased from 9.5% in 0-20% cancer group to 32.9% in 41-100% cancer group (Table 3). In multivariate analysis, percentage of cancer in the biopsy specimen was an independent risk factor for PSM (OR: 15.56; 95% CI, 7.14 to 33.90).

Palisaar et al. assessed the oncological outcomes of patients treated with open RP for prostate cancer and who had previously undergone TURP (18). They reported that the overall PSM rate was insignificantly higher in cases who had RP after TURP. However after 1 year of follow-up the BCR (PSA>0.04 ng/mL) did not differ significantly in patients who had RP after TURP vs RP alone. Jaffe et al. reviewed outcomes for men with a history of TURP who underwent laparoscopic RP for prostate cancer and reported that these patients have worse outcomes about PSM (19). Gupta et al. analyzed and compared surgical, oncological, and functional outcomes of robot-assisted laparoscopic RP in patients with and without previous TURP and showed that post TURP patients were found to have significantly greater margin positivity rates (20). In our study, in the univariate analysis, PSM rates were higher in patients who underwent RP after TURP, however in the multivariate analysis, there was no correlation between the PSM rates and TURP history.

Chun et al. investigated the association between surgical volume (SV) and the rate of PSM after RP in a large single-institution cohort of patients (21). They reported that patients treated by surgeons with a very high volume (>1000 cases) can expect to have a significantly lower rate of PSM. In a recent study, learning curve for surgical margins after open RP was assessed in a cohort included 7765 prostate cancer patients who were treated with RP by one of 72 surgeons at four major United States academic medical centers (22). In multivariable analysis, surgeon experience was strongly associated with surgical margin status. In this abovementioned study, the authors reported that the probability of a PSM was 40% for a surgeon with 10 prior cases, and decreased to 25% for a surgeon with 250 prior cases. Eastham et al. examined the variations in the rate of PSMs among surgeons after controlling for the severity of disease and volume of cases per surgeon (23). A total of 4629 men were treated with RP by 1 of 44 surgeons at 2 large urban centers between 1983 and 2002 for clinical stage T1-T3NxM0 prostate cancer. In abovementioned study, multivariable analysis had been showed that, surgical volume was associated with surgical margin status after controlling for all other clinical and pathological variables. In our study, PSM rates had been decreased below 10% with the SV more than 300 cases. Furthermore, in multivariate analysis, surgeon experience is an independent factor for surgical margin status.

Palisaar et al. evaluated whether NS procedure itself is a risk factor for BCR in carefully selected patients (18). They suggested that NS RP is an oncologically safe procedure provided that appropriate preoperative selection of patients by means of a validated nomograms. Sofer et al. reported the results of 734 RP procedures in which 240 of them had NS technique (24). They suggested that in patients with localized prostate cancer, neither margin status nor biochemical-free survival

within 5 years of surgery were altered by the nerve preservation technique. In our study, in univariate analysis, PSM rates were lower in patients who underwent bilateral NS RP than the patients with non-NS RP. This can be a result of patient selection for NS surgery. In multivariate analysis, unilateral NS technique was an independent risk factor for surgical margin status.

Our study has some limitations. First, we could not assess the relationship between the surgical technique (open, laparoscopic and robot-assisted) and PSM since the data of laparoscopic and robot-assisted series were insufficient. Second, we could not evaluate the location of surgical margin on the radical prostatectomy specimens. Because this was a multicenter study and pathology specimens were assessed by different pathologist from different centers.

In conclusion, parameters related to the prostate cancer, such as preoperative PSA level, clinical stage, biopsy Gleason score, percentage of positive cores, history of TURP, surgical experience and NS technique were all significantly associated with the PSM rates. Preoperative PSA level, percentage of cancer in biopsy specimens, surgical experience and surgical technique are independent predictive factors for surgical margin status in patients who underwent RP for prostate cancer.

Conflict of interest

There are no conflicts of interest.

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