Clinical significance of surgical margin status in patients subjected to radical prostatectomy

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KEY WORDS
prostate » prostate cancer » radical prostatectomy » positive surgical margins

ABSTRACT
The aim of this study is to evaluate the clinical value of positive surgical margins (PSM) in patients subjected to radical prostatectomy (RP).

The data of men who were subjected to RP from the 1st of January, 2001 to the 30th of May, 2010 were analyzed. Specimens with PSM were again evaluated to confirm the presence of positive margins.

PSM were found in 64 (25%) out of 255 analyzed patients. Out of all clinical features, only biopsy Gleason score and clinical stage of the disease were found to be predictive of PSM. Biochemical recurrence (BR) was found in 42 (16.5%) men, among them 17 (26.6%) had PSM and 25 (13.1%) had negative margins. The risk of BR in those with „focal” PSM (<3 mm) did not differ from the risk of BR observed in patients without PSM. In contrast, the likelihood of BR was significantly greater in cases of PSM in which maximum longitude exceeded 3 mm. Reevaluation of the PSM specimens revealed equivocal margins status in six cases.

PSM are not inevitably associated with BR. The risk of failure is influenced by their length. Reevaluation of the prostate specimen may lead to surgical margins status modification.

MATERIALS AND METHODS
After institutional review board approval we retrospectively analyzed prospectively collected data of all consecutive men subjected to RP between the 1st of January, 2001 and the 31st of May, 2010. Patients who had received neoadjuvant hormonal therapy or were found to have positive lymph nodes were excluded from the analysis, as were patients subjected to aEBRT. Finally, the data of 255 men was assessed. All patients had undergone either retropubic radical prostatectomy (n = 64) or endoscopic extraperitoneal radical prostatectomy (n = 191). Standard lymph node dissection was performed in each case before vesico-urethral anastomosis. Prostatectomy specimens were evaluated according to the Stanford technique and analyzed by a single uropathologist. Pathological stage was assessed according to 1997 TNM criteria against obligatory implementation of aEBRT in all patients with PSM after RP. The present study is aimed at the evaluation of clinicopathological data, which would predict the BR of PCa following RP with special attention put on the role of PSM magnitude and the influence of a second pathological evaluation on the surgical margins status.
Statistical analysis was done using STATISTICA 8.0 software. The Kaplan–Meier method was used to estimate biochemical free survival. The factors that influence BFS were assessed using Cox proportional hazard regression model. P < 0.05 was considered as significant.

### RESULTS

Correlation of margin status and clinicopathological data of entire cohort

| Surgical margins status | Entire cohort | P value |
|-------------------------|--------------|---------|
| Negative margins        | 191 (74.9%)  |         |
| Focal positive margins  | 47 (18.4%)   |         |
| Extensive positive      | 17 (6.7%)    |         |
| margins                 | 255          | Not applicable |
| Age (mean ±SD)          | 62.0 ±6.6    | 62.6 ±6.3 |
| PSA (mean ±SD)          | 9.35 ±5.49   | 8.97 ±5.15 |
| PSAD (mean ±SD)         | 0.27 ±0.20   | 0.23 ±0.16 |
| Prostate volume (mean ±SD) | 42.6 ±24.4 | 44.1 ±22.4 |
| Abnormal DRE            | 102 (53.4%)  | 24 (51.1%) |
| Abnormal TRUS           | 107 (56.0%)  | 31 (66.0%) |
| Number of positive biopsy cores | 2.8 ±1.6 | 3.0 ±2.1 |
| Maximum percentage of cancer in biopsy core | 51.4 ±27.9 | 55.9 ±28.5 |

### Table 1. Descriptive data of entire cohort

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Fig. 1. Biochemical progression free survival depending on margin status (NSM – negative surgical margins, fPSM – focal positive surgical margins, ePSM – extensive positive surgical margins).

