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.

INTRODUCTION

Prostate cancer (PCa) is one the most common malignancies found in men. It is estimated that in 2012, PCa was diagnosed in 241,740 men [1]. Simultaneously, 28,170 men succumbed to the disease. This made PCa the second leading cause of cancer-related death in the US. In Poland, a similar PCa epidemiology is observed. It is the second most frequently diagnosed cancer and the second most common cause of cancer-related death in men [http://85.128.14.124/krn]. The majority of newly diagnosed cases are organ confined [2]. Mainstay therapy for localized disease is radical prostatectomy (RP) [3]. Despite providing excellent local cancer control, 25-63% of those subjected to RP will experience cancer recurrence and 3-13% of them will eventually die of the disease [4]. Apart from biological cancer features, positive surgical margins (PSM) remain one of the most important negative prognostic factors established after RP. To decrease future cancer recurrence risk, adjuvant external beam radiotherapy (aEBRT) is recommended to those with PSM. A recently updated randomized trial confirmed the favorable influence of aEBRT on overall survival of men subjected to RP due to locally advanced disease [5]. However, not all candidates to aEBRT will experience cancer recurrence. In fact, 40-60% among those in the observation arm with undetectable PSA following RP stay free from cancer recurrence [6].

It has been clearly shown that PSM after RP are associated with BR. To better stratify the risk, many subdivisions of patients with PSM were proposed depending on the length, number and, according to some, location of the margins [7, 8]. A recent series of adjuvant treatment-naive patients has shown that those with PSM have a 57.5% 5-year disease free survival (DFS) [9]. Nevertheless, 10-year DFS for those with focal PSM and for those with extensive PSM varies significantly and equals 64% and 38% respectively [10]. Furthermore, pathological assessment of surgical status might be the subject of bias, especially in those with focal margins. It argues 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.

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 to avoid misinterpretation of older (<2002) prostate specimens. PSM were defined as the presence of cancer tissue at the inked surface of the specimen. PSM were characterized as focal (fPSM) and extensive (ePSM) if their longitude amounted to or exceeded 3 mm respectively. Patients were followed at our institution at three to six month intervals. Mean follow-up was 3.79 yrs. (range from three months to 9.75 years).

The primary end-point was biochemical free survival (BFS) in patients according to surgical margins status and its extensiveness. BR was defined as PSA exceeding 0.2 ng/ml. BFS was defined as the time from surgery date to the time of BR.

Specimens with PSM were again reevaluated by the pathologist who primarily observed and formally stated the positivity of the margins.

Table 1. Descriptive data of entire cohort

	Surgical margins status			Entire cohort	P value
	Negative margins	Focal positive margins	Extensive positive margins		
Number of pts. (rate)	191 (74.9%)	47 (18.4%)	17 (6.7%)	255	Not applicable
Age (mean ±SD)	62.0 ±5.6	62.6 ±6.3	64.0 ±5.4	62.3 ±5.7	0.359
PSA (mean ±SD)	9.35± 5.49	8.97±5.15	8.86 ±4.71	9.24 ±5.36	0.870
PSAD (mean ±SD)	0.27 ±0.20	0.23 ±0.16	0.23 ±0.18	0.26 ±0.20	0.479
Prostate volume (mean ±SD)	42.8 ±24.4	44.1 ±22.4	49.7 ±32.2	43.5 ±24.6	0.536
Abnormal DRE	102 (53.4%)	24 (51.1%)	11 (64.7%)	137 (53.7%)	0.617
Abnormal TRUS	107 (56.0%)	31 (66.0%)	8 (47.1%)	146 (57.3%)	0.334
Number of positive biopsy cores	2.8 ±1.6	3.0 ±2.1	2.9 ±1.6	2.9 ±1.7	0.780
Maximum percentage of cancer in biopsy core	51.4 ±27.9	55.9 ±28.5	62.4 ±33.1	53.0 ±28.5	0.234
Clinical stage:					
Organ confined	165 (93.2%)	9 (5.1%)	3 (1.7%)	177 (69.4%)	<0.001
Locally advanced	26 (33.3%)	38 (48.7%)	14 (18.0%)	78 (30.6%)	
Biopsy Gleason score	5.7 ±1.4	5.2 ±1.2	6.4 ±1.2	5.7 ±1.4	0.003
Pathological stage:					
T2a	39 (20%)	0	0	39 (15%)	<0.001
T2b	124 (65%)	3 (6%)	4 (24%)	131 (51%)	
T3a	15 (8%)	39 (83%)	12 (71%)	66 (26%)	
T3b	13 (7%)	5 (11%)	1 (6%)	19 (7%)	
Specimen Gleason score	6.4 ±1.3	5.9 ±1.4	7.0 ±1.1	6.3 ±1.3	0.009

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

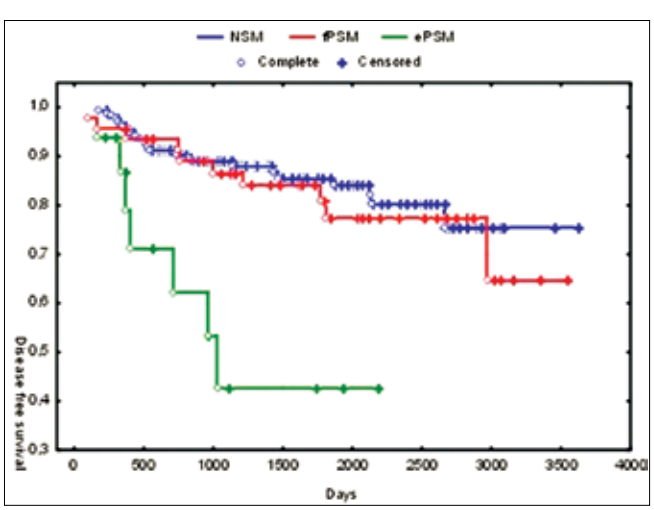

Fig. 1. Biochemical progression free survival depending on margin status (NSM – negative surgical margins, fPSM – focal positive surgical margins, ePSM – extensive positive surgical margins).

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 fPSM had lower biopsy GS values than those with ePSM (5.7 ±1. *vs.* 5.2 ±1.2 *vs.* 6.4 ±1.2, p = 0.003). Similarly, patients with NSM and fPSM 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 (54.5%) *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

Table 2. Descriptive data of patients with biochemical recurrence

	Biochemical recurrence		P value
	No	Yes	
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
Clinical stage of PCa:			
Organ confined	162 (91.5%)	15 (8.5%)	<0.001
Locally advanced	51 (65.4%)	27 (34.6%)	
Biopsy Gleason score	5.7 ±1.4	5.7 ±1.4	0.805
Pathological stage of PCa:			
T2a	35 (16.4%)	4 (9.5%)	<0.001
T2b	122 (57.3%)	9 (21.4%)	
T3a	46 (21.6%)	20 (47.6%)	
T3b	10 (4.7%)	9 (21.4%)	
Specimen Gleason score	6.2 ±1.3	6.7 ±1.6	0.046
Margins status			
NSM	166 (86.9%)	25 (13.1%)	0.007
fPSM	37 (78.7%)	10 (21.3%)	
ePSM	10 (58.8%)	7 (41.2%)	

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).

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
Clinical stage of PCa:		
Organ confined	3.91	<0.001
Locally advanced		
Biopsy Gleason score	1.18	0.125
Pathological stage of PCa:		
T2	4.01	<0.001
T3a		
T3b	3.49	0.004
Specimen Gleason score	1.47	0.001
Surgical margins status		
PSM	1.54	0.005
NSM *vs.* fPSM	1.19	0.647
NSM *vs.* fPSM *vs.* ePSM	1.91	0.007
NSM + fPSM *vs.* ePSM	4.74	0.002

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				
Specimen Gleason score	1.47	0.001	1.40	0.003

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

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-yrs 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

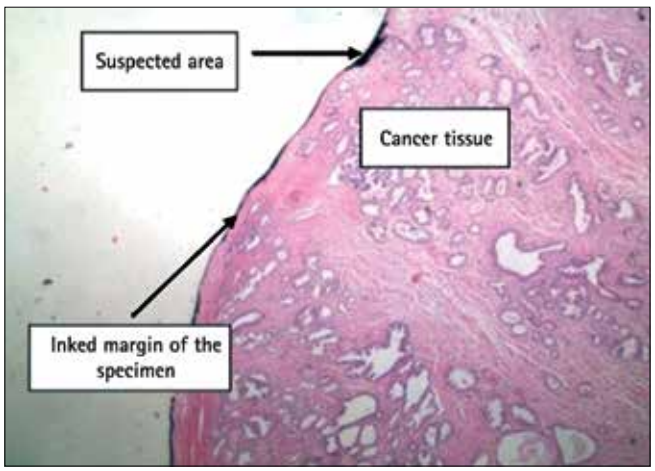

Fig. 2. Equirogl surgical margin.

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 PCa. 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 PCa 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.

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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