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Prostate cancer that is within 0.1 mm of the surgical margin of a radical prostatectomy predicts greater likelihood of recurrence

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Abstract

Purpose—Surgical margin status at prostatectomy is an important predictor of biochemical recurrence. The current convention is to categorize a margin as negative if tumor cells are not at the inked margin, even if they are within a few cells of the margin. We hypothesized that cancer within 0.1 mm of the margin conferred an increased risk of biochemical recurrence.

Materials and Methods—We determined the risk of biochemical recurrence based on surgical margin status in a cohort of 1588 patients who underwent radical prostatectomy for prostate cancer between 1998 and 2011. Surgical margins were categorized as positive, close (<0.1 mm from tumor cells) or negative. Multivariate hazard ratios for biochemical recurrence were determined by margin status.

Results—We identified 1588 patients of whom 193 had prostate cancer recurrence. The margin status was negative in 1,058 (67%), close in 232 (15%) and positive in 298 (19%). Cancer that was close to the margin was a significant and independent predictor of biochemical recurrence (HR 1.53, 95% CI 1.00 – 2.32) and was not statistically different than a positive surgical margin (HR 2.10, 95% CI 1.48 – 2.99).

Conclusions—Cancer that is within 0.1 mm of the surgical margin of a prostatectomy is associated with an increased risk of prostate cancer recurrence. Patients with that margin status may be reasonable candidates for adjuvant local therapy.

Introduction

Positive surgical margins at the time of radical prostatectomy (RP) are an independent predictor of biochemical recurrence (BCR), local recurrence, distant metastasis and, in some series, prostate cancer (PCa) specific mortality (1-6). A positive surgical margin may also be the strongest predictor of the utility of adjuvant radiotherapy following RP (7). However, some men with clinically localized disease do experience BCR and progression even in the absence of a positive surgical margin (1, 6, 8, 9).

If positive surgical margins impact recurrence rates by leaving cancer tissue in the body, it is conceivable that *close* but negative surgical margins may have an impact on outcomes. Very small tumor to margin distances may represent occult positive surgical margins that are simply not sampled in the standard sections of a totally embedded RP. Small tumor-to-margin distances correlate with increased recurrence rates of other cancers. Margin distances of less than 2 mm correlate with increased rates of breast cancer recurrence (10, 11). Likewise, circumferential resection margins of rectal carcinomas that are less than 2 mm correlate with increased rates of local and distant recurrences and decreased overall survival (12, 13). Most studies of PCa have not found an association between margin distance and recurrence rates (14-16). However, these studies were limited by a small sample size. One recent study reported that margin distances of less than 0.1 mm are associated with increased recurrence rates (17).

At our institution we have categorized the margin status of RP done for PCa based on threshold values of tumor-to-margin distances. We hypothesized that a small tumor to margin distance in margin-negative RP specimens correlate highly with occult margin positivity and predict for increased recurrence rates.

MATERIALS AND METHODS

Study population

We queried a prospectively maintained database at our institution for all RP specimens since 1998. Beginning that year, the margin status of the specimens was classified as positive (*ink touching tumor cells*), close (*tumor cells within 0.1 mm of the inked margin*) or negative (Figure 1). The large majority of specimens were reviewed and reported by one GU pathologist (LT) prior to 2005. From 2005 to the present multiple pathologists reported RP specimens using a standard prostatectomy template. All RP specimens were handled based on a standard protocol. In brief, the surface of the specimens was inked using four colors and fixed overnight in phosphate buffered formalin. Serial transverse sections were then made from apex to base. These were submitted for processing and embedding in paraffin as approximately 3 mm thick blocks, from which single 4 micron thick sections were taken. Cancers from 1998 -2005 were graded according to criteria conventional at the time (18). Cancers after 2005 were graded using the 2005 ISUP Modified Gleason grading system (19). Tumor volume was determined morphometrically. The regions of cancer on the slides from each case were circumscribed by ink. The area of each cancer region was determined by superimposing a template over the slides. The volume of cancer in each case was the multiplicand of the summed areas of cancer and average block thickness, which is 0.3 cm.

Patients were excluded from this analysis if they had received neoadjuvant therapy, had node positive disease or if their post-operative PSA did not reach an undetectable level. Patients missing stage, cancer grade or follow-up data were also excluded, as were patients who underwent salvage RP. Follow-up schedules were individualized based on surgeon preference and patient disease characteristics.

Data collection and coding

Data collection was performed after approval from the Institutional Review Board. Information regarding age, race, preoperative PSA, pathological T stage, Gleason score, surgical approach, use of adjuvant radiotherapy, total prostate volume and PCa tumor volume were collected. Pre-operative PSA was divided into categories of <4, 4 – 10, and 10 ng/ml. Age was analyzed as the categorical variables <50, 50-59, 60-69 and ≥ 70. PCa tumor volume was categorized into 1.0 cubic centimeter increments (0-0.9, 1.0-1.9, 2.0-2.9, 3.0-3.9, 4.0) and prostate volume was categorized into quartiles.

Disease progression was defined as a PSA ≥ 0.2ng/mL, treatment with salvage radiotherapy or initiation of androgen deprivation therapy (ADT). Time to disease progression was determined from date of RP.

Statistical Analysis

Differences in patient demographic and pathologic variables by margin status were compared by Chi-squared tests. Univariate and multivariate Cox proportional hazards regression analysis were used to determine the hazard ratios and 95% confidence intervals for risk of recurrence. All of the above covariates were included in the multivariate model. The proportional hazards assumption for the Cox model was evaluated with Schoenfeld goodness of fit testing. Statistical analysis was performed using Stata Software, Version 12 (Stata, Inc. College Station, TX).

RESULTS

Data from 1588 patients were available for analysis. Patient characteristics are reported in Table 1. The overall positive surgical margin rate was 18.8%. Margins that were close represented 15% of pathology specimens. Table 2 shows the distribution of pathologic factors by margin status. Significant differences in margin status were observed within pathologic T stage and Gleason score (both $p < 0.001$). Margins that were close and positive were more frequent in patients with pT3 tumors compared to those with pT2 tumors. The proportion of cases with margins close and positive increased with higher Gleason grades. Higher pre-operative PSA values were associated with higher rates of positive surgical margins ($p < 0.01$).

Overall, 193 of 1588 patients (12.5%) experienced disease recurrence with a median follow-up of 25 months (range 0.26 – 149 months). Adjuvant XRT was infrequently used (1.3% of the total cohort), most commonly (8%) for those patients with pT3 tumors and/or positive surgical margins.

The overall recurrence rates, stratified by margin status and unadjusted risk of recurrence by clinical and pathological factors, are reported in Tables 3 and 4 respectively. Compared to patients with a negative surgical margin, close margins predicted higher risk of recurrence (HR 1.72, 95% CI 1.15-2.57). Figure 2 shows Kaplan Meyer recurrence free survival curves for patients stratified by margin status. Other univariate predictors of recurrence were pathological T stage, larger tumor volumes, higher Gleason score, the use of adjuvant radiotherapy and higher preoperative serum PSA levels. In the multivariate model, positive

surgical margins and close surgical margins remained independent predictors of recurrence. Compared to those with a negative surgical margin, a close margin was associated with a greater than 50% increased risk of recurrence (HR 1.53, 95% CI 1.00 – 2.32). There was no significant difference in recurrence between close and positive surgical margins ($p = 0.15$). Subgroup analysis for those patients with more than 2 years of follow-up revealed an even higher risk of recurrence in our multivariate model for those with close margins compared to those with negative margins (HR 1.71, 95% CI 0.93 – 3.13, $p = 0.08$). Excluding those who received adjuvant XRT also did not significantly change the risk estimates (data not shown).

DISCUSSION

In this study, we found that patients whose tumors are within 0.1 mm of the surgical margin have significantly higher rates of recurrence than those patients whose prostatectomy specimens have negative surgical margins. Furthermore, the recurrence rates of tumors with close margins were similar to those with positive surgical margins. Our data supports the hypothesis that tumors that are within 0.1 mm of the surgical margin may represent occult positive margins (20).

Two studies, using an ocular micrometer to measure tumor-to-margin distances in RP specimens, looked at the risk of biochemical recurrence of cancer in node-negative cases. In a case control study of 101 men of whom 52 experienced biochemical progression there was no difference in disease recurrence based on mean tumor-to-margin distances. Furthermore, tumor-to-margin distance was not associated with BCR in their multivariate model(15). However, progression after RP is not solely determined by margin status as there are multiple risk factors reported for progression(21-25). Therefore, a retrospective sampling of 52 patients who experienced tumor progression may not accurately reflect the prognostic value of tumor-to-margin distance. Further, that study was of men treated from 1982 to 1988 which may not be representative of a contemporary, PSA screened population. A second study of 278 consecutive patients with margin negative PCa found that patients who experienced biochemical recurrence had a closer median tumor to margin distances (0.4mm, range 0.0 – 1.8) than those without biochemical recurrence (0.5mm, 0.0 – 5.0). However, this finding was not statistically significant ($p = 0.06$). Since only 23 patients experienced biochemical recurrence, multivariate analysis was not performed. Our analysis of a much larger population ($n=1,588$) has greater power to detect a significant difference. Rather than measuring an absolute tumor-to-margin distance, we prospectively categorized our cases by margin status - positive, within 0.1 mm of the margin, and negative. This approach helps to minimize the effect of outliers that may skew data distribution. In the first case-control study described above, the median tumor-to-margin distance was 0.3 mm in the controls and 0.275 mm in the cases(15). In the second study, the median distance was 0.5 mm(14). Potentially, the previous studies of tumor-to-margin distance may have failed to find a significant difference because too large a distance was analyzed. By categorizing patients based on a shorter tumor-to-margin distance of 0.1 mm we were more likely to find a true difference.

In a recently published study, Lu et al. examined the prognostic importance of tumor-to-margin distances of < 0.1 mm(17). Of 894 patients with a median followup of 9.9 years, 277 experienced biochemical recurrence. The multivariate analysis found that close margins

were significantly associated with biochemical recurrence, characterized by a hazard ratio of 2.1 (95% CI 1.04 – 4.33). These results are similar to ours, wherein we also found a statistically significant recurrence rate that was 1.53 times higher in those with close margins than those with negative surgical margins. It is likely that there is a continuum of strength of correlation between recurrence rate and tumor-to-margin distance. This explanation is biologically plausible if we assume that the majority of patients with increased recurrence rates result from occult positive margins. The closer the surgical margin, the more likely it is that cancer cells are actually at the surgical margin deeper in a paraffin block. Humphrey showed that increasing the number of sections of the margins of a radical prostatectomy specimen increases the extent of margin positivity(26). That finding is not surprising since we do not routinely sample for margin-positive events to a degree that will identify all such events. Conventional practice is to obtain 4 or 5 micron thick sections of 2 to 3 mm thick blocks of tissue. This represents a sampling frequency of 1 in 400 to 1 in 750.

There are some limitations to our study. First, pathologists may vary in their visual estimates of 0.1 mm tumor to margin distance. As previously reported, genitourinary pathologists vary in their assessments of surgical margin status (27). However, our finding may be more realistic and generalized since several pathologists were involved with the pathologic interpretations. This staffing characterizes most practices. Second, the median follow-up of our patient cohort was only 25 months (range 0.26 – 149 months). Despite this short follow-up, we had enough events (n=193) to find a difference in recurrence rates categorized by margin distance. We would expect that further follow-up will strengthen the association between tumor-to-margin distance and recurrence rates as was shown in our subgroup analysis of those patients with at least 2 years of follow-up.

The use of biochemical recurrence as an endpoint may be seen as a limitation, as not all of those who suffer a recurrence will progress to death (28-30). However, using cancer specific survival as the primary endpoint ignores the patient distress and morbidity resulting from both disease progression and the side effects associated with treatment. Additionally, showing a difference in cancer specific survival by margin status would require patient numbers well beyond the scope of this study.

Finally, we did not use an ocular micrometer to measure tumor-to-margin distance. Instead we used a simpler approach of stratifying distances based on visually estimating whether the tumor was within 0.1 mm of the margin. A readily available measurement tool is the microscope. In one widely used microscope, one fifth of the visual field diameter viewed through a 40x objective and 10x ocular is 0.1 mm.

Despite these limitations, we have shown in a large cohort of prostate cancer patients treated with radical prostatectomy that men with a close surgical margin, defined as a tumor to surgical margin distance of < 0.1 mm, have an increased risk of recurrence compared to those with negative margins. The risk of recurrence in this group is not statistically different from those patients with positive surgical margins. These findings have implications for pathologic reporting of margin status, counseling of postoperative patients and consideration for adjuvant therapy.

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Figure 1. Depiction of our novel classification of surgical margin status

A: Represents tumor with a negative surgical margin. B: Cancer cells in this specimen extend to the inked surface. This represents a positive surgical margin. C: Cancer cells are within 0.1 mm of the surgical margin. This specimen is classified as a “**close**” margin.

Figure 2.
Kaplan Meyer curves of recurrence free survival stratified by margin status.

Table 1

Characteristics of study cohort.

Overall		
	Patients (n = 1588)	Frequency (%)
Age		
< 50	115	7%
50 - 59	656	41%
60 - 69	663	42%
70	154	10%
Race		
White	1228	77%
Non White	96	6%
Unknown	264	17%
Margin Status		
Negative	1,058	67%
Close	232	15%
Positive	298	19%
pT Stage		
pT2	1,337	84%
pT3a	206	13%
pT3b	45	3%
Gleason Score		
6	672	42%
3 + 4	600	38%
4 + 3	136	9%
8	180	11%
PSA at Surgery		
< 4.0	324	20%
4 - 10	1,019	64%
10	202	13%
Missing	43	3%
Tumor Volume (cc)		
< 1.0	450	28%
1.0 - 1.9	412	26%
2.0 - 2.9	285	18%
3.0 - 3.9	175	11%
4.0	263	17%

Table 2

Patient characteristics stratified by surgical margin status.

	Negative (N = 1,058)	Close (N = 232)	Positive (N = 298)	Total (N = 1,588)	P value
Age					
< 50	78 (67.8%)	16 (13.9%)	21 (18.3%)	115	p = 0.876
50 – 59	436 (66.5%)	102 (15.6%)	118 (18.0%)	656	
60 – 69	438 (66.1%)	97 (14.6%)	128 (19.3%)	663	
70	106 (68.8%)	17 (11%)	31 (20.1%)	154	
Race					
Caucasian	831 (67.7%)	168 (13.7%)	229 (18.6%)	1228	p = 0.435
Non Caucasian	71 (74.0%)	10 (10.4%)	15 (15.6%)	96	
Unknown	156 (59.1%)	54 (20.5%)	54 (20.5%)	264	
pT Stage					
pT2	952 (71.2%)	180 (13.5%)	205 (15.3%)	1,337	p < 0.001
pT3a	88 (42.7%)	42 (20.4%)	76 (36.9%)	206	
pT3b	18 (40.0%)	10 (22.2%)	17 (37.8%)	45	
Gleason Score					
6	499 (74.3%)	89 (13.2%)	84 (12.5%)	672	p < 0.001
3 + 4	388 (64.7)	91 (15.2%)	121 (20.2%)	600	
4 + 3	83 (61.1%)	16 (11.8%)	37 (27.2%)	136	
8 – 10	88 (48.9%)	36 (20%)	56 (31.1%)	180	
Pre-op PSA					
< 4.0	229 (70.7%)	48 (14.8)	47 (14.5%)	324	p = 0.001
4.0 – 10.0	680 (66.7%)	149 (14.6%)	190 (18.6%)	1,019	
10.0	114 (56.4%)	29 (14.4%)	59 (29.2%)	202	
Missing	35 (81.5%)	6 (14.0)	2 (4.7%)	43	
Tumor Volume (cc)					
< 1.0	379 (84.2%)	40 (8.9%)	31 (6.9%)	450	p < 0.001
1.0 - 1.9	292 (70.9%)	55 (13.4%)	65 (15.8%)	412	
2.0 - 2.9	167 (58.6%)	58 (20.4%)	60 (21.1%)	285	
3.0 - 3.9	109 (62.3%)	29 (16.6%)	37 (21.1%)	175	
4.0	109 (41.4%)	50 (19.0%)	104 (39.5%)	263	
Prostate Volume (cc)					
< 36	248 (57.9%)	79 (18.5%)	101 (23.6%)	428	p < 0.001
36 - 43	227 (62.7%)	59 (16.3%)	76 (21.0%)	362	
43 - 55	277 (69.1%)	57 (14.2%)	67 (16.7%)	401	
55	301 (77.6%)	37 (9.5%)	50 (12.9%)	388	

Table 3

Unadjusted recurrence rates stratified by margin status.