PSM were identified in 64 (25%) of 255 analyzed cases (this includes PSM reevaluated as false positives further on). Among them, fPSM and ePSM were established in 47 (18%) and in 17 (7%) cases respectively. Clinical and pathological data of the entire cohort is presented in Table 1. Out of all features only biopsy Gleason score (GS) and clinical stage of the disease were found to be predictive of PSM. Those with negative surgical margins (NSM) and PSM had lower biopsy GS values than those with ePSM (5.7 ± 1.4 vs. 5.2 ± 1.2 vs. 6.4 ± 1.2, p = 0.003). Similarly, patients with NSM and PSM had lower specimen GS than those with ePSM (6.4 ± 1.3 vs. 5.9 ± 1.4, 7.0 ± 1.1, p = 0.009). However those with fPSM had lower biopsy as well as specimen GS than those with NSM (p < 0.05). Focal PSM and ePSM were found in 38 (48.7%) and 14 (18.0%) out of 78 clinically, locally advanced PCa cases respectively (p < 0.001). Again, fPSM and ePSM were found in 44 (51.8%) and 13 (15.3%) out of 85 locally advanced PCa cases respectively (p < 0.001). Among all 177 cases of clinically organ-confined disease, fPSM and ePSM were identified in nine (5%) and three (1.7%) cases, respectively. Again, fPSM and ePSM were found in three (1.8%) and four (2.4%) out of 170 pathologically organ confined PCa cases, respectively.

### Correlation of clinicopathological data and clinical outcome

BR was observed in 42 (16.5%) patients (Table 2). In comparison to those without, those with BR had significantly greater PSA (8.9 ng/ml ± 5.2 vs. 10.9 ng/ml ± 6.1, p = 0.03), abnormal TRUS (115 (54.9%) vs. 31 (73.8%), p = 0.04), greater number of positive biopsy cores (2.7 ± 1.6 vs. 3.4 ± 2.1, p = 0.04), greater maximum percentage of cancer in biopsy core (50.2 ± 27.5 vs. 66.9 ± 29.2, p < 0.001), and greater specimen GS (6.7 ± 1.6 vs. 6.2 ± 1.3, p < 0.05). BR was also more frequently identified in those men who had clinically (64.3%) and pathologically (69.1%) locally advanced disease as opposed to
those with clinically (64.3% vs. 24.2%, p < 0.001) and pathologically (69.1% vs. 30.9%, p < 0.001) organ-confined PCa (Table 2).

**Correlation of margin status and clinical outcome**

BR was observed in 17 (26.6%) men among those with PSM and in 25 (13.1%) men among those with NSM (p = 0.01). However DFS for those with fPSM did not differ significantly from the survival for those without PSM (Table 2). For both groups, DFS was significantly longer than the survival observed in those with ePSM (Fig. 1).

In univariate Cox regression analysis DFS was significantly associated with the following features: PSA, maximum percentage of cancer in biopsy core, clinical and pathological stage of PCa, presence of extraprostatic extension and seminal vesicle invasion, specimen GS, positivity of margin status, as well as the presence of focal or extensive PSM (Table 3). However, only PSA, specimen GS, and extraprostatic extension were significant variables associated with DFS in multivariate analysis (Table 4).

**Reevaluation of the specimens with positive surgical margins**

Reevaluation of the specimens with PSM showed equivocal character in six of them. These were all classified as focal ones. The cancer tissue was found very close to the inked margin of the specimen. They could be classified as negative. One of the false positive cases is shown (Fig. 2).

**DISCUSSION**

**Role of positive surgical margins**

The negative impact of PSM after radical prostatectomy on BR is widely known [7, 10, 11, 12]. In our cohort of patients surgically treated due to PCa, 27% of men with PSM experienced cancer recurrence in contrast to 13% of those who had no PSM. A recently published analysis of data that referred to similar dates also shows almost the same correlation between margin status and cancer outcomes (31.5% vs. 8.9% for PSM vs. NSM, respectively) [8]. As suspected, the rates of positive margins rose together with pathological stage and GS. The bigger the tumor and the greater the GS, the higher the probability of PSM. Several techniques

