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### Authors

Mithal, P  
Howard, LE  
Aronson, WJ  
et al.

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# Positive surgical margins in radical prostatectomy patients do not predict long-term oncological outcomes: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort

Prabhakar Mithal, Lauren E. Howard<sup>†‡</sup>, William J. Aronson<sup>§¶</sup>, Martha K. Terris<sup>\*\*††</sup>, Matthew R. Cooperberg<sup>‡‡</sup>, Christopher J. Kane<sup>§§</sup>, Christopher Amling<sup>¶¶</sup> and Stephen J. Freedland<sup>‡\*\*\*</sup>

Department of Urology, University of Rochester Medical Center, Rochester, NY, <sup>†</sup>Department of Biostatistics and Bioinformatics, Duke University School of Medicine, <sup>‡</sup>Division of Urology, Veterans Affairs Medical Center, Durham, NC, <sup>§</sup>Urology Section, Department of Surgery, Veterans Affairs Greater Los Angeles Healthcare System, <sup>¶</sup>Department of Urology, UCLA School of Medicine, Los Angeles, CA, <sup>\*\*</sup>Section of Urology, Veterans Affairs Medical Center, <sup>††</sup>Section of Urology, Medical College of Georgia, Augusta, GA, <sup>‡‡</sup>Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, <sup>§§</sup>Urology Department, University of California San Diego Health System, San Diego, CA, <sup>¶¶</sup>Division of Urology, Department of Surgery, Oregon Health and Science University, Portland, OR, and <sup>\*\*\*</sup>Division of Urology, Department of Surgery, Cedars Sinai Medical Center, Los Angeles, CA, USA

## Objective

To assess the impact of positive surgical margins (PSMs) on long-term outcomes after radical prostatectomy (RP), including metastasis, castrate-resistant prostate cancer (CRPC), and prostate cancer-specific mortality (PCSM).

## Patients and Methods

Retrospective study of 4 051 men in the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort treated by RP from 1988 to 2013. Proportional hazard models were used to estimate hazard ratios (HRs) of PSMs in predicting biochemical recurrence (BCR), CRPC, metastases, and PCSM. To determine if PSMs were more predictive in certain patients, analyses were stratified by pathological Gleason score, stage, and preoperative prostate-specific antigen (PSA) level.

## Results

The median (interquartile range) follow-up was 6.6 (3.2–10.6) years and 1 127 patients had >10 years of follow-up. During this time, 302 (32%) men had BCR, 112 (3%) developed CRPC, 144 (4%) developed metastases, and 83

(2%) died from prostate cancer. There were 1 600 (40%) men with PSMs. In unadjusted models, PSMs were significantly associated with all adverse outcomes: BCR, CRPC, metastases and PCSM (all  $P \leq 0.001$ ). After adjusting for demographic and pathological characteristics, PSMs were associated with increased risk of only BCR (HR 1.98,  $P < 0.001$ ), and not CRPC, metastases, or PCSM (HR  $\leq 1.29$ ,  $P > 0.18$ ). Similar results were seen when stratified by pathological Gleason score, stage, or PSA level, and when patients who underwent adjuvant radiotherapy were excluded.

## Conclusions

PSMs after RP are not an independent risk factor for CRPC, metastasis, or PCSM overall or within any subset. In the absence of other high-risk features, PSMs alone may not be an indication for adjuvant radiotherapy.

## Keywords

prostate cancer, prostatectomy, adjuvant radiotherapy, disease progression

## Introduction

While positive surgical margins (PSMs) after radical prostatectomy (RP) are consistently and independently associated with higher risk of biochemical recurrence (BCR) [1–3], the impact of PSMs on long-term outcomes including metastasis, castrate-resistant prostate cancer

(CRPC), and prostate cancer-specific mortality (PCSM) remains less clear with mixed results in prior studies [4–7]. Despite this, a PSM is often used as an indication for adjuvant radiotherapy (ART) [8–10]. Furthermore, studies examining the impact of ART on mortality also have shown conflicting results [11,12].

