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Original scientific paper

Impact of Positive Surgical Margins after Radical Prostatectomy on Disease Progression and Adjuvant Treatment in Pathologically Localized Prostate Cancer

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ABSTRACT

The aim of our study was to evaluate the impact of margin positivity in clinically and pathologically localized prostate cancer (pT2) after radical prostatectomy on biochemical recurrence and time to adjuvant treatment. We analyzed data from 371 patients who underwent radical prostatectomy. At the mean follow up of 36 (25-54) months, impact of margin positivity in pT2 patients on prostate specific antigen (PSA) recurrence and time to introduction of adjuvant treatment was noted. Out of 371 radical prostatectomies there were 277 (74.6%) pT2 and 94 (25.4%) pT3 (locally advanced) prostate cancers. Mean age was 67.6 years, mean Gleason score 6.78, mean preoperative PSA 11.45 ng/mL. Out of 277 pT2 pts., 233 (84%) had negative (SM-) and 44 (16%) positive surgical margins (SM+). Only 3% of SM- pts. had biochemical relapse (BCR). Among pT2 patients with SM+, 18 (41%) had BCR while 26 were free of recurrence at 3 years follow up. Positive surgical margins had an adverse impact on biochemical progression free survival (3% SM- vs. *41% SM+; p<0.001). No difference was found in age, preoperative PSA, Gleason score or follow up between BCR-SM+ and BCR+SM+ patients. Mean time to PSA recurrence in surgical margin positive pT2 patients was 15.7 months. Surgical margin status pT2 disease has an impact on biochemical progression but only 41% of margine positive patients show biochemical recurrence at 3 yr follow up. Not all SM+ patients need to receive treatment after radical prostatectomy. Longer follow up should be awaited to see the impact on overall survival in this group of patients.*

Key words: *prostate cancer, prostatectomy, bladder neck, frozen sections, surgical margins, prostatic neoplasms, prostatectomy, surgical margins, treatment outcome, models, biochemical recurrence*

Introduction

Radical prostatectomy (RP) is well established and effective treatment for localized prostate cancer[1]. Positive surgical margins (SM+) in RP specimens for the treatment of localized prostate cancer (PCa) are reported in 11–48% of men and are a recognized risk factor for prostate-specific antigen (PSA)-defined biochemical recurrence (BCR). There is a 2.3-fold increased risk of BCR among men with SM+ treated in the later PSA era after adjusting for all standard parameters[2]. Recurrence depends on many factors such as preoperative PSA, PSA kinetics, clinical stage, pathologic stage, Gleason score and surgical margin status[3]. According to risk groups, RPs resulted in SM+ in 19.1% in the low-risk group, 26.0% in the intermediate-risk group, 39.5% in the high-risk group, and 81.8% in the very-high-risk disease group of patients[4]. Positive margin is not uniquely defined, although most would accept that it reflects any tumor cells at the inked margin of the surgically removed specimen[5,6]. It is in cases in which the evidence of extracapsular extension is not clear that the margin status becomes somewhat difficult to define[7]. In pT2 disease positive surgical margin may pose a question of whether such specimen should be classified as pT3. In most cases this represents incision into the prostatic cap-

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TABLE 1
DESCRIPTIVE STATISTICS OF SURGICAL MARGIN POSITIVE PT2 PATINETS

pT2 SM+		$\overline{X}$	Median	SD	Minimum	p	p value
Age	BCR+	65.67	66.00	5.82	56	76	0.15
	BCR–	68.15	69.50	4.81	58	77	
Gleason score	BCR+	6.83	7.00	0.51	6	8	0.83
	BCR–	6.77	7.00	0.59	5	8	
Preoperative PSA	BCR+	12.26	11.00	5.45	4.9	25	0.62
	BCR–	11.89	9.60	6.49	3.5	27	
Follow up (months)	BCR+	35.50	34.50	9.77	20	54	0.86
	BCR–	35.27	34.50	10.88	21	54	

