Impact of positive surgical margins on biochemical relapse after radical retropubic prostatectomy (RRP)

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KEY WORDS

biochemical relapse ▶ positive surgical margins ▶ radical retropubic prostatectomy

ABSTRACT

Introduction. RP (radical prostatectomy) technique continues the major treatment option for men with potential cure and life expectancy exceeding 10 years. The aim of the study is to assess the impact of PSM on BR (biochemical relapse), to identify PSM risk factors, to clarify the factors involved in BR in the absence of PSM.

Material and methods. Consultation of 171 medical-records from patients submitted to RRP (radical retropubic prostatectomy) between January/2000-December/2005. Mean-age: 64 yr. Mean – PSA (positive surgical margin): 11.88 ng/ml. Clinical staging: 67.8% cT1, 32.2% cT2. GS: ≤6 (66.1%), =7 (21.1%), 8-10 (12.3%). PS: pT0 1.2%, pT2 50.3%, pT3a 36.3%, pT3b 12.9%, pT4 0.6%. pathological Gleason score: ≤6 39.2%, =7 40.9%, 8-10 19.3%. RB definition was PSA ≥0.2 ng/ml. Adjusted Odds-Ratios with 95% confidence intervals (CI) were estimated through univariate logistic regression.

Results. There were PSM in 46 specimens, 28 had single PSM and 18 multiple PSM (≥2). BR occurred in 57 patients (33.3%), with an average time after surgery of 23.5 months – 26 patients had PSM and 31 had not. Statistical significant results for BR in variables PSA, PS and PSM. Quadruples if PSM (p <0.0001), triples in single PSM (p = 0.01) and is 6x higher in multiple PSM (p = 0.001). Regarding factors that influence the presence of PSM, only PS ≥pT3a reach statistical significance (p <0.0001). Patients with BR but without PSM (54.38%), variables statistically significant were: initial PSA >10, (p = 0.029) and pathological Gleason score ≥8 with a risk nearly 4x higher than pathological Gleason score ≤6 (p = 0.027).

Conclusions. Statistical risk analysis concluded that the presence of PSM in RRP is strongly influenced by PS ≥pT3a. The presence of PSM and their number increase significantly the risk of BR compared to other factors. In the absence of PSM, the factors that seem to be crucial and with greater impact on BR are initial PSA>10 and pathological Gleason score ≥8.

INTRODUCTION

Positive surgical margins at radical prostatectomy for the treatment of prostate cancer vary tremendously in the literature (4% to 45.2%) [1]. Their presence suggests that the primary tumor has not been completely excised. It may occur because prostate cancer extends outside the prostate to the margins of resection or because there was a disruption of the prostatic capsule and exposition of neoplastic glands. A PSM may also be caused by pathological artifact (tissue trauma) during intraoperative retraction of the prostate or during the processing of the specimens. Given the multiple

Table 1. Clinical and pathological characteristics of the entire studied population.

Age (median age = 64 yr.)	No	%
<50	2	1
50-60	33	19
60-70	98	58
>70	38	22
PSA (median PSA = 11.9 ng/dl)	No	%
<4	6	4
4-10	93	54
>10	72	42
Clinical staging (CS)	No	%
cT1	116	68
cT2	55	32
Gleason score of biopsy (GS)	No	%
≤6	113	66
7	36	21
8-10	21	12
Mucinous	1	1
Pathological *Gleason score*	No	%
≤6	67	39
7	70	41
8-10	33	19
Mucinous	1	1
Pathological staging (PS)	No	%
pT0	3	2
pT2	93	54
pT3a	62	36
pT3b	12	7
pT4	1	1
Positive surgicalmargins (PSM)	46	27
Without PSM	125	73
Biochemical relapse (BR)	57	33
Early (≤3 years)	46	81
Late (>3 years)	11	19

Table 2. Influence of risk factors on BR

Variables	B	S.E.	Wald	df	Sig.	OR	95% C.I. for OR	
							Lower	Upper
Age	.030	.029	1.123	1	.289	1.031	.974	1.091
PSA 4–10	20.287	16408.555	.000	1	.999	646182073.676	.000	–
PSA >10	20.899	16408.555	.000	1	.999	1192359778.808	.000	–
PSA >10	.701	.330	4.523	1	.033	2.016	1.057	3.845
Clinical staging cT2	.359	.344	1.091	1	.296	1.432	.730	2.808
Gleason score = 7	.054	.406	.018	1	.893	1.056	.476	2.341
Biopsy ≥8	.693	.482	2.067	1	.151	2.000	.777	5.146
Pathological =7	.212	.372	.325	1	.568	1.236	.597	2.562
Gleason ≥8	.802	.446	3.230	1	.072	2.229	.930	5.343
Pathological pT2	-.602	1.250	.231	1	.630	.548	.047	6.355
Stage pT3a	.564	1.251	.203	1	.652	1.758	.151	20.403
pT3b	1.030	1.358	.575	1	.448	2.800	.196	40.057
pT4	-20.510	40192.970	.000	1	1.000	.000	.000	–
Pat. stage ≥pT3a	1.1193	.338	12.443	1	.000	3.297	1.699	6.397
PSM	1.372	.362	14.323	1	.000	3.942	1.937	8.021

causes of PSM the associated BR rate is highly variable. Conflicting studies have been reported regarding the prognostic significance of multiple *vs.* solitary PSM´s, PSM at apical *vs.* other locations and extensive *vs.* focal PSM. Another controversial issue is the treatment of patients with a positive surgical margin after radical retropubic prostatectomy. Options include observation, radiation therapy and early hormone therapy. Making the appropriate choice should be based on an understanding of the risk of recurrence without treatment [2].

PATIENTS AND METHODS

We conducted a consultation of 171 medical records from patients submitted to RRP between January 2000 and December 2005 (6 years). The sample was evaluated concerning clinical patients data, tumor and tumor development (Table 1). The definition of PSM was the presence of prostate cancer cells touching the inked surface of the excised prostate gland. Lymph nodes status was not a criterion studied in this series. The mean age was 64.44 years (46-76). The mean PSA was 11.88 ng/ml (1.4-42.3). Clinical staging (CS) was 67.8% CT1 and 32.2% CT2. The

Table 3. PSM population

Positive surgical margins (PSM) n = 46	No	%
Single	28	61
Multiple (≥2)	18	39
Apical	7	15
Non-apical	39	85
BR	26	57
Non-BR	20	43

Table 4. Patients with BR and PSM

Biochemical Relapse (BR) n = 57	No	%
PSM	26	46
Without PSM	31	54

Gleason score of biopsy (GS) was divided between ≤6 (66.1%), equal to seven (21.1%) and 8-10 (12.3%). The pathological stage (PS) was pT0 in two cases (1.2%), pT2 in 86 (50.3%), pT3a in 62 (36.3%), pT3b in 22 (12.9%) and pT4 in one case (0.6%). Pathological *Gleason score* was ≤6 in 39.2%, equal to seven in 40.9% and 8-10 in 19.3%. The definition of RB was the value of PSA ≥0.2 ng/ml. Adjusted *Odds Ratios* (OR) with 95% confidence intervals (CI) were estimated through univariate logistic regression to assess risk factors.

RESULTS

We obtained statistical significant results for BR in the variables PSA, PS and PSM (Table 2). There were PSM in 46 specimens (26.9%), 28 (61%) had single PSM and 18 (39%) multiple PSM (≥ 2); 39 (85%) presented non-apical PSM and only seven (15%) were reported to have apical PSM (Table 3). BR occurred in 57 patients (33.3%) with an average time after surgery of 23.5 months (3-72). From the 46 patients with PSM only 26 patients had BR i.e. there were 31 patients with BR and without PSM (Table 4).

It was found that the risk of BR quadruples in patients with PSM (OR = 3.94 95% CI [1.94-8.02], p <0.0001), triples in single PSM (n = 28) (OR = 3.03 95% CI [1.30-7.06], p = 0.01) and is six times higher in patients with multiple PSM (n = 18) (OR = 6.06 95% CI [2.10-17.52], p = 0.001) (Table 5).

Regarding factors that influence the presence of PSM (Table 6), only PS ≥pT3a reach statistical significance, being linked to a seven times higher risk than the lower stages (OR = 6.76 95% CI [3.12-14.67], p <0.0001) (Table 7).

Table 5. Influence of PSM on BR

	B	S.E.	Wald	df	Sig.	OR	95% C.I. Lower	OR Upper
PSM	1.372	0.362	14.323	1	.000	3.942	1.937	8.021
SINGLE PSM	1.109	0.431	6.625	1	.010	3.032	1.303	7.057
MULTI-PLE PSM (≥2)	1.802	0.541	11.092	1	.001	6.065	2.100	17.517

Table 6. Sub-populations with and without PSM

Positive Surgical Margins (PSM) n = 46	No	%	Without PSM n = 125	No	%
PSA					
≤4		0	0%	7	6%
4-10		24	52%	67	54%
>10		22	48%	51	41%
Clinical staging					
cT1		32	70%	85	68%
cT2		14	30%	40	32%
GS biopsy					
≤6		30	65%	82	66%
=7		8	17%	29	23%
8-10		8	17%	13	10%
Pathological Staging (PS)					
pT0		0	0%	2	2%
pT2		11	24%	75	60%
pT3a		30	65%	32	26%
pT3b		4	9%	18	14%
pT4		1	2%	0	0%
Pathological Gleason					
≤6		14	30%	67	54%
=7		21	46%	70	56%
8-10		11	24%	32	26%
Surgeon	**Total**				
BG	1	0	0%	1	
ML	11	2	18%	9	
MFC	3	2	67%	1	
FR	26	6	23%	20	
JF	29	10	34%	19	
PC	24	3	13%	21	
JV	27	9	33%	18	
FF	31	9	29%	22	
CG	7	2	29%	5	
CP	12	3	25%	9	

In patients with BR but without PSM (54.38%), the variables that showed statistical significance were the initial PSA >10, with a 2.5 times higher risk (OR = 2.52 95% CI [1.10-5,78], p = 0.029) and pathological *Gleason score* ≥8 with a risk nearly four times higher than in pathological *Gleason score* ≤6 (OR=3.77 95% CI [1.16-12.21], p=0.027) (Table 8).

DISCUSSION

The Seminar Article written by *Fleshner et al* reviewing a total of 39 cases series and ranging cohort´s sizes from 100 to 7,268 cases, reported a tremendous variation in the incidence of PSM and in the number of risk factors for it. The overall PSM rates varied from 4% to 45.2%. The risk factors included pathologic stage, tumor volume and prostate specific antigen (PSA) level, tumor grade, type of resection, surgical experience and pathologic processing/interpretation.

Rates for PSM vary according to pathologic stage. Generally, PSM rates in patients with organ-confined tumors (pT2) are lower than those with pT3 disease or higher. In our series the range of PSM in men with pT2 disease was 24%. Among men with pT3 disease or higher the rate of PSM was 76%. We could reach statistical significance in this variable. Patients with PS ≥pT3a showed to have almost seven times higher risk of PSM than the lower stages (OR = 6.76 95% CI [3.12-14.67], p <0.0001).

The pathologic grade, tumor volume and stage are highly correlated, making it difficult to assess the multivariate impact of grade on PSM. It can generally be claimed that patients with higher-grade disease are at higher risk of PSM 3, 4. We did not find statistical significance of pathological Gleason *score* as risk factor for PSM but in cases of BR without PSM, patients with pathological *Gleason score* ≥8 had a risk nearly four times higher than in pathological Gleason *score* ≤6 (OR = 3.77 95% CI [1.16-12.21], p = 0.027).

There is a correlation between tumor volume, PSA and the presence of PSM in radical prostatectomy. These covariates were used in clinical practice in the 1990 in the form of the Partin tables 5. Over the past decade, the value of PSA as a predictor of tumor

Table 7. Factors that influence the presence of PSM

Variables		B	S.E.	Wald	df	Sig.	OR	95% C.I. for OR	
								Lower	Upper
PSA	<4			.284	2	.868			
	4–10	20.176	16408.728	.000	1	.999	578680957.615	.000	.
	>10	20.362	16408.728	.000	1	.999	696875597.651	.000	.
	>10	.272	.347	.613	1	.434	1.312	.665	2.590
Clinical staging	cT2	-.073	.373	.038	1	.845	.930	.447	1.933
GS biopsy	≤6			.986	2	.611			
	=7	-.327	.452	.525	1	.469	.721	.297	1.747
	≥8	.267	.509	.276	1	.599	1.306	.482	3.542
Pathological stage ≥pT3a		1.911	.395	23.379	1	.000	6.761	3.116	14.672
Pat. Gleason	≤6			2.421	2	.298			
	=7	.484	.398	1.479	1	.224	1.622	.744	3.539
	≥8	.685	.478	2.048	1	.152	1.983	.777	5.064

Table 8. Risk factors that influence BR without PSM

Variables		B	S.E.	Wald	df	Sig.	OR	95% C.I. for OR	
								Lower	Upper
Age		.022	.037	.355	1	.551	1.022	.951	1.098
PSA > 10		.923	.424	4.750	1	.029	2.517	1.097	5.775
Clinical staging		.209	.437	.230	1	.632	1.233	.524	2.902
GS biopsy	≤6			4.915	2	.086			
	=7	.181	.513	.124	1	.725	1.198	.439	3.271
	≥8	1.326	.600	4.879	1	.027	3.765	1.161	12.206
Pathological stage pT0				5.759	3	.124			
pT2		-.648	1.255	.267	1	.606	.523	.045	6.117
pT3a		-.405	1.291	.099	1	.753	.667	.053	8.372
pT3b		1.204	1.426	.713	1	.398	3.333	.204	54.532
pT0				2.087	2	.352			
pT2		-.648	1.255	.267	1	.606	.523	.045	6.117
≥pT3a		-.038	1.270	.001	1	.976	.963	.080	11.614
Pat. Gleason	≤6			5.150	2	.076			
	=7	.568	.488	1.354	1	.245	1.765	.678	4.598
	≥8	1.299	.573	5.142	1	.023	3.667	1.193	11.271

volume has come into question owing to stage migration, extensive prostate biopsy strategies, and lower thresholds for biopsy. Stamey et al have shown that PSA >12 ng/ml is not associated with tumor volume, extra prostatic extension (EPE) or PSM [6]. Others have contradicted these findings [7]. Recent data have shown that the tumor volume still remains a predictor of PSM in the more recent era of prostate cancer detection and treatment [8]. We did not have statistical significance with the variable PSA.

The experience and technical quality of the surgeon performing the RRP is increasingly being recognized as an independent predictor of PSM and BR [9]. Like many other medical procedures, this phenomenon is volume outcome associated, however, large cohorts of low volume, well-performing surgeons exist as well as high-volume poor performing surgeons [9]. Vickers et al,

in a recent paper, demonstrated that approximately 250 radical prostatectomies (PR) were necessary to achieve a low-rate of PSM nine nine and that fellowship trained surgeons seem to acquire these skills better than those who are non-fellowship trained [10]. In our series, probably because of the lower number of interventions done by each surgeon, we could not found statistical differences between them. Further research is needed in order to better understand the interactions between patient selection, specific intraoperative maneuvers, capsular incision, and outcome following PR.

A PSM in the radical prostatectomy impacts on outcome in the form of biochemical relapse, in the use of salvage therapies and perhaps in mortality. The impact of PSM on BR is well accepted among patients with ECE. The implications of BR on additional out-

comes are more controversial and statistically less significant. The reason for this is the relatively long natural history of BR in terms to metastatic disease (9 years on average) and death (14 years on average) [11]. In our series we saw that 43% of patients with PSM did not had PSA recurrence. These facts seem to be associated with false positivity of the pathology, extremely slow growing disease that never manifests and difficult area around the resection margin, which results in cellular death (by cauterization, desmoplasia or ischemia) [12].

On the other hand we tried to found which were the risk factors for BR that in the absence of PSM were responsible for the PSA recurrence. We found in these patients (31 of 57 patients, 54.38%) statistical significance for initial PSA >10, with a 2.5 times higher risk (OR = 2.52 95% CI [1.10-5,78], p = 0.029) and pathological Gleason *score* ≥ 8 with a risk nearly four times higher than in pathological Gleason *score* ≤6 (OR = 3.77 95% CI [1.16-12.21], p = 0.027) (Table 8). Since tumor grade, stage and tumor volume are often tightly correlated, it is not surprising that tumors that are high grade are more likely to fail than lower grade tumors, especially if margins are positive. Generally, tumors of high grades (Gleason 8-10) tend to fail more often than lower grade tumors.

The impact of PSM on mortality has only recently been assessed. Duke et al has shown that PSM is a predictor of death post-RP. Walther et al [13], Karakiewicz and colleagues [14] have reported a negative impact on overall survival among patients with T3 disease and PSM compared with patients with a negative surgical margin. Even though other factors may be responsible for this observation. It is evident that a PSM puts a man at higher risk for BR and one cannot die from prostate cancer without a BR.

What about the location of PSM? Typically and as is described in most of the literature they occur predominantly at the prostate apex or posterolaterally near the neurovascular bundle (NVB) and less frequently at bladder neck, base and anterior zone. The high rate of apical PSM seems to be related to the predisposition of the area to trauma, increasing the probability of ink touching tumor and the desire of the surgeon to have a long supramembranous urethra. The cone pathologic processing technique applied to this area is the best way to minimize pathologic artifacts. In our series we only found 15% of apical margins and 85% non-apical. In most series that have examined the impact of the apical PSM on BR, the tumor control is equivalent to that of an organ-confined tumor [5, 16]. The bladder neck margins and its significance are more controversial. Theoretically, the involvement of the bladder neck indicates pT4 disease and the majority of patients have also other PSM. Rare cases of PSM only at the bladder neck have been reported. Some series describe a higher risk of BR hereas other do not [16-20].

The impact of number and degree of margin positivity has been long realized as an important predictor of disease recurrence. Multiple studies describe that patients with multifocal margins are at higher risk for disease recurrence [21, 22]. We obtained in our series a probability four times higher of BR in patients with PSM (OR=3.94 95% CI [1.94-8.02], p <0.0001), three times higher in patients with single PSM (n = 28) (OR= 3.03 95% CI [1.30-7.06], p = 0.01) and six times higher in patients with multiple PSM (n=18) (OR = 6.06 95% CI [2.10-17.52], p = 0.001) (Table 5). An extensive margin involvement is also more predictive than a focally positive margin [21, 23].

Another issue of extreme relevance and very controversial that needs to be discussed is how to manage patients with PSM and other risk factors of BR? There is no doubt that PSM leads to a higher utilization of second therapies for prostate cancer, such as adjuvant radiotherapy (RT), salvage (RT) and androgen deprivation therapy. There are only two published randomized controlled trials of adjuvant RT in prostate cancer [24, 25]. The

European Organization for Research and Treatment of Cancer (EORTC) 22911 randomized 1005 patients with pT3 disease at RP between adjuvant RT and a "wait and see" policy (that were recommended to have salvage RT only if they had local recurrence and not for PSA failure alone) [24]. The Southwest Oncology Group (SWOG) 8794 (National Cancer Institute of Canada, NCIC, PR-2) had a similar design – 425 men with pT3 disease were randomized to either adjuvant RT of the prostate bed or observation, with a median follow-up at the time of analysis of 10.6 years [25]. These studies provided good evidence that RT after RP can reduce the risk of PSA failure and of local recurrence. However, the standard practice after RP has developed since the SWOG and EORTC studies that were designed in the 1980's. Specially, salvage RT is now given earlier, at the time of BR rather than when local recurrence is clinically palpable, leading to a significant improvement in the efficacy of salvage treatment. Thus, the results provide a strong rationale for a comparison between adjuvant RT and the current standard of care, which is observation with early salvage RT for BR. We think that the trial Medical Research Council-National Institute of Canada (RADICALS), upcoming soon, will attempt to answer this question [26].

CONCLUSIONS

Statistical risk analysis of the studied series concluded that the presence of PSM in RRP is strongly influenced by PS ≥pT3a and that the presence of PSM and their number increase significantly the risk of BR compared to other factors. In the absence of PSM, the factors that seem to be crucial and with greater impact on BR are initial PSA >10 and pathological Gleason *score* ≥8. It is important to consider initial PSA, pathological Gleason *score* and surgical margins status when making treatment decisions after radical prostatectomy.

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