Margin Status	Recurrence		Total
	No	Yes	
Negative	972 (91.9)%	86 (8.1)%	1058
Close	199 (85.8)%	33 (14.2)%	232
Positive	224 (75.2)%	74 (24.8)%	298
Total	1395 (87.8)%	193 (12.2)%	1588

Table 4

Univariate and multivariate analysis of risk of recurrence:

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% Confidence Interval	P Value	Hazard Ratio	95% Confidence Interval	P Value
Age						
< 50	Referent	Referent	Referent	Referent	Referent	Referent
50 - 59	0.87	0.50 – 1.54	0.642	0.64	0.35 - 1.14	0.13
60 - 69	1.07	0.61 – 1.85	0.818	0.71	0.39 – 1.27	0.242
70	1.43	0.75 – 2.74	0.275	0.70	0.34 – 1.41	0.314
Race						
White	Referent	Referent	Referent	Referent	Referent	Referent
Non White	0.96	0.66 – 1.40	0.843	0.92	0.63 – 1.36	0.677
PSA at Surgery						
< 4.0	Referent	Referent	Referent	Referent	Referent	Referent
4 - 10	1.61	1.04 – 2.49	0.031	1.55	0.98 - 2.43	0.057
10	3.32	2.04 – 5.40	<0.001	1.97	1.16 - 3.34	0.012
Margin Status						
Negative	Referent	Referent	Referent	Referent	Referent	Referent
Close	1.72	1.15 - 2.57	0.008	1.53	1.00 - 2.32	0.047
Positive	2.91	2.13 - 3.98	<0.001	2.10	1.48 - 2.99	<0.001
pT Stage						
pT2	Referent	Referent	Referent	Referent	Referent	Referent
pT3a	3.12	2.27 – 4.29	<0.001	1.46	1.01 – 2.12	0.044
pT3b	2.11	1.03 – 4.33	0.039	0.81	0.37 – 1.75	0.587
Gleason Score						
6	Referent	Referent	Referent	Referent	Referent	Referent
3 + 4	1.84	1.26 – 2.68	0.001	1.66	1.10 - 2.50	0.016
4 + 3	3.41	2.05 – 5.69	<0.001	3.22	1.86 - 5.59	<0.001
8	6.44	4.36 – 9.51	<0.001	4.71	2.90 - 7.63	<0.001
Prostate Volume						
< 36	Referent	Referent	Referent	Referent	Referent	Referent
36 - 43	1.08	0.73 - 1.59	0.705	0.95	0.63 - 1.41	0.786
43 - 55	1.07	0.73 - 1.56	0.738	1.19	0.80 - 1.77	0.382
55	0.80	0.52 - 1.22	0.299	0.91	0.56 - 1.46	0.693
Tumor Volume (cc)						
< 1.0	Referent	Referent	Referent	Referent	Referent	Referent
1.0 - 1.9	1.33	0.84 – 2.12	0.221	0.93	0.57 – 1.52	0.761
2.0 - 2.9	1.53	0.93 – 2.51	0.094	0.71	0.41 – 1.24	0.225
3.0 - 3.9	1.74	1.00 – 3.00	0.046	0.81	0.44 – 1.47	0.478
4.0	3.75	2.45 – 5.72	< 0.001	1.30	0.77 – 2.17	0.319
Adjuvant Radiotherapy						
No	Referent	Referent	Referent	Referent	Referent	Referent

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% Confidence Interval	P Value	Hazard Ratio	95% Confidence Interval	P Value
Yes	3.07	1.57 - 6.00	0.001	0.94	0.45 – 1.95	0.864

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