To help clarify the prognostic value of PSMs with regard to harder clinical endpoints and thereby shed light on their use as an indication for ART, we examined the long-term outcomes of men treated with RP within the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort. Furthermore, we stratified by pathological grade, pathological stage, and preoperative PSA level to identify if there were subsets of patients for whom PSMs were particularly strong predictors of systemic progression and PCSM.

## Patients and Methods

After obtaining Institutional Review Board approval, data from patients who underwent RP between 1988 and 2013 at the Veterans Affairs Medical Centers in West Los Angeles, Palo Alto, and San Diego, California; Augusta, Georgia; and Durham and Asheville, North Carolina were collected and combined into the SEARCH database [13]. Patients treated with preoperative androgen deprivation or RT were excluded. Of the 5 073 patients in the SEARCH database, 4 937 (97%) patients had information available on SMs from the analysis of the RP specimen. The 122 patients who had positive lymph nodes were excluded from analysis because these patients are at high risk for poor disease outcomes, regardless of SM status. Finally, we excluded patients with missing data on extracapsular extension or seminal vesicle invasion (169 patients), pathological Gleason score (251), pathological stage (149), PSA level (107), time from surgery to BCR (79), race (4), and CRPC or recurrence status (5), resulting in a study population of 4 051 patients.

Patients were followed to determine clinical endpoints after RP. BCR after RP was defined as a single PSA level of  $>0.2$  ng/mL, two values of 0.2 ng/mL, or secondary treatment for an elevated postoperative PSA level. CRPC was defined as having a PSA level increase of 2 ng/mL and 25% greater than the nadir after hormone treatment despite continuous therapy with an LHRH agonist, antagonist, or after orchidectomy [14]. Development of metastases was determined by bone scans or other imaging. PCSM was defined as having metastatic progressive CRPC at time of death with no obvious indication of another cause of death.

Demographic and pathological information between patients with and without PSM were compared using *t*-tests and Wilcoxon rank-sum tests for normally and non-normally distributed continuous variables, respectively, and chi-square tests for categorical variables. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs of PSMs in predicting BCR, CRPC, metastases, and PCSM. All models were adjusted for age (continuous), race (White vs Black vs Other race), preoperative PSA level (continuous, log-transformed), pathological Gleason score (2–6 vs 3+4 vs 4+3 vs 8–10), seminal vesicle invasion (yes

vs no), extracapsular extension (yes vs no), year of surgery (continuous), surgical centre, and receipt of ART (yes vs no). We repeated the analysis of the adjusted models, stratifying by pathological Gleason score (2–6, 3+4, 4+3, 8–10), pathological stage (T2, T3/T4), and preoperative PSA level ( $<4$ , 4–9.9, 10–19.9,  $\geq 20$  ng/mL) to determine if PSMs were more strongly tied to long-term outcomes in certain subsets of patients. Analyses were also repeated excluding men who received ART as well as using competing risks regression, treating non-prostate cancer death as a competing risk for each of the endpoints (except overall survival). All analyses were performed using Stata 13.0 (Stata, Corp., College Station, TX, USA). Statistical significance was two-sided with  $P < 0.05$  considered to indicate statistical significance.

## Results

The clinical and pathological characteristics of patients separated by SM status are shown in Table 1. There were 1 600 (40%) patients with PSMs. PSMs were significantly associated with younger age, race, less recent year of surgery, higher preoperative PSA level, worse pathological stage, higher Gleason score, extracapsular extension, seminal vesicle invasion, higher likelihood of receiving ART or salvage RT, and shorter time until recurrence (all  $P < 0.01$ ).

**Table 1** Demographic, clinical, and pathological characteristics of patients by SM status.

Variable	PSM	Negative SM	P
Number of patients (%)	1 600 (40)	2 451 (60)	
Mean (SD) age, years	61.8 (6.4)	62.3 (6.1)	0.010
Race, n (%)			
White	862 (54)	1 510 (62)	<0.001
Black	645 (40)	769 (31)	
Other	93 (6)	172 (7)	
Median (IQR) year of surgery	2004 (1999, 2009)	2005 (2000, 2010)	0.002
Median (IQR) PSA level, ng/mL	7.4 (5.1, 11.4)	6.0 (4.5, 8.7)	<0.001
N (%)			
Pathological stage			
T2	960 (60)	2 109 (86)	<0.001
T3/T4	640 (40)	341 (14)	
Pathological Gleason score			
2–6	381 (24)	1 026 (42)	<0.001
7 (3+4)	715 (45)	818 (33)	
7 (4+3)	251 (15)	370 (15)	
8–10	253 (16)	237 (10)	
Extracapsular extension, n (%)	516 (32)	263 (11)	<0.001
Seminal vesicle invasion, n (%)	246 (15)	135 (6)	<0.001
ART, n (%)	92 (6)	19 (1)	<0.001
Salvage RT, n (%)	235 (15)	81 (3)	<0.001
Median (IQR) months from RP to BCR*	11.4 (3.6, 34.3)	21.8 (6.6, 49.8)	<0.001

\*Among patients who had BCR.

The median (interquartile range) follow-up time among all patients who did not develop BCR was 6.6 (3.2–10.6) years. There were 1 127 (28%) patients who had >10 years of follow-up. During the follow-up period, 1 302 (32%) patients had BCR, 112 (3%) developed CRPC, 144 (4%) developed metastases, and 83 (2%) died from prostate cancer. Altogether, 942 (23%) died during follow-up from all causes. In the unadjusted models, PSMs were significantly associated with increased risk of all prostate cancer outcomes, BCR, CRPC, metastases and PCSM (all HR  $\geq 2.0$ ,  $P \leq 0.001$ ; Table 2), but not overall survival ( $P = 0.37$ ). After adjusting for demographic and pathological characteristics, PSMs remained significantly associated with increased risk of BCR (HR 1.98, 95% CI 1.75–2.23,  $P < 0.001$ ). However, they were not independently associated with CRPC (HR 1.20, 95% CI 0.96–1.83,  $P = 0.41$ ), metastases (HR 1.29, 95% CI 0.88–1.88,  $P = 0.19$ ), PCSM (HR 1.28, 95% CI 0.78–2.11,  $P = 0.33$ ), or overall survival (HR 0.96, 95% CI 0.83–1.11,  $P = 0.59$ ). These results were consistent even after adjusting for receipt of salvage RT as a time-dependent covariate (Table 2). After stratifying by pathological Gleason score, pathological stage, or PSA level group, PSMs remained associated with increased

risk of BCR on multivariable analysis (Table 3). The lack of association between PSMs and long-term outcomes held after stratification by pathological Gleason score, pathological stage, or PSA level group (Table 3). All results held when patients receiving ART were excluded (Tables S1 and S2). Results were also largely unchanged when the analysis was repeated with competing risks regression (Table S3).

## Discussion

We found that among >4 000 men undergoing RP with a median follow-up of 6.6 years and >1 100 having >10 years of follow-up, PSMs were predictive of BCR, but not the harder clinical endpoints of CRPC, metastasis, or PCSM. All patients with positive lymph node status were excluded from our present analysis, as these patients are already at very high risk of recurrence. The present results suggest that while PSMs predict BCR, they are not independent predictors of long-term outcomes. If confirmed, these results question the value of using PSMs alone to decide on the need for ART, if the goal of ART is to reduce PCSM.

**Table 2** HRs for PSM outcomes after RP.

	BCR		CRPC		Metastases		PCSM		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
PSMs										
Crude	2.58 (2.31–2.88)	<0.001	2.01 (1.38–2.93)	<0.001	2.00 (1.43–2.78)	<0.001	2.21 (1.43–3.44)	<0.001	1.06 (0.93–1.21)	0.370
Adjusted*	1.98 (1.75–2.23)	<0.001	1.20 (0.96–1.83)	0.408	1.29 (0.88–1.88)	0.186	1.28 (0.78–2.11)	0.327	0.96 (0.83–1.11)	0.588
Adjusted†	–	–	1.19 (0.78–1.82)	0.425	1.29 (0.89–1.89)	0.184	1.28 (0.78–2.11)	0.328	0.97 (0.84–1.13)	0.700

HRs are vs negative SMs. \*Adjusted for age, race, preoperative PSA level, pathological Gleason score, seminal vesicle invasion, extracapsular extension, year of surgery, surgical centre, and receipt of ART. †Adjusted for age, race, preoperative PSA level, pathological Gleason score, seminal vesicle invasion, extracapsular extension, year of surgery, surgical centre, receipt of ART, and receipt of salvage RT (time-dependent).

**Table 3** HRs for PSMs predicting prostate cancer outcomes, stratified by pathological Gleason score, pathological stage, and PSA level groups.

	BCR		CRPC		Metastases		PCSM	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Pathological Gleason score*								
2–6	2.14 (1.69–2.71)	<0.001	1.42 (0.43–4.75)	0.568	1.18 (0.56–2.49)	0.669	1.81 (0.45–7.25)	0.401
7 (3+4)	1.92 (1.59–2.34)	<0.001	0.82 (0.36–1.89)	0.647	1.12 (0.50–2.54)	0.780	1.58 (0.51–4.84)	0.427
7 (4+3)	1.92 (1.42–2.58)	<0.001	1.26 (0.40–3.97)	0.694	1.13 (0.40–3.19)	0.815	0.70 (0.20–2.50)	0.582
8–10	1.99 (1.47–2.69)	<0.001	1.22 (0.67–2.85)	0.579	1.30 (0.67–2.51)	0.431	1.24 (0.57–2.69)	0.588
Pathological stage†								
T2	2.43 (2.08–2.84)	<0.001	1.65 (0.83–3.28)	0.151	1.69 (0.95–3.01)	0.074	2.05 (0.83–5.06)	0.121
T3/T4	1.28 (1.06–1.55)	0.010	0.90 (0.52–1.54)	0.693	0.99 (0.61–1.63)	0.981	1.08 (0.59–1.97)	0.803
PSA level, ng/mL‡								
<4	2.39 (1.40–4.10)	0.001	0.32 (0.02–4.83)	0.408	1.26 (0.30–5.33)	0.752	N/A	–
4–9.9	1.98 (1.69–2.33)	<0.001	1.28 (0.67–2.46)	0.454	1.37 (0.80–2.34)	0.254	1.31 (0.60–2.89)	0.496
10–19.9	2.04 (1.62–2.58)	<0.001	1.01 (0.47–2.15)	0.985	1.01 (0.50–2.03)	0.978	1.04 (0.96–1.10)	0.931
$\geq 20$	2.22 (1.43–3.44)	<0.001	1.46 (0.46–4.61)	0.521	1.55 (0.44–5.47)	0.496	1.05 (0.23–4.84)	0.950

HRs are vs negative SMs. \*Adjusted for age, race, preoperative PSA level, seminal vesicle invasion, extracapsular extension, year of surgery, surgical centre, and receipt of ART.

†Adjusted for age, race, preoperative PSA level, pathological Gleason score, year of surgery, surgical centre, and receipt of ART. ‡Adjusted for age, race, pathological Gleason score, seminal vesicle invasion, extracapsular extension, year of surgery, surgical centre, and receipt of ART. N/A indicates that model did not converge because of low event counts.

Our present results are consistent with prior studies showing that PSMs are predictive of BCR [1,2,15]. However, less than half of patients with BCR are likely to progress to systemic disease and rates of 10-year PCSM are consistently reported below 5% [16], calling into question the use of higher BCR risk alone as an indication for immediate treatment. Indeed, after a median follow-up of 6.6 years in the present study, the risk of prostate cancer death was only 2%. As such, it is noteworthy that few studies have examined the impact of PSMs on the harder clinical endpoints of CRPC, metastasis and PCSM. Of the larger studies, Wright et al. [4] used the Surveillance Epidemiology and End Results (SEER) database to conduct a population based study of >65 000 men undergoing RP. PSMs significantly predicted PCSM only in patients in the high-grade and stage groups. Limitations of that study were the short median follow-up of 50 months, as well as a lack of data on PSA levels. A recent single-institutional study of 1 712 patients by Mauermann et al. [7] from Laval University in Quebec, had a slightly longer median follow-up of 75 months and compared single and multiple PSMs with negative SMs. Although our present study confirmed their finding that PSMs predicted only BCR and no later endpoints, they were unable to look at subgroups due to low numbers of metastasis and PCSM. A study of comparable follow-up time to our own was done in 2010 by Boorjian et al. [6], while Eggener et al. [5] conducted the largest study to date (>11 500 patients) using longer follow-up times. In both cases, results were similar to our present results, in that PSMs predicted BCR but not PCSM. However, no stratification was done to assess for whether certain subgroups were at increased risk.

