Importance of Reporting the Gleason Score at the Positive Surgical Margin Site: Analysis of 4,082 Consecutive Radical Prostatectomy Cases

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Purpose: Since 2010 pathologists at our institution have routinely been documenting the Gleason score at the margin and length of the positive surgical margin after prostatectomy. In this study we evaluate how the Gleason score and positive surgical margin length correlate with the grade and adverse pathological characteristics of the final specimen, and whether the positive surgical margin Gleason score affects the risk of early biochemical recurrence.

Materials and Methods: A total of 4,082 consecutive patients undergoing radical prostatectomy and pelvic lymph node dissection between 2010 and 2014 for localized prostate cancer were included in the study, of whom 405 had a Gleason score of 7 or greater of the primary nodule and a positive surgical margin with the length and Gleason score recorded at the margin. Concordance rates between the Gleason score at the margin and the final pathological specimen were compared. Logistic regression models were used to predict the risk of unfavorable pathology. Cox proportional hazards models controlling for Gleason score, preoperative prostate specific antigen, pathological stage and adjuvant radiation were used to predict biochemical recurrence, and Kaplan-Meier estimates of recurrence-free survival were calculated by Gleason score.

Results: Among patients with positive margins biochemical recurrence was identified in 22% (vs 5.6% without positive margins), metastases in 3% (vs 0.5%) and adjuvant radiation in 30% (vs 4.1%). Mean followup was 22 months (range 12 to 48). The Gleason score at the positive surgical margin was the same as the final pathology specimen in 44% of patients, and a lower Gleason score in 56% of patients. A shorter positive surgical margin was independently associated with a lower Gleason score at the margin (p=0.02). Kaplan-Meier estimates demonstrated improved freedom from biochemical recurrence among patients with a lower Gleason score at the margin. In multivariate Cox models having a lower grade margin was associated with a decreased risk of biochemical recurrence (HR 0.50, OR 0.25–0.97).

Conclusions: A lower Gleason score at the positive surgical margin is independently associated with a shorter margin length and a decreased risk of early biochemical recurrence. Thus, the Gleason score at the margin should be documented.

Key Words: prostatic neoplasms, prostatectomy, neoplasm grading

Abbreviations and Acronyms

BