Outcomes

Tumor Grade at Margins of Resection in Radical Prostatectomy Specimens Is an Independent Predictor of Prognosis

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OBJECTIVES
To assess whether reporting the grade of cancer at the site of positive margins in a radical prostatectomy (RP) specimen was independently prognostic of the outcome.

METHODS
We restricted our study to 108 patients with Gleason score (GS) 7, nonfocal extraprostatic extension (EPE) (Stage pT3a), and positive surgical margins. Patients with a tertiary pattern 5, those who had received neoadjuvant therapy, and those with positive margins because of an intraprostatic incision were excluded.

RESULTS
The overall GS was 3 + 4 in 73 patients (67%) and 4 + 3 in 35 (33%). The median length of the positive margin was 3.0 mm (range 0.5-10). The GS at the margin was 3 + 3, 3 + 4, 4 + 3, and 4 + 4 in 40 (37%), 41 (38%), 16 (14.8%), and 11 (10.2%) cases, respectively. Of the 108 patients, 45 (42%) remained free of disease after RP (median follow-up 6 years, range 3-13). Univariate and multivariate analyses showed no correlation between biochemical recurrence and either the preoperative serum prostate-specific antigen level ($P = .7$) or overall GS ($P = .5$). A strong association was noted between biochemical recurrence and the GS at the positive surgical margin ($P = .007$), with length of cancer at the margin also predictive ($P = .015$) on multivariate analysis. Using the median length of the positive margin (3 mm) as the cutoff, the association with biochemical recurrence was significantly different between the 2 groups ($P = .004$) using Kaplan-Meier analysis.

CONCLUSIONS
This is the first study to show that the grade of cancer at the site of a positive margin influences the outcome. We were able to stratify the grade into 3 categories: 3 + 3, 3 + 4, and 4 + 3 or greater (4 + 3 and 4 + 4 at the positive margin provided equal prognostic information). UROLOGY 76: 1206-1211, 2010. © 2010 Elsevier Inc.

Positive surgical margins at radical prostatectomy (RP) can be associated with extraprostatic extension (EPE) of cancer or can result from areas of intraprostatic incision where the surgeon inadvertently cut into the prostatic parenchyma. Positive surgical margins can also be located at the apex of the prostate, where it is usually difficult to differentiate EPE from intraprostatic incision because of the ambiguity of the anatomic boundaries of the prostate in this region.1-6 Surgical margins status has long been associated with biochemical recurrence (BCR) and clinical recurrence after RP.4,7-11 It has also been shown that the extent of positive margins evaluated either as focal versus extensive involvement or as single versus multiple positive margins correlates with BCR.6,7,12,13 Very few studies to date have analyzed the value of recording the extent of positive margins in millimeters, and none has evaluated the influence of the grade of cancer present at the positive margins in relation to the clinical outcome.14-16

MATERIAL AND METHODS
To focus on whether the grade of tumor at the surgical margin affects the prognosis, we restricted inclusion to patients with a Gleason score (GS) of 7 with EPE (pT3a) and positive surgical margins. Patients with a tertiary pattern 5, those who had received neoadjuvant therapy, and those with positive margins because of an intraprostatic incision were excluded. Intraprostatic incision into tumor refers to the urologist transecting malignant prostatic tissue, such that the edge of the prostate in this region is left within the patient (Stage pT2+). This refers to when the surgeon inadvertently develops the resection plane within, rather than exterior to, the prostate.

From 1995 and 2008, 108 RP procedures performed at our institution met the inclusion criteria. It has typically been difficult to determine whether tumor at the apex is associated with EPE or intraprostatic incision owing to the ambiguities of the boundaries of the prostate in this region. In the present study, whether the positive margin was present at the apex or elsewhere was not associated with BCR ($P = .08$).
Thus, patients with positive margins at the apex were included within the 108 patients as long as evidence of EPE was found elsewhere in the specimen. Those with positive margins at the apex without evidence of EPE elsewhere were not included because those tumors were considered Stage pT2+, not Stage pT3a.

After fixation, the RP specimens were inked. The proximal (bladder neck) margin was removed as a 1-mm, thin-shave (en face) margin, and the presence of any tumor on the bladder neck margin slice was considered positive. The distal 5-8 mm of the prostate was amputated and then sectioned parallel to the urethra in 2-3-mm-thick slices; the presence of tumor at the inked perpendicular margins was considered positive. The remaining prostate was sectioned at 2-3-mm intervals and submitted in its entirety for histologic examination.

The following pathologic parameters were recorded: overall GS of the dominant nodule (3 + 4 vs 4 + 3), total millimeters of tumor at the margin, and GS of cancer at the margin (3 + 3, 3 + 4, 4 + 3, or 4 + 4). The rationale for considering the GS at the margin instead of only the Gleason pattern (ie, 3 vs 4) was that analyzing only the Gleason pattern would allow assessment of only GS 6 versus GS 8 at the margin, instead of the more comprehensive potential differences of 3 + 3 versus 3 + 4 versus 4 + 3 versus 4 + 4 at the margin. When >1 section showed a positive margin, the overall length of the positive margin was obtained by adding the lengths of all areas of cancer in contact with ink. When 2 consecutive slides going from the apex to the base showed positive margins, the length of the positive margin on these 2 slides was calculated as 3 mm (because 1.5 mm was one half the thickness of each tissue section on a slide), provided that none of these slides showed a positive margin >3 mm. The largest diameter of cancer in the bladder neck slide (if present) was considered the length of the positive margin on that slide, regardless of its proximity to the ink because this margin was taken en face. Histologic features were assessed in a fashion blinded to the outcome. Because conflicting data have been published regarding the prognostic importance of the positive margin location in RP specimens, with recent data, including our own (submitted for publication) showing no independent prognostic significance, we did not record the positive margin location in the present study.

Cancer present at a margin was assigned a GS independent of the GS for the entire case (Fig. 1A,B). In slides in which cancer at the margin showed obscuring cautery artifact, the GS at the margin was assigned according to the grade of uncauterized cancer in direct continuity with the cauterized cancer (Fig. 1C).

BCR was defined as a postoperative serum prostate-specific antigen (PSA) level of $\geq0.2$ ng/mL. The preoperative serum PSA level, overall GS, GS at the surgical margin, and total length of margin positivity were correlated with each other using the Pearson correlation coefficient and with progression using the Cox multivariate analysis (StataCorp, College Station, TX). The Johns Hopkins Medical Institution institutional review board approved the present study.

RESULTS

All patients had nonfocal EPE (as defined in previous studies). The overall GS was 3 + 4 in 73 patients (67%) and 4 + 3 in 35 (33%). The positive margin location was apical in 26 (24%), with the remaining having a peripheral and/or bladder neck location. The mean length of the positive margin was 3.4 mm (median 3, range 0.5-10).

In 46 patients, the length of the positive margin was <3 mm. The GS at the margin was 3 + 3, 3 + 4, 4 + 3, and 4 + 4 in 40 (37%), 41 (38%), 16 (14.8%), and 11 (10.2%) cases, respectively. Of the 40 patients with a GS of 3 + 3 at the margins, the overall GS was 3 + 4 = 7 in 34 and 4 +
3 = 7 in 6. Although no correlation was found between the overall GS and the length of the positive margin (P = .95), a weak association was seen between the GS at the margin and the length of the positive margin (Pearson correlation coefficient = 0.1). However, this association was only significant between GS 3 + 3 and GS 3 + 4 at the margin with a mean positive margin length of 2.6 and 4.2 mm, respectively (P = .009). Although the overall GS correlated with the GS at the margin, this correlation was not strong (P = .02); for example, some patients with an overall GS of 3 + 4 or 4 + 3 had cancer with GS 3 + 3 at the positive margin.

Of the 108 patients, 63 (58%) developed BCR at a mean follow-up of 3.0 years (median 2.1-10), and 45 (42%) were free of disease at a mean follow-up period of 6 years after RP (median 6, range 3-13). The mean preoperative PSA level was 18.7 ng/mL (median 7.1, range 0.8-41.1). Univariate and multivariate analyses showed no correlation between BCR and either the preoperative PSA level (P = .5; Table 1) or overall GS (P = .5).

In contrast, a strong association was noted between BCR and both the GS at the margin (P = .007) and the length of cancer at the margin (P = .015). This association remained significant on multivariate analysis, with the overall model predictive of BCR (P = .005). Using 3 mm as the cutoff, the association with BCR was different (P = .004; Fig. 2). Similarly, dividing the grade of cancer at the margin into 3 + 3, 3 + 4, and 4 + 3 or greater correlated with BCR (P = .006; Fig. 3).

