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Positive surgical margins at radical prostatectomy predict prostate cancer-specific mortality: support for optimizing surgical technique and pathological evaluation at radical prostatectomy

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Abstract

Purpose—Positive surgical margins (PSM) in men undergoing radical prostatectomy (RP) for prostate cancer (PCa) are associated with an increased risk of biochemical recurrence. Little data have evaluated the role of PSM in PCa-specific mortality (PCSM). Using a large, population-based national cancer registry, we evaluate the risk of PCSM associated with margin status.

Methods—The SEER cancer registry data for patients diagnosed in 1998–2006 were used to identify men undergoing RP for PCa. Margin status, pathologic stage, Gleason grade and post-operative radiation therapy were recorded along with demographic data. Multivariate Cox regression analysis was used to estimate the risk of PCSM associated with PSMs.

Results—A total of 65,633 patients comprised the cohort in which 291 (0.44%) PCa-specific deaths occurred over an average follow-up of 50 months. PSMs were reported in 21.2% and were more common in pT3a than pT2 tumors (44% vs. 18%, $p<0.001$) and higher grade tumors (28% vs. 18%, $p<0.001$). The 7-year disease-specific survival rates for those at highest risk of PCSM (higher grade pT3a) were 97.3% for cases with negative surgical margins and 92.4% for those with PSMs. PSMs were associated with a 2.9-fold increased risk of PCSM (HR 2.55, 95% CI 2.02 – 3.21). PSM remained an independent predictor of PCSM in the multivariate analysis (HR 1.70, 95% CI 1.32 – 2.18).

Conclusion—These data demonstrate the independent role of positive surgical margin in PCSM. These finding support the importance of optimizing surgical technique to achieve a sound oncologic surgical outcome with negative surgical margins when possible.

Keywords

prostate cancer; surgical margin; survival; population-based; radical prostatectomy

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Introduction

A number of nomograms exist for predicting outcomes after radical prostatectomy (RP) for prostate cancer patients (PCa).[1-6] Several clinical and pathologic factors have been included in these models, most of which cannot be altered by the treating physician (e.g., pathologic stage, Gleason score, pre-treatment PSA and age). There are also various nomograms available to predict the probability of extracapsular extension and thus guide the surgeon to consider "wide field" cavernosal nerve resection versus a nerve-sparing in an attempt to reduce positive surgical margins (PSMs).[7, 8]

Most studies have found PSMs to be an independent predictor of biochemical recurrence (BCR) after RP.[9-14] However, BCR represents an early event in the natural history of PCa with heterogeneous outcomes, and BCR has not been accepted as an accurate surrogate for PCa-specific mortality (PCSM), a more informative end-point.[15, 16] For example, worse PCSM has only been shown for men with BCR and a short PSA doubling time (PSADT) or rapid time to BCR from primary treatment.[17, 18]

Small studies have evaluated the relation between PSM and biopsy proven local recurrence[12] and PCSM[14] after RP, but these have been limited by few events ($n < 10$) and the potential for referral bias. In addition, because of the low case-fatality rate from PCa, it may be that surgical margins do not appreciably add to the more established pathological factors that impact PCSM. Only a large study with enough events can evaluate whether PSM is an independent predictor of PCSM. In this study, using a national population-based tumor registry with margin status data, we investigate the risk of PCSM due to PSMs.

Methods

Data Source

The Surveillance, Epidemiology, and End Results (SEER) Program database was used to identify the cohort of patients for this study. SEER collects cancer incidence, primary treatment and survival data from 17 population-based cancer registries accounting for approximately 26% of the United States population.[19] Data from 1998 through 2006 from 13 SEER registries were used (metropolitan areas of San Francisco-Oakland, San Jose-Monterey, Los Angeles, Atlanta, Detroit, Seattle-Puget Sound and the states of Connecticut, Hawaii, New Mexico, Utah, Iowa). Cases prior to 1998 were excluded since margin status was not reported prior to that date. The registries from Greater California, Kentucky, Louisiana and New Jersey were excluded since they did not report to SEER for the entire study period having joined in 2000. The Alaska and Rural Georgia registries were also excluded since they provided less the 0.4% of the total cases.

Study Population

Potential subjects were identified using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) site codes for the prostate (C61.9) and ICD-O-3 histology codes for adenocarcinoma (8550) and acinar cell carcinoma (8140). Only cases treated with RP were included. There were 71,509 eligible cases. Cases with missing tumor grade ($n = 333$, 0.5%) or stage ($n = 1,835$, 2.5%) were excluded. Margin status is not reported for pathologic stage pT3b (seminal vesicle invasion) or pT4 (adjacent organ invasion). We also excluded patients with node positive disease ($n = 830$, 1.3%). There were 3,181 (4.4%) pT3b and 1,088 (1.5%) pT4 cases that were excluded. One hundred (0.14%) cases received radiation therapy (XRT) prior to RP and were excluded.

Data Collection and Coding

Margin status and pathologic T-stage was determined from the site-specific staging codes for prostate. The SEER grading system was used since specific Gleason grades were not recorded prior to 2004. The SEER grading system uses "Well Differentiated," "Moderately Differentiated," and Poorly Differentiated," which correspond to Gleason scores "2 –4", "5 – 7", and "8 – 10" respectively. Gleason score 7 was moved from "Moderately Differentiated" to "Poorly Differentiated" with cases diagnosed after January 1, 2003. Only 1.5% of cases were graded as "Well Differentiated" during the study period. For this analysis, "Well Differentiated" and "Moderately Differentiated" were combined into a "Lower Grade" category with the remaining cases considered "Higher Grade." The XRT variable in SEER does not distinguish between adjuvant and salvage radiation therapy. Race was categorized as Caucasian, African-American or Other. Age was categorized in 5-year age groups (< 55, 55 – 59, 60 – 64, 65 – 69, ≥ 70).

Statistical Analysis

We used univariate statistics to compare demographic and pathological characteristics between subjects with and without PSMs. Kaplan-Meier curves were used to plot time to PCSM by margin status. Multivariate Cox regression was performed to evaluate the risk of PCSM associated with margin status. Covariates selected for inclusion in the final model based on an *a priori* relationship with PCa-survival included stage, grade, additional XRT, age and race. In addition, tumor regristry and year of diagnosis were included in the multivariate model. Robust standard errors were used. Because of the strong effect of pathologic stage and grade on outcomes after RP and their relationship with margin status, we performed stratified analyses based on stage (pT2 vs. pT3a); grade (lower grade vs. higher grade); and combinations of grade and stage (pT2 lower grade; pT2 higher grade; pT3a lower grade, pT3a higher grade). The same covariates were included as in the full model except for the stratified variable(s). Potential interaction between margin status and stage/grade were evaluated with the likelihood ratio test. Hazard ratios are presented along with their 95% confidence intervals. All statistical analyses were conducted using Stata® software version 8.

Results

A total of 65,633patients with PCa underwent RP and were available for analysis. PSMs were recorded in 21.2% of cases overall. The median follow-up for the cohort was 50 months (range 1 – 107 months). A total of 2,927 (4.5%) cases died of non-PCa related causes and 291 (0.5%) died due to PCa. The cumulative PCSM over the study period was greater in those with positive margins than in those with negative margins (0.86% vs 0.33%, $p < 0.001$) while the non-PCa cumulative mortality was similar between positive and negative margin cases (4.5% and 4.3% respectively, p=0.42).

Table 1 compares the clinical and pathologic characteristics between those with and without PSMs. Margin positivity varied substantially across registries (11.3% to 28.5%). The annual PSM frequency ranged between 17.9% to 23.5%, although it declined steadily for the last 5 years of the study period ($p < 0.001$). As expected, a PSM was more common in patients with pT3 disease (43.8% vs. 17.7%, $p < 0.001$) and higher grade disease (275% vs. 18.3%, $p < 0.001$). Receiving post-RP radiation therapy (data not shown) was rare overall (3.4%) and given more frequently to patients with PSMs (10.2%) than to those without PSMs (1.5%, $p < 0.001$). XRT was also more common in those with pT3a disease. The prevalence of XRT for pT2 with negative surgical margins (NSM), pT2 with PSM, pT3a with NSM and pT3a with PSM was < 1.0%, 6.7%, 7.7% and 19.2%, respectively, $p < 0.001$).

Table 2 lists the 5- and 7-year disease-specific survival (DSS) rates (along with 95% CI) for men by margin status stratified by grade and stage. For lower grade, pT2 tumors, the disease-specific survival is essentially identical for PSM and NSM (99.7% and 99.8%, respectively). The 5- and 7-yr disease-specific survival for higher grade pT2 and lower grade pT3a tumors are slightly higher for men with NSMs versus PSMs, although there is some overlap in the 95% CIs. For higher grade pT3a tumors, the 7-yr disease-specific survival is greater for those with NSMs than PSMs (97.3% vs. 92.4%, respectively ($p < 0.001$)).

Figure 1 shows the Kaplan-Meier curve for the PCSM in men with and without PSMs. Men with PSMs had significantly greater PCSM ($p < 0.0001$) corresponding to a2.6-fold increased risk of PCSM in the univariate Cox regression model (HR 2.55, 95% CI 2.02 – 3.21). Figure 2 shows the PCSM Kaplan-Meier curves, stratified by stage and margin status (Figure 2A); grade and margin status (Figure 2B); and grade, stage and margin status (Figure 2C). In Table 3, the results of the multivariate model are shown. PSM remained an independent predictor of PCSM, with a 70% increased risk (HR 1.70, 95% CI 1.32 – 2.18). Higher grade disease, pT3 disease and additional XRT were also predictive of PCSM in the multivariate model

In Table 4, the multivariate models (adjusting for the same variables in the full model) are stratified by stage and grade. The HRs for PCSM are presented within each strata as there was evidence for effect modification by the likelihood ratio test for an interaction between margin status with stage ($p = 0.04$), and margin status with grade ($p = 0.12$). In each case, PSM is associated with an increased risk of PCSM, although it only reached statistical significance in those with higher grade tumors (HR for PSM: 1.97, 95% CI 1.41 – 2.76); pT3a tumors (HR for PSM: 2.42, 95% CI 1.58 – 3.72) and for those tumors that are both pT3a and higher grade (HR for PSM: 2.72, 95% CI 1.62 – 4.54).

Discussion

Although PSMs have been shown to be associated with BCR after RP, studies showing its significance in disease-specific mortality have not been reported. In this large, population-based study of over 65,000 RP patients, we report the independent predictive role of surgical margin status on men undergoing RP. Our findings support the importance of achieving negative surgical margins when possible, especially in those with higher grade disease and suspicion of extracapsular extension who are at greatest risk of early PCSM.

Multiple studies have found PSMs to be associated with higher rates of BCR after RP.[9-14] However, many patients experiencing BCR will not die from PCa and consequently BCR is not a universally accepted surrogate for PCSM.[15, 16] Studies evaluating margin status in relation to the more clinically robust endpoint of PCSM have been lacking. Recently, German investigators reported a series of 406 patients undergoing RP with PSM seen in 18%.[14] PSMs were associated in multivariate analysis with BCR (114 patients, HR 3.2, 95% CI 2.1 – 4.9), local recurrence (22 patients, HR 4.6, 95% CI 1.8 – 12.1) and distant metastasis (HR 16 patients, HR 6.65, 95% CI 1.9 – 23.1). Although there were too few events to evaluate the impact of PSMs on PCSM in multivariate analysis, in the univariate analysis, PCSM was more common in those with PSMs compared to NSMs (8.6% vs. 0.6%, $p < 0.001$). In our study, we found in multivariate analysis that PSMs remains an independent predictor of PCSM, with a 70% increased risk of death due to PCa compared to patients with NSMs.

In our study, PSMs were associated with a increased risk of PCSM within each strata of stage and grade, although the HR only reached statistical significance in those with higher

grade tumors (HR for PSM: 1.97, 95% CI 1.41 – 2.76) or pT3a disease (HR for PSM: 2.42, 95% CI 1.68 – 3.72) or both pT3a and high grade tumors (HR for PSM: 2.72, 95% CI 1.62 – 4.54). It is possible that with increased follow-up and more events, margin status may reach statistical significance in pT2 and lower grade tumors. However, due to the low disease-specific death rate for these patients, surgical margin status may only become a significant contributor to PCSM in those with a life expectancy > 10 years for whom the risk of PCSM is higher. In contrast, when looking at those at highest risk of PCSM (those with pT3a higher grade disease), the 7-year PCa-specific survival rates are 97.6% and 92.4% for NSMs and PSMs, respectively. This absolute 5.0% difference is similar to the difference reported in the Scandinavian randomized trial between surgery and watchful waiting.[20] Our findings indicate that surgical technique, not just surgery alone, appears to be associated with improved disease-specific survival.

Intra-operatively, PSMs can occur due to extensive cancer for which complete resection is impossible/unadvisable; or due to technical error (e.g, capsular incision). Pathological interpretation of margin status is complicated by surgical artifact (crush, tears, thermal or electrocautery) causing unpredictable tracking of ink, which can lead to variability in reporting of surgical margins even for expert urologic pathologists.[21] Additionally, the pathological processing of the prostate can introduce variance in margin detection due to differences in tissue handling and processing. Differences in sampling prostatectomy specimens can result in higher false negative rates at those institutions where sampling is selective rather than comprehensive, viz. where the prostate is totally embedded and sectioned.[22] Sampling methods that are biased toward the peripheral zone of the prostate, the zone in which the majority of cancers occur, undersample the transition zone, in which at least 15 % of prostate adenocarcinomas are located.[23] A potential consequence of not sampling the anterior aspect of the prostate is missing margin-positive areas in this zone. Future efforts to minimize these effects to reduce ‘false’ positive (or negative) margins are needed to help better standardize margin status and its impact on disease outcomes. The importance of accurate margin status has been demonstrated in an analysis of EORTC trial 22911 of adjuvant XRT after prostatectomy.[24] Patients reported to have PSM after review of the prostate specimen by a pathologist with urologic oncology expertise was the strongest predictor of benefit from adjuvant radiation therapy in this randomized trial. The multivariate association of XRT with worse PCSM in our study should be interpreted with caution as we are unable to distinguish between adjuvant or salvage XRT thus selection bias may play a role in this finding.

This study has limitations. We do not have PSA data or information on the precise pathological factors such as the presence of lymphovascular invasion, number of PSMs and location of PSMs which have been reported to affect BCR.[11, 25, 26] In addition, we do not have central pathologic review, which could lead to misclassification. However, the reported rates of PSMs from the different tumor registries in our series (11% – 29%) are similar to those reported in a recent review that found PSM rates of 11% – 38%.[27] Further, the association between common pathologic criteria and margin status (higher PSMs with higher stage and higher Gleason score) support the reliability of abstracted margin status by the SEER registries. Finally, we do not have data on whether or not the RP was nerve sparing. Despite these limitations, this large population-based series show a difference in PCSM associated with PSMs. These data demonstrate the importance of optimizing surgical technique to achieve a negative surgical margin in PCa and underscore the need for pathologic standardizations of tissue processing to accurately define surgical margin status.

Acknowledgments

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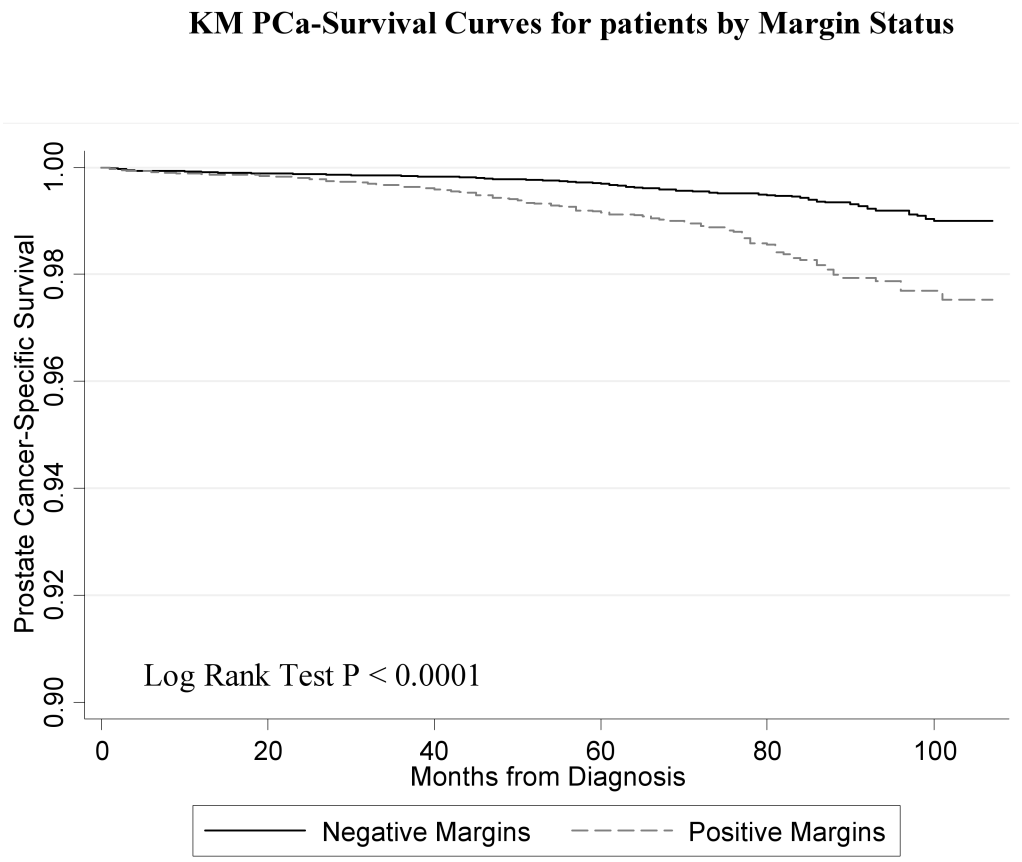

Figure 1.
Kaplan Meier prostate-cancer specific survival plots stratified by surgical margin status ($p < 0.001$).

Figure 2a:

KM PCa-Survival Curves for patients grouped by Stage and Margin Status

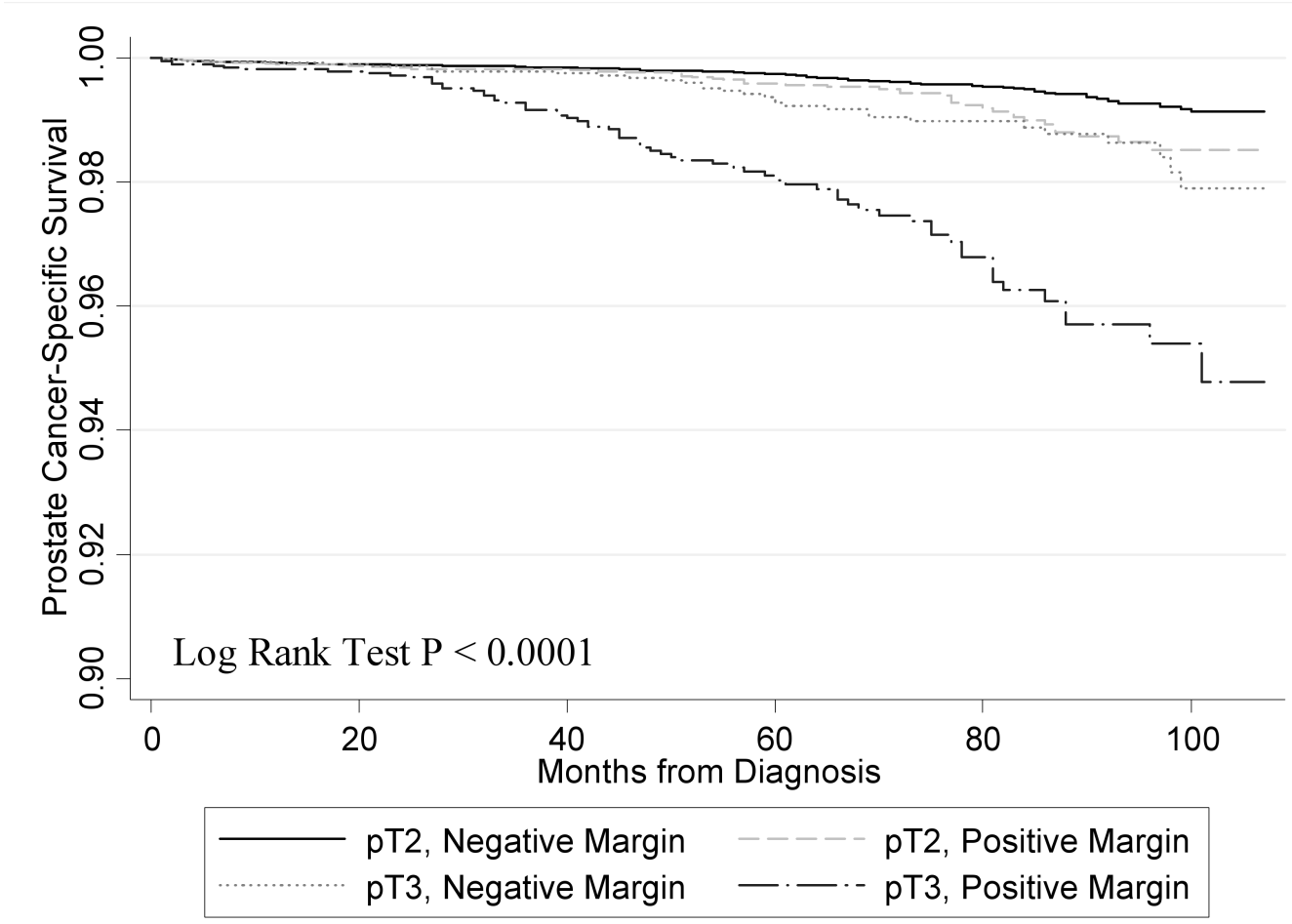

Figure 2b:

KM PCa-Survival Curves for patients grouped by Grade and Margin Status

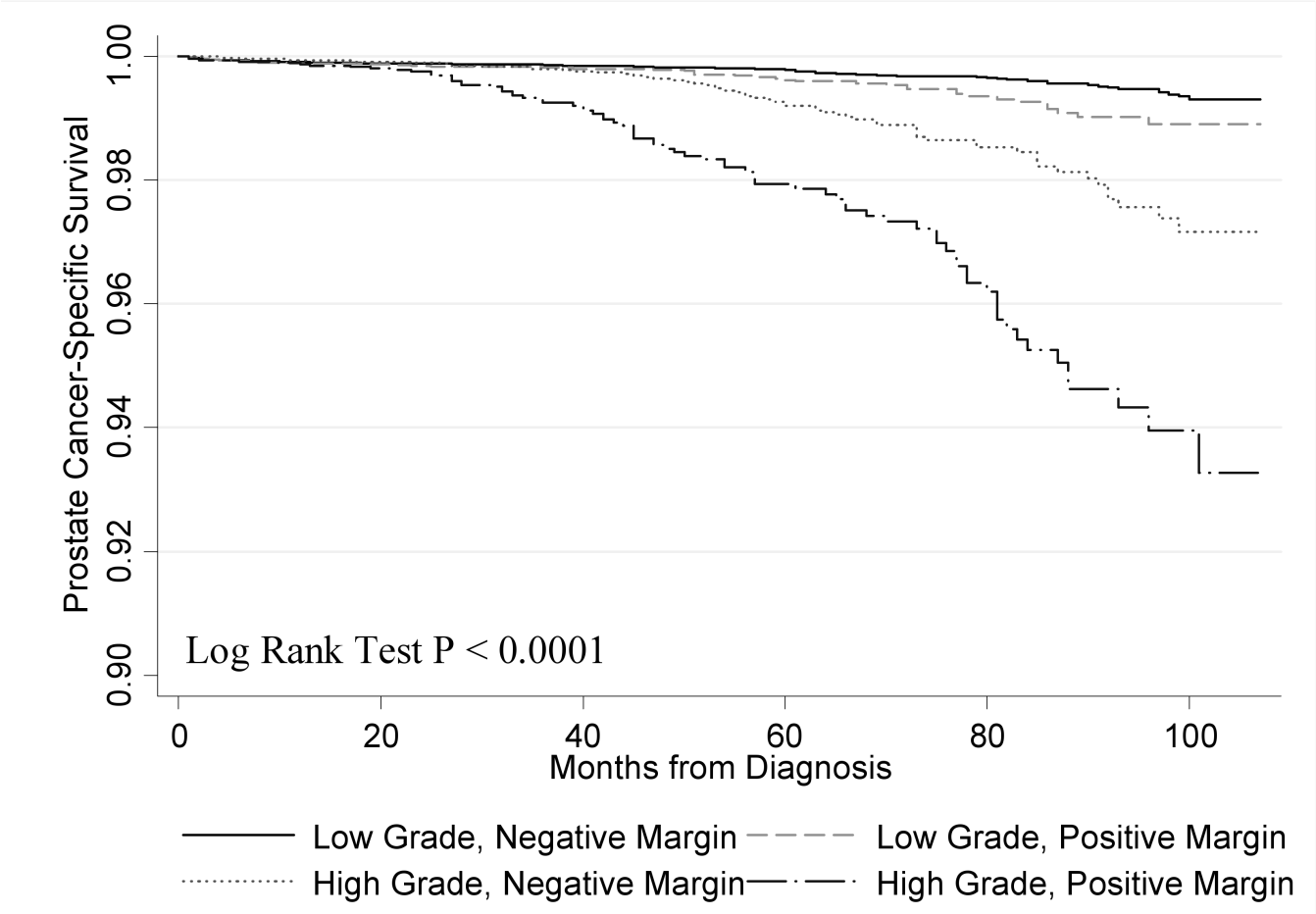

Figure 2c:

KM PCa-Survival Curves for patients grouped by Stage, Grade and Margin Status

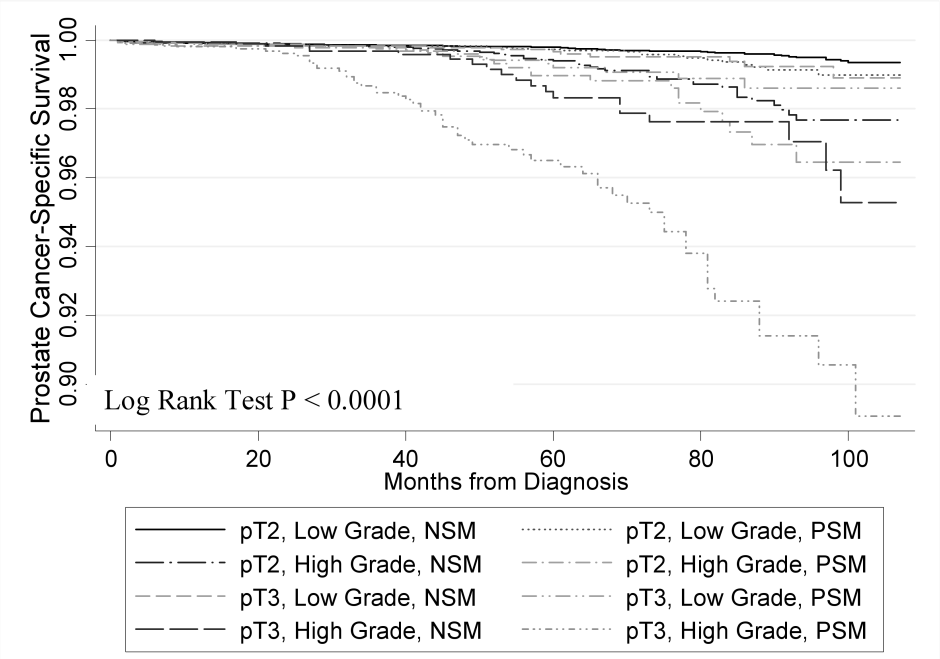

Figure 2.
Kaplan Meier prostate-cancer specific survival plots stratified by (a) pathologic stage and surgical margin status; (b) pathologic grade and surgical margin status; (c) pathologic stage, grade and surgical margin status. All p-value < 0.001.

Table 1

Distribution of Clinical and Pathological Characteristics of 65,633 Radical Prostatectomy Patients by Surgical Margin Status

	Negative Margins N (%)	Positive Margins N (%)	P-value
Overall	51,728 (78.8)	13,905 (21.2)	
Age (years)			
< 55	9,699 (79.3)	2,533 (20.7)	0.27
55 – 59	11,499 (79.1)	3,036 (20.9)	
60 – 64	12,497 (78.8)	3,360 (21.2)	
65 – 69	11,084 (78.3)	3,071 (21.7)	
70 +	6,947 (78.5)	1,904 (21.5)	
Race			
Caucasian	43,216 (78.3)	11,313 (20.8)	< 0.001
African-American	5,359 (75.3)	1,754 (24.7)	
Other	3,153 (79.0)	838 (21.0)	
Tumor Registry			
San Francisco-Oakland	4,988 (82.4)	1,066 (17.6)	< 0.001
Connecticut	4,744 (81.4)	1,084 (18.6)	
Detroit (Metro)	7,341 (79.9)	1,843 (20.1)	
Hawaii	1,039 (79.3)	271 (21.7)	
Iowa	4,341 (78.1)	1,221 (22.0)	
New Mexico	2,427 (84.3)	453 (15.7)	
Seattle/Puget Sound	6,296 (77.6)	1,821 (22.4)	
Utah	3,083 (71.5)	1,231 (28.5)	
Atlanta (Metro)	3,194 (88.7)	407 (11.3)	
San Jose-Monterey	2,542 (75.9)	786 (23.6)	
Los Angeles	11,733 (75.9)	3,722 (24.1)	
Year of Diagnosis			
1998	4,987 (79.8)	1,261 (20.2)	< 0.001
1999	5,569 (78.4)	1,536 (21.6)	
2000	5,545 (78.3)	1,540 (21.7)	
2001	5,854 (78.1)	1,643 (21.9)	
2002	5,884 (76.5)	1,812 (23.5)	
2003	5,710 (77.7)	1,632 (22.2)	
2004	6,240 (78.4)	1,715 (21.6)	
2005	5,716 (80.3)	1,407 (19.8)	
2006	6,223 (82.1)	1,359 (17.9)	
Pathologic Stage			
pT2	46,818 (82.3)	10,074 (17.7)	< 0.001
pT3a	4,910 (56.2)	3,831 (43.8)	
Grade			
Lower Grade	36,786 (81.7)	8,233 (18.3)	< 0.001

	Negative Margins N (%)	Positive Margins N (%)	P-value
Higher Grade	14,942 (72.5)	5,672 (27.5)	

Table 2

5- and 7-year Prostate Cancer-Specific Survival Based on Surgical Margin Status in Men Undergoing Radical Prostatectomy Stratified by Stage and Grade

	5-year DSS (95% CI)		7-year DSS (95% CI)	
	Negative Margin	**Positive Margin**	**Negative Margin**	**Positive Margin**
pT2				
Lower Grade	99.8 (99.7 – 99.8)	99.7 (99.5 – 99.8)	99.6 (99.5 – 99.7)	99.4 (99.0 – 99.6)
Higher Grade	99.4 (99.1 – 99.6)	99.0 (98.2 – 99.4)	98.6 (98.1 – 99.0)	97.3 (95.5 – 98.4)
pT3a				
Lower Grade	99.7 (99.3 – 99.8)	99.2 (98.5 – 99.6)	99.4 (98.8 – 99.7)	98.9 (97.9 – 99.4)
Higher Grade	98.3 (97.1 – 99.0)	96.5 (95.1 – 97.5)	97.6 (96.0 – 98.6)	92.4 (89.7 – 94.5)

Table 3
Risk of PCa-Specific Mortality in Men Undergoing Radical Prostatectomy

	Univariate		*Multivariate*	
	HR	**95% CI**	**HR** *	**95% CI**
Positive Margin	2.55	2.02 – 3.21	1.70	1.32 – 2.18
Grade				
Low Grade	1.00	Referent	1.00	Referent
High Grade	2.05	1.80 – 2.32	3.45	2.69 – 4.42
Additional XRT	4.04	2.89 – 5.66	1.77	1.20 – 2.61
Stage				
pT2	1.00	Referent	1.00	Referent
pT3	3.43	2.69 – 4.36	2.01	1.55 – 2.60

* Adjusted for all other covariates in the table along with age, race, registry and year of diagnosis

Table 4

Adjusted Risk of Prostate Cancer-Specific Mortality in Men undergoing Radical Prostatectomy, Stratified by Stage and Grade

	N (%)	HR *	95% CI
Grade			
Lower Grade			
Negative Margin	36,786 (81.7)	1.00	Referent
Positive Margin	8,233 (18.3)	1.36	0.91 – 2.04
Higher Grade			
Negative Margin	14,942 (72.5)	1.00	Referent
Positive Margin	5,672 (27.5)	1.97	1.41 – 2.76
Pathologic Stage			
pT2			
Negative Margin	46,818 (82.3)	1.00	Referent
Positive Margin	10,074 (17.7)	1.29	0.90 – 1.84
pT3a			
Negative Margin	4,910 (56.2)	1.00	Referent
Positive Margin	3,831 (43.8)	2.42	1.58 – 3.72
Stage and Grade			
pT2			
Lower Grade			
Negative Margin	34,309 (83.9)	1.00	Referent
Positive Margin	6,575 (16.1)	1.21	0.75 – 1.95
Higher Grade			
Negative Margin	12,509 (78.1)	1.00	Referent
Positive Margin	3,499 (21.9)	1.38	0.80 – 2.38
pT3a			
Lower Grade			
Negative Margin	2,477 (59.9)	1.00	Referent
Positive Margin	1,658 (40.1)	1.84	0.79 – 4.27
Higher Grade			
Negative Margin	2,433 (52.8)	1.00	Referent
Positive Margin	2,173 (47.2)	2.72	1.62 – 4.54

* Adjusted for stage and grade when not the stratified variable. Also adjusted for xrt, age, race, registry and year of diagnosis