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ORIGINAL ARTICLE

Impact of positive surgical margin on biochemical recurrence following radical prostatectomy in locally advanced prostate cancer

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Abstract This study aimed to determine the effect of surgical margin positivity on biochemical recurrence (BCR) in patients with locally advanced prostate cancer (PCa) who underwent radical retropubic prostatectomy (RRP). The medical records of all patients with locally advanced PCa that underwent RRP were retrospectively reviewed. Patient demographics, digital rectal examination findings, prostate biopsy Gleason score, prostate volume, pre- and post-treatment prostate-specific antigen (PSA) levels, definitive pathology Gleason score, surgical margin status, seminal vesicle invasion, perineural invasion, absence or presence of BCR, and the time to BCR were analyzed. The study included 130 patients. The final pathologic examination showed that seven (5.4%) patients had T3a disease and 123 (94.6%) had T3b disease. In all, 93 (71.5%) patients had a positive surgical margin [SM(+)], whereas 37 (28.5%) patients had a negative surgical margin [SM(−)]. Among the seven patients with pT3a disease, four (57.1%) had SM(+), whereas 89 (72.4%) of the 123 patients with pT3b disease had SM(−). BCR occurred in 11.8% (11 of 93) of patients with SM(+) and in 45.9% (17 of 37) of those with SM(−) ($p < 0.001$). Multivariate logistic regression analysis showed that SM(+) was the only significant predictor of BCR following RRP (relative risk, 0.163; 95% confidence interval (0.062–0.433); $p < 0.001$). SM(+) in RRP specimens is not always indicative of BCR in patients with locally advanced PCa. RRP should be considered an effective treatment choice for selected patients with locally advanced PCa, despite the associated high SM(+) rate.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Prostate cancer (PCa) is the most common solid neoplasm in males in Europe, with an incidence of 214 cases per 1000 males [1]. Both genetic and epigenetic factors play a role in the etiopathogenesis and progression of PCa [1,2]. Radical prostatectomy (RP) is the most common treatment in patients with localized PCa and a life expectancy >10 years. Despite the favorable rate of cancer control associated with RP, approximately 25% of all patients [3] and ≤60% of patients with locally advanced PCa that undergo RP experience biochemical recurrence (BCR) within 10 years of treatment [4].

The prostate biopsy Gleason score (GS) and pretreatment serum prostate-specific antigen (PSA) level are well-known predictors of BCR following RP [5,6]. Surgical margin positivity (SM+), which occurs in ≤38% of patients who undergo RP, is also thought to be associated with BCR [6]. The present study aimed to determine the effect of SM+ on BCR in patients with locally advanced PCa that underwent radical retropubic prostatectomy (RRP).

Material and methods

The medical records of all patients with pathologically locally advanced PCa who underwent RRP between October 1, 2005 and October 1, 2015 were retrospectively reviewed. Patients with a history of neoadjuvant or adjuvant therapy for PCa were excluded from the study. The same RRP technique was performed by multiple surgeons. Extended lymph node dissection was performed in patients considered high-risk, according to D'Amico's risk classification [7].

Patient demographics, digital rectal examination (DRE) findings, prostate biopsy GS, prostate volume, pre- and post-treatment PSA levels, free/total PSA ratio, definitive pathology GS, surgical margin status, seminal vesicle invasion, perineural invasion, presence of BCR, and time to BCR were analyzed. BCR was defined as a post-RRP PSA level ≥ 0.2 ng/mL [8]. BCR was stratified as early (occurring within 1 year of RRP) and late (occurring >1 year after RRP). Suspected extraprostatic extension based on DRE was defined as DRE positive (+) and the absence of extraprostatic extension in DRE was defined as DRE negative (−).

Statistical analysis was performed using SPSS v.21 (IBM SPSS Statistics version 21). The study variables were investigated using visual and analytical methods (Kolmogorov–Simirnov test) to determine the normality of their distribution. Normally distributed variables are shown as mean ± standard deviation. Dual comparisons between groups were made using Student *t* test, Mann–Whitney *U* test, and Chi-square test. Multivariate logistic regression analysis was used to identify the factors associated with BCR. The level of statistical significance was set at $p < 0.05$.

Results

The study included 130 patients with locally advanced PCa who underwent RRP. The mean age of the patients was 64.30 ± 6.03 years, and the mean preoperative PSA level was 8.74 ± 6.16 ng/mL. The final pathologic examination showed that seven (5.4%) of the patients had T3a disease and 123 (94.6%) had T3b disease. Additionally, perineural invasion was observed in 67 (51.5%) patients.

In all, 93 (71.5%) of the patients had SM(+), versus 37 (28.5%) who had SM(−). There were no significant differences in mean age, preoperative PSA level, preoperative prostate biopsy GS, prostate volume, or free/total PSA ratio between SM(+) and SM(−) patients, whereas the final pathology GS was significantly lower in SM(+) patients than in SM(−) patients ($p = 0.001$; Table 1). In total, four (57.1%) of the seven patients with pT3a disease had SM(+) and 89 (72.4%) of the 123 patients with pT3b disease had SM(−).

Among the 130 patients, 28 had BCR after RRP: 12 patients had early BCR, versus 16 with late BCR. BCR occurred in 11.8% (11 of 93) of patients with SM(+) and in 45.9% (17 of 37) of patients with SM(−); the difference was significant ($p < 0.001$). There was no significant difference in the mean time to BCR after RRP between SM(+) patients (17.36 ± 14.37 months) and SM(−) patients (19.65 ± 12.8 months). The mean follow-up period after RRP in all patients was 32 ± 17.08 months (range, 7–90 months), whereas the patients without BCR had a mean follow-up of 30.6 ± 17.4 months (range, 7–90 months).

Multivariate logistic regression showed that SM(+) was the only significant predictor of BCR after RRP (relative risk, 0.163; 95% confidence interval (0.062–0.433); $p < 0.001$) rather than DRE, lymph node involvement (LNI), seminal vesicle involvement (SVI), or perineural invasion (PNI). Moreover SM(+) was associated with PNI ($p = 0.001$), but not with DRE, LNI, or SVI (Table 2).

Suspicion of extracapsular extension based on DRE was noted in 34 (26.2%) patients. There were not significant differences in mean age, PSA level, prostate volume, or the free/total PSA ratio between the DRE(+) and DRE(−) patients; however, there was a significant difference in preoperative prostate biopsy GS and final pathology GS ($p < 0.001$ and $p < 0.001$, respectively). The time to BCR after RRP was significantly longer in DRE(−) patients ($p = 0.001$). Furthermore, there was a positive correlation between DRE(+) and final pathology GS ($p < 0.001$); however, DRE(+) was negatively correlated with SVI ($p < 0.001$).

Table 1 Patient characteristics according to SM status.

	SM(−)	SM(+)	*p*
No. of patients ($n = 130$)	37 (28.5%)	93 (71.5%)	
Age ± SD (y)	64.86 ± 5.55	64.08 ± 6.23	0.5
PSA (ng/mL)	9.56 ± 7.56	8.41 ± 5.51	0.15
Biopsy GS	6.33 ± 0.81	6.28 ± 0.82	0.7
Final pathology GS	6.99 ± 0.9	6.33 ± 0.85	0.001
Prostate volume	38.27 ± 15.99	39.52 ± 14.49	0.66
Free/total PSA	13.97 ± 7.78	14.88 ± 6.92	0.51
Time to BCR ± SD (min)	19.65 ± 12.8	17.36 ± 14.37	0.52

BCR = biochemical recurrence; GS = Gleason score; PSA = Prostate-specific antigen; SD = standard deviation; SM = surgical margin.

Table 2 Distribution of patients according to BCR status.

	BCR(−)	BCR(+)	Number of patients	*p*
No. of patients ($n = 130$)	102 (78.5%)	28 (21.5%)	130	
SM(−)	20	17	37	<0.001
SM(+)	82	11	93	
DRE(−)	79	17	96	0.07
DRE(+)	23	11	34	
SVI(−)	5	2	7	0.64
SVI(+)	97	26	123	
PNI(−)	56	11	67	0.14
PNI(+)	57	12	69	
LNI(−)	40	10	50	0.73
LNI(+)	62	18	80	

BCR = biochemical recurrence; DRE = digital rectal examination; LNI = lymph node involvement; PNI = perineural invasion; SM = surgical margin; SVI = seminal vesicle involvement.

Discussion

Numerous tools for predicting the recurrence of PCa following definitive treatment have been developed during the past 20 years. The most well known of such tools are the Kattan nomogram, the Stephenson nomogram, D'Amico criteria, and CAPRA-S (Cancer of the Prostate Risk Assessment score) [9–13]. Additionally, the Partin tables are used to predict if PCa will be confined to the prostate, based on GS, the PSA level, and the clinical stage of PCa [14]. In addition to preoperative predictors, other factors associated with surgery and final pathology might play a role in the recurrence of PCa; however, final pathology might not be a reliable tool for predicting oncologic outcome, as some patients with prostate-confined disease develop recurrence and others with nonorgan confined PCa remain disease-free [10,15].

SM(+) is considered a significant predictor of disease recurrence following RP [16–21]. In contrast, some researchers report that there is no association between disease recurrence and the surgical margin status of RP specimens [22]. Karakiewicz et al. [19] observed a 3.7-fold increase in the risk of progression after RP in patients with a final pathology of SM(+) ($p = 0.001$), and reported that surgical margin status was associated with final pathology GS ($p = 0.008$) and LNI ($p < 0.001$). It was also reported that the frequency of SM(+) in patients with pT3a disease (30.5%) and pT3b-4 disease (48.5%) was significantly higher than in those with pT2 disease (8.2%) ($p < 0.001$) [18]. The same study also reported that the BCR rate in patients with SM(+) was 64.3% and that the local recurrence rate was 18.6%, both of which were significantly higher than in patients with SM(−) ($p < 0.001$) [18].

Boorjian et al. [20] suggested that SM(+) is a risk factor for BCR, local recurrence, and the need for salvage therapy. The 10-year BCR-free rate in patients with SM(+) was 56%, versus 77% in those with SM(−); the difference was significant ($p < 0.001$). Among the 3651 patients in their study with SM(+), 56.8% had pT2N0 disease, 21.7% had T3aN0 disease, and 13.4% had T3b/4N0 disease. Alkhateeb et al. [21] studied the effect of SM(+) on BCR after RP, according to PCa risk groups. The SM(+) rate in patients with pT2 disease (13.6%) was significantly lower than in those with pT3 disease (35.7%) ($p < 0.0001$). At a median follow-up of 79 months, the biochemical progression-free survival (BPFS) rate in patients with SM(+) was 79.9%, compared with 93.8% in those with SM(−) ($p < 0.001$). The researchers concluded that SM(+) might be a predictor of BPFS in patients with moderate- and high-risk PCa, but not in patients with low-risk disease. Another study reported that SM(+) was associated with BCR in patients with pT3a disease and a GS ≤6, but not in patients who had organ-confined high-grade PCa, and SVI and LNI [23].

In contrast with these earlier studies, Stamey et al. [22] reported that SM(+) is not an independent predictor of BCR after RP. In another study, a preoperative PSA level >10 ng/mL and a final pathology GS ≥7 were associated with BCR in patients with pathologically organ-confined disease and SM(−) [15]. Additionally, the BCR risk in patients with organ-confined PCa (pT2) and SM(+) was found similar in those with pT3 disease and a PSA level ≤10 ng/mL by Eminaga et al. [6]. Moreover, the SM(+) rate in patients with pT2, pT3a, and pT3b PCa was 24.7%, 54.9%, and 58.2%, respectively. Furthermore, the preoperative PSA level in patients with SM(+) was significantly higher (13.1 ng/mL) than in those with SM(−) (9.4 ng/mL) ($p < 0.001$). SM(+) was also associated with higher rate of BCR in pT2 patients than was SM(−), but not in pT3 patients [6]. In concordance with Eminaga et al. [6], Corcoran et al. [24] reported that SM(+) is a risk factor for BCR in patients with intermediate disease (PSA, 10–20 ng/mL; stage, pT2; GS, 7). They also noted that the BCR risk in high- and low-risk patients is associated with intrinsic tumor biology, and that SM(+) has a limited effect on BCR [24].

In the present study, BCR occurred in 11.8% of patients with SM(+) and in 45.9% of patients with SM(−). Multivariate regression analysis in the present study showed that SM(+) was the only significant negative predictor of BCR. Accordingly, the findings show that SM(+) is not always indicative of BCR after RP in patients with locally advanced PCa. This finding is in contrast to the generally accepted understanding of the effect of SM(+) on BCR, and the difference might be associated with the present study's small patient population and the short duration of follow-up. In addition, as mentioned above, intrinsic tumor biology might have the greatest effect on BCR in patients with locally advanced PCa following RP.

Limitations

In the present study SM(+) in patients with T3a and T3b disease was 57.1% and 72.4%, respectively. Although the SM(+) rate in the present study's patients with T3a disease was similar to that in earlier reports, the SM(+) rate in the present study's patients with T3b disease was higher than previously reported. This difference might have been due to the long learning curve of different surgeons or due to stiffness and extent of the cancer tissue. Moreover, not all surgeons in the present study had undergone uro-oncology fellowship training. As such, we think additional larger-scale prospective studies based on surgery performed by

only one surgeon or only those with uro-oncology training are needed.

Conclusion

SM(+) is widely considered a poor prognostic factor and a predictor of BCR in PCa patients after RP. Despite the large number of relevant studies, the effect of SM(+) on PCa progression and cancer-specific survival following RP remains unclear. Furthermore, the accuracy of preoperative prediction of SM(+) in RP specimens via radiological imaging, physical examination, and the preoperative PSA level and GS has yet to be proven.

The present findings show that surgical SM(+) in RP specimens is not always indicative of BCR in patients with locally advanced PCa. RP should be considered an effective treatment choice for selected patients with locally advanced PCa, despite the high SM(+) rate. Additional larger-scale prospective randomized studies are needed to confirm the present study's findings.

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