**COMMENT**

BCR after RP has been associated with multiple factors, including the pre-treatment serum PSA level, pathologic stage, final GS, and margin status.6,18-21 The rate of positive surgical margins is reported to be between 5%-46%, and, in general, this rate has been decreasing in the past decade in large academic centers.4,5,22 Positive margin status is an independent predictor of progression even in the presence of EPE or high-grade (GS $\geq$7) cancer.7,11,23

To date, only 3 studies have investigated the relationship between the length (in millimeters) of a positive surgical margin and outcome. Shikanov et al15 studied 161 RP specimens with positive margins and reported an independent association between the length of the positive margin and BCR (<1 mm positive margins had a similar recurrence rate as negative margins compared with 1-3 mm and $>3$ mm). The follow-up period in that study was short (median 12 months). In a study of 117 RP specimens with positive margins (median follow-up 43 months), Ochiai et al14 reported that both GS of $\geq$8 and a margin of $\geq$3 mm were independent predictors of BCR. However, in these 2 studies,14,15 patients with a positive margin in areas of intraprostatic incision were included. In a study from our institution of 135 RP specimens with positive margins due to intraprostatic incision, the 5-year risk of BCR was 20.0% and 55% for $<3$ mm and $\geq3$ mm of tumor at the margin, respectively.24 Similarly, in the present study, the total length of the positive margins was a significant predictor of clinical behavior after RP, with patients with positive surgical margins $>3$ mm having a significantly worse prognosis than those with positive surgical margins of $\leq3$ mm in terms of BCR. It is important to note that a continuum was present in terms of the extent of the positive margins and outcome and the 3-mm cutoff was chosen for illustrative purposes, not as an exact determinant of the prognosis.

The patient cohort in the present study was unique in that it was a homogenous group with a similar pathologic stage and GSs and a long follow-up period. Our results support that the total length of the positive margin in millimeters is a significant independent prognostic factor after RP. The present study is also the first to show that the grade of cancer at the site of a positive margin influences the outcome. We were able to stratify the length into 3 categories: 3 + 3, 3 + 4, and 4 + 3 or greater (4 + 3 and 4 + 4 at the positive margin provided equal prognostic information). In patients with a GS of 7, some
areas of the tumor might be composed of a pure pattern 3 (ie, 3 + 3), which, if present, at the margin was associated with a lower risk of postoperative BCR. This previously unreported, but intuitive, finding can be explained by the biologic aggressive nature of high-grade cancer, which, in the event of incomplete removal by RP, will be able to survive and grow more than would lower grade cancers, leading to greater BCR rates. In the vast majority of cases in the present study, we were able to directly assign a grade to the cancer present at the positive margin without difficulty, even in the presence of limited cautery artifact at the margin. Rarely, when extensive cautery artifact prevents proper grading, using the grade of the contiguous uncauterized cancer seemed to be an acceptable alternative. We were able to stratify the cases in terms of prognosis using this method when blinded to the outcome, indicating that it is feasible in daily practice.

CONCLUSIONS

Our data support including the GS at the positive margin and the total length of the positive margin in millimeters in the reporting of RP specimens. These 2 parameters independently predicted the likelihood of BCR after RP. The most common scenario in which this would be applicable is for tumors with an overall GS of 7 and positive margins, with a GS of 3 + 3, 3 + 4, or 4 + 3 or more at the margin. Using these grades at the margin and the cutoff of ≥3 mm for the positive margin length can help stratify men who are more likely to have progression after RP and identify those patients more likely to benefit from adjuvant radiotherapy.

References


EDITORIAL COMMENT

Positive surgical margins and their relevance in predicting biochemical recurrence (BCR) is currently a "hot" topic in urology studies. Recent publications have suggested that more detailed annotation of the pathologic parameters related to a positive margin might provide additional prognostic information. Brimo et al\(^1\) are the first to highlight an association between the Gleason score at a positive surgical margin and BCR in 108 patients with an overall Gleason score of 7, extraprostatic extension (EPE), and margin positivity. Given the strong predictive value of the Gleason score, independent of stage,\(^2\) it is, as the authors suggest, rather intuitive that a more biologically aggressive tumor component present at a surgical margin would lead to greater BCR rates than a lower grade component. These investigators argue that, from their results, the Gleason score of the tumor at a positive surgical margin should be routinely incorporated into the pathology reports.