The importance of stratification becomes apparent when looking at the outcomes of high- vs lower-risk groups. Both intermediate- and lower-risk groups have excellent survival profiles, regardless of treatment. [16]. As Spahn and Joniau [17] speculated, one could argue that the lack of significance of PSMs in the prior studies mentioned may in part be due to large proportions of low- and intermediate-risk patients. The present study is the first sizable study with at least intermediate follow-up times, which stratifies across multiple risk groups. As such, it is an important observation that we did not find any association between PSMs and CRPC, metastasis or PCSM in even the highest risk patients. This is unlikely to have been limited by the study size as we had >100 patients undergoing systemic progression and 80 patients dying from prostate cancer.

Importantly, all our present results held true even when all patients receiving ART were excluded, reinforcing the notion that a PSM alone is not an adequate reason to initiate ART, as these men are not at increased risk of long-term poor outcomes. In the three major trials examining the impact of ART vs observation for men at high-risk of progression after RT, whereas a major reduction in BCR risk has consistently

been shown, a reduction in PCSM risk has generally not been seen with the exception of one trial [11,12,18–20]. Thus, while achieving negative SMs remains a critical goal for the urological surgeon to avoid the stress and morbidities of BCR, and the further treatments that accompany it, the strong likelihood of overtreatment resulting from PSMs in the absence of other adverse features predictive of PCSM must be considered. It is possible that most patients may be able to adequately delay disease progression with salvage RT; however, the results of ongoing trials comparing salvage RT and ART are yet to be published.

The present study has several limitations. The present study was conducted in a population of patients who underwent only RP within the Veterans Affairs (VA) health system. However, all VA hospitals in SEARCH are academically affiliated and surgeries are performed by attending academic surgeons, reducing concerns about surgical technique. Nonetheless, most surgeries in our present study involved a resident participating in the surgery. The degree to which this influenced the rate of PSMs is unclear. Indeed our SM rate was high, although this may also reflect the relatively high-risk population being treated at the VA. Whether similar results would be seen in a population with a lower overall rate of PSMs is unknown. As we only included men who had complete data, this may have introduced a bias. However, as we had complete data on 80% of patients this is likely not to be a major concern. Furthermore, there was no central pathological review and thus the interpretation of a PSM probably varied across institutions. We also could not comment on the number, location and extent of SMs, or the tumour volume, each of which would be useful in further qualifying our results. Lastly, given the long natural history of prostate cancer, longer follow-up durations are needed to confirm our present findings.

In conclusion, in our present cohort, PSMs after RP were not an independent risk factor for CRPC, metastasis, or PCSM overall or within any subsets of RP patients, even when patients undergoing ART were excluded. These findings suggest that in the absence of other high-risk features, PSMs may not worsen long-term outcomes and may not be an indication for ART.

## Conflicts of Interest

The authors have no conflicts of interest.

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**Correspondence:** Stephen J. Freedland, Division of Urology, Department of Surgery, Cedars Sinai Medical Center, 8635 West 3rd Street Suite 1070W Los Angeles, CA 90048, USA.

**e-mail:** Stephen.Freedland@cshs.org

**Abbreviations:** BCR, biochemical recurrence; CRPC, castrate-resistant prostate cancer; HR, hazard ratio; PCSM, prostate cancer-specific mortality; RP, radical prostatectomy; (A)RT, (adjuvant) radiotherapy; (P)SM, positive surgical margin; VA, Veterans Affairs.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** HRs for PSM outcomes after RP in patients not receiving ART.

**Table S2.** HRs for PSMs predicting prostate cancer outcomes, stratified by pathological Gleason score, pathological stage, and PSA level groups in patients not receiving ART.

**Table S3.** HRs for PSM outcomes after RP with non-prostate cancer death as a competing risk.