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**Table 2.** Descriptive data of patients with biochemical recurrence

| Biochemical recurrence | No | Yes | P value |
|------------------------|----|-----|---------|
| Number of pts. (rate)  | 213 (83.5%) | 42 (16.5%) | Not applicable |
| Age (mean ±SD)         | 62.4 ±5.7 | 61.5 ±6.0 | 0.318 |
| PSA (mean ±SD)         | 8.91 ±5.15 | 10.92 ±6.12 | 0.027 |
| PSAD (mean ±SD)        | 0.25 ±0.19 | 0.30 ±0.20 | 0.129 |
| Prostate volume (mean ±SD) | 43.5 ±24.8 | 43.4 ±24.0 | 0.968 |
| Abnormal DRE           | 110 (51.6%) | 27 (64.3%) | 0.133 |
| Abnormal TRUS          | 115 (54.5%) | 31 (73.8%) | 0.021 |
| Number of positive biopsy cores | 2.7 ±1.6 | 3.4 ±2.1 | 0.043 |
| Maximum percentage of cancer in biopsy core | 50.2 ±27.5 | 66.9 ±29.2 | <0.001 |

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**Table 3.** Features associated with DFS in 255 patients subjected to radical prostatectomy based on proportional Cox regression model (univariate analysis)

| Evaluated feature | HR   | p   |
|-------------------|------|-----|
| Age               | 0.98 | 0.382 |
| PSA               | 1.05 | 0.044 |
| PSAD              | 3.19 | 0.110 |
| Prostate volume   | 1.00 | 0.838 |
| Abnormal DRE      | 1.53 | 0.180 |
| Abnormal TRUS     | 1.72 | 0.108 |
| Number of positive biopsy cores | 1.12 | 0.133 |
| Maximum percentage of cancer in biopsy core | 1.02 | 0.001 |

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**Table 4.** Selected features associated with DFS based upon uni- and multivariate analysis

| Evaluated feature | Univariate analysis | Multivariate analysis |
|-------------------|---------------------|-----------------------|
|                   | HR | p   | HR | p   |
| PSA               | 1.05 | 0.028 | 1.05 | 0.034 |
| Pathological stage of PCa: | | | |
| T2                | 4.01 | <0.001 | 4.01 | <0.001 |
| T3a/T3b           | 4.01 | <0.001 | 4.01 | <0.001 |
| Specimen Gleason score | 1.47 | 0.001 | 1.47 | 0.001 |
including frozen sections failed to prevent the presence of PSM [13]. A recently published series points at a new technique using intraoperative photodynamic diagnosis to decrease the rates of positive margins and seems promising, but needs further evaluation [14]. Preoperative planning and surgical experience might play a role in diminishing the rates of positive margins after radical prostatectomy [15].

The group of patients who were found to have PSM is not homogenous. The quality of margins varies substantially. For better prediction, several attempts were made to subdivide patients with PSM. To this end, the extent and number of positive margins were evaluated. We have shown, as have others, that extensive PSM significantly increases the risk of PSA failure. In contrast, patients with fPSM had better prognosis, the prognosis that did not differ from the one observed in the group of men with negative margins. The role of the extent of PSM was the ultimate goal of many studies. The majority of them conclude the bigger the positive margin is, the greater the risk of recurrence [9], even in organ-confined disease [10]. However, 5-ys disease-free survival associated with extensive margins amounts to 31-39% [7, 9], and the majority of patients with ePSM stay cancer free for noticeably long periods of time.

Surprisingly, multivariate analysis did not reveal any significant role of surgical margins status in defining the risk of PSA failure. This was also true in another study [12], which included a similar number of patients for analysis indicating that an independent influence of margins positivity per se is not as high as expected. However, it requires much larger numbers of patients. Also, multivariate analysis, done upon data of about 2000 men, did not show a significant influence of margins positivity on BR in high GS cases [9, 10]. Conversely, our results suggest that pathological stage, preoperative PSA, and maximum percentage of cancer in biopsy core are the strongest discriminators of DFS (Table 4). None of these depend on surgical technique.

To our knowledge there is no published data concerning a second opinion regarding margins status after radical prostatectomy. Intra- and interobserver variability of GS assessment is widely known. Our data show that, in cases of focal PSM, reevaluation of the specimen might have a role in postoperative care especially when there is no proof of extracapsular extension of the disease, which would qualify the patient to adjuvant radiation anyway.

**Clinical significance of positive surgical margins**

Clinical significance of PSM is not well understood. Three large studies were dedicated to the role of adjuvant radiotherapy administered in men who were found to have PSM and/or extracapsular extension and/or seminal vesicle involvement. [5, 16, 17]. Their results among others indicated that those men who were found to have one of the above-mentioned negative features, including PSM, benefited from adjuvant radiotherapy as opposed to those subjected to observation at least at the beginning. However, at least 40% of patients randomized into the control group did not experience PSA failure after 12.5 yrs. of median follow-up. Furthermore, salvage treatment was administered late, when PSA by far exceeded 0.2 ng/ml in many cases and about one third received salvage therapy upon clinical failure. The time schedule of salvage management was not clearly suggested and therapy was not uniformly implemented. Not all patients received radiation. The different strata of extracapsular extension and positive margins were not analyzed. The message coming from the studies is that radiation administered shortly after radical prostatectomy improves clinical outcome in a select group of patients. From the other side it is known that adjuvant radiotherapy is associated with an increased risk of toxicity when compared to the salvage method. The Southwest Oncology Group adjuvant RT trial reported a significantly higher overall rate of adverse events among men in the adjuvant EBRT group (28.8%) than in the observation cohort (11.9%) [5]. Furthermore, there is no evidence that would support implementation of adjuvant EBRT instead of salvage radiation done at the very beginning of PSA recurrence (0.2-0.5 ng/ml).

The discovery of PSA significantly improved the management of patients with PCs. This includes follow-up after radical prostatectomy. The test allows recognition of cancer failure very early in its clinical course. It is widely known that salvage radiation is associated with the most favorable results when implemented in patients with low PSA values (<1.0 ng/ml), especially in those with PSM. The probability of complete biochemical remission amounts to 70% in this setting [8]. Finally, a recently published analysis conducted on the data of 11,521 men subjected to RP revealed that PSM are not associated with PCa mortality [18]. Therefore, we propose that positive margins should not be the only feature that would qualify patients to adjuvant radiation since many of them will not experience PSA failure. This is especially true in men in whom there is no proof of extracapsular extension of PCs and the positive margin is focal.

It is worth to stress the value of second evaluation of margins status after radical prostatectomy. The risk of false positivity should always be taken into consideration since this phenomenon is not negligible [19]. Reassessment of prostate specimens in those who experienced BR influences pathological staging and grading in 71% of them. These facts should be widely discussed with the patient when counseling further management after radical prostatectomy when unfavorable histological results are discovered.

**Limitations**

We acknowledge several limitations of this study. The majority of them result from its retrospective nature (referral, selection, inclusion, etc.). A greater number of patients and longer follow-up would likely increase clinical significance of focal PSM as the Kaplan-Meier curves started to diverge at the end of observation. We hope that the upcoming years will provide an answer. On the other hand, the majority of patients with biochemical failure are diagnosed within two years after surgery [20]. Even in the worst scenario, patients with fPSM have greater probability to remain without BR than to experience PSA failure. This argues against implementation of adjuvant radiation in this group of patients, as it would be unnecessary in the majority of them.

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Fig. 2. Equirogl surgical margin.
CONCLUSIONS

PSM found after radical prostatectomy impose a significant risk on a patient’s prognosis. The group of PSM is heterogeneous and involves at least two distinctive groups with focal and extensive margins. Those men who were diagnosed with the former ones would need to be subjected to close follow-up as their risk of PSA failure is not high. The clinical value of extensive margins would fit to the model of adjuvant radiation as the probability of future recurrence is high. However, the final decision of EBRT administration would lie in the patient’s hands after reevaluation of prostate specimen and proper counseling.

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