SM+ – positive surgical margins, SD – standard deviation

sule or absence of evident extraprostatic extension which would allow it to be classified as pT3[8]. Although positive surgical margins are independent predictors of recurrence[4,9] not all patients are deemed to failure and progression[10,11]. The clinical course of patients with BCR is highly variable ranging from no threat to longevity to progression to clinical metastasis[11, 12]. Definition of biochemical relapse is not unique. PSA usually fells to undetectable levels 4-6 weeks after RP. After that time any detectable PSA could be considered relapse but it can also represent residual benign tissue[13]. Commonly used clinical definition for BCR suggests two consecutive measurements of PSA> 0.2ng/mL as proposed by European Association of Urology and American Association of Urology[14] while others suggest 0.4ng/mL[12]. While most agree that margin status is important, some are reserved[15,16]. In the present study we examined the impact of margin positivity in clinically and pathologically localized prostate cancer (cT2 and pT2) on biochemical recurrence and type and time to adjuvant treatment on our material.

Patients and Methods

We analyzed data from 371 radical prostatectomy performed for clinically localized prostate cancer. All patients had pelvic lymphadenectomy and lymph nodes were examined on frozen sections. In cases where no tumor was found in lymph nodes, retropubic radical prostatectomy was performed. None of the patients received neoadjuvant therapy. The mean follow up was 36 (18-54) months. Mean preoperative PSA was 11.45 ng/mL. Each specimen was examined by single genitourinary pathologist to determine margin positivity. Positive surgical margin was defined as any tumor reaching inked margin on a whole-mount specimen. Location of positive margin was noted. Positive margins were not further subclassified to focal or extensive. PSA recurrence was defined by two consecutive elevations of PSA after radical prostatectomy exceeding 0.2 ng/mL. Patients were followed by DRE and PSA measurement every 3 months after RP in the first year, semiannually after that. Impact of margin positivity on PSA recurrence and time to introduction of adjuvant treatment was noted. Statistics: T-test was used for numerical variables that follow normal distribution and Mann Whitney was used for data that do not follow normal distribution. Distribution of data was tested using Kolgomorov-Smirnov´s test. $p<0.05$ was considered statistically significant.

Results

Out of 371 radical prostatectomy there were 277 (74.6%) pT2 and 94 (25.4%) pT3 prostate cancers. Mean age was 67.6 years, mean Gleason score 6.78, mean preoperative PSA 11.45 ng/mL. The location of positive margins were posterolateral 44%, apical 31%, basal 16% and multifocal 9%. 233 out of 277 (84%) pT2 tumors had negative surgical margins while positive surgical margin was noted in 44 out of 277 (16%) pT2 cancers. Only 3% of negative surgical margin pts. had biochemical relapse at three years follow up. Among patients with SM+ in pathologically organ confined disease (pT2), 18 (41%) had biochemical relapse while 26 (59%) were free of recurrence (BCR-) at 3 years follow up. Comparison of pT2 SM- pts. to pT2 SM+ in terms of BCR revealed significant difference ($p<0.001$). Mortality rate was 0% in both margin negative and margin positive patients. Descriptive statistics of SM+pT2 patients is presented in Table 1. No difference was found with respect to age, preoperative PSA, Gleason score or follow up between BCR- and BCR+ SM+ patients (Figures 1-3). Mean time to PSA recurrence in surgical margin positive pT2 patients was 15.7 months. Mean PSA at the introduction of adjuvant therapy in pts. who relapsed was 1.2 (range 0.3 - 2.0 ng/ml). Four men experienced early recurrence (<9 months after RP) and received combined or hormonal only therapy. 14 men had late recurrence and were treated with irradiation and observation (PSA<1ng/mL). Twelve pts who received radiation have PSA below 0.2 ng/mL and two progressed in spite of given therapy so androgen deprivation therapy was introduced.

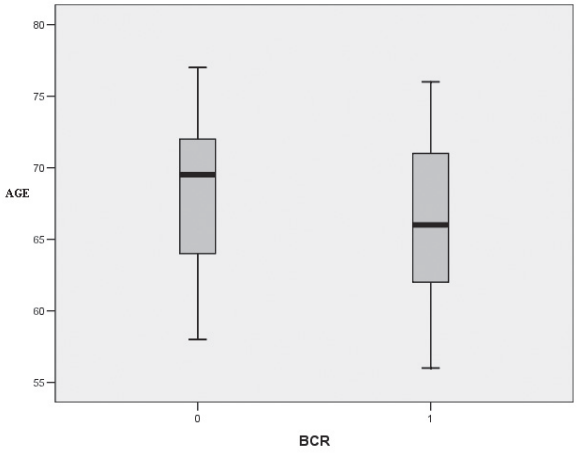

Fig. 1. No statistical difference was found in age between biochemical relapse negative (BCR-) and positive (BCR+) patients (0 for BCR- and 1 for BCR+; t=1.493; df=32.028; p=0.146).

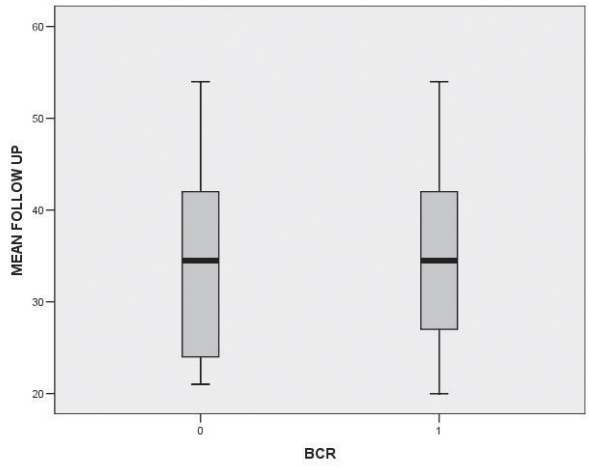

Fig. 2. No statistical difference in follow up between biochemical relapse negative (BCR-) and positive BCR+ patients (0 for BCR- and 1 for BCR+; U=228.5; p=0.857).

Discussion

Prognostic significance of positive surgical margin in otherwise organ confined prostate cancer is not well understood and the data are conflicting and scarce[17]. Furthermore it is not clear whether the extent of margin positivity or location of positive margin is important since some report their significance while others disagree[15]. Therapy in these cases is not strictly defined and should be individually tailored incorporating risk assessment[18].

In our study, at three years follow up only 18/44 of SM+ pT2 pts showed BCR. 26/44 (59%) patients with positive surgical margins and pT2 disease did not show signs of biochemical relapse at three years of follow up nor they received any adjuvant treatment after RP. These results are in congruence with other authors recently reporting on this subject. Vis reported 38/211 pts. to have positive surgical margins and pT2 disease[15]. Out of those 38, only 11(29%) had biochemical relapse at 7 years. Margin status was independent predictor of BCR but there was no difference between men with a focal or extensive positive margin with respect to BCR nor was the location of positive margin important. No adjuvant treatment was introduced based solely on the SM status after RP. Advantage of immediate irradiation for pts. with adverse prognostic features was showed in EORTC 22911 study comprising both pT2 and pT3 pts.[19].

Caveats of our study are the size of the group and relatively short time of follow up. In response to that criticism we remind that 90% of patients that recur do so in the first five years so we would expect that most recurrences already happened[16]. Longer follow up should be awaited to see the impact on overall survival in this group of patients. Nevertheless, reports on this particular subgroup of patients are rare and as this group matures there may be new comprehensions to arise. The advantage of our study

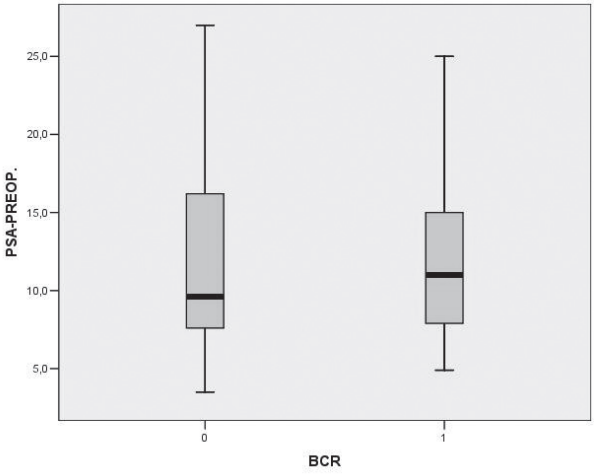

Fig. 3. No statistical difference in preoperative PSA between biochemical relapse negative (BCR-) and positive (BCR+) patients (0 for BCR- and 1 for BCR+; U=213; p=0.616).

comparing to others is relatively recent, single institution, study population that better resembles nowadays prostate cancer patients in the PSA era.

The analysis of this type is important in terms of unifying the practice in patients with positive surgical margin since practicing urologists show diversity of treatments offered to their patients ranging from no treatment to immediate radiation after report of positive margins after RP. Since there are no randomized trials comparing placebo vs. adjuvant treatment in BCR patients, nor there are proofs that active treatment prolongs survival or prevents development of progressive disease, guidelines for treatment of these pts have been difficult to establish[12].

Conclusion

These results show that although statistically significant predictors of relapse, positive surgical margins solely have limited practical value in pT2 patients since most men will not recur nor have clinical progression and are actually cured in spite the fact procedure itself was not »radical«. These findings suggest that clearly not all the patients with positive margins in pT2 pts. after RP need immediate adjuvant treatment and at least in some it can be omitted. It is that minority of men with SM+ who are in danger of progression and death that needs to be identified and offered treatment. More studies are necessary to better define this subgroup.

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UTJECAJ POZITIVNIH KIRURŠKIH RUBOVA NAKON RADIKALNE PROSTATEKTOMIJE NA PROGRESIJU BOLESTI I ADJUVANTNO LIJEČENJE U PATOLOŠKI LOKALIZIRANOM KARCINOMU PROSTATE

SAŽETAK

Cilj studije je procijeniti utjecaja pozitivnih kirurških rubova u klinički i patološki lokaliziranom raku prostate (pT2) nakon radikalne prostatektomije na biokemijski recidiv (BCR) i vrijeme do adjuvantnog liječenja. Analizirali smo utjecaj pozitivnih kirurških rubova u bolesnika pT2 na biokemijski recidiv i vrijeme do uvođenja adjuvantne liječenja nakon 371 radikalne prostatektomije tijekom praćenja od 36 (18-54) mjeseci. Od 371 radikalnih prostatektomija imali smo u 277 slučajeva pT2 stadij (74,6%) i 94 (25,4%) pT3 stadij karcinoma prostate. Srednja dob je 67,6 godina, srednji Gleason zbroj 6,78, srednja vrijednost preoperativnog PSA 11,45 ng / mL. Od 277 pT2 bolesnika 233 (84%) je imalo negativne (SM-) i 44 (16%) pozitivne kirurške rubove (SM+). Samo 3% SM- bolesnika imalo je biokemijski relaps (BCR+). Među pT2 bolesnicima s SM+, 18 (41%) je imao BCR, a 26 su bili slobodni od recidiva nakon 3 godine praćenja. Pozitivni kirurški rubovi imali su negativan utjecaj na preživljenje bez BCR (3% SM- vs 41% SM + p <0,001). Nije utvrđena razlika u dobi, preoperativnom PSA, Gleason zbroju ili vremenu praćenja između BCR-SM+ i BCR+SM+ bolesnika. Srednje vrijeme do PSA recidiva u SM+ pT2 bolesnika je 15,7 mjeseci. Kirurški status rubova kod pPT2 bolesnika utječe na biokemijsku progresiju, ali samo 41% SM+ bolesnika pokazuju biokemijski recidiv nakon 3 god praćenja. Nisu svi SM+ pacijenti osuđeni na progresiju niti trebaju nedvojbeno primiti adjuvantni tretman nakon radikalne prostatektomije. Dulje praćenje treba kako bi se vidio učinak na cjelokupno preživljenje u ovoj skupini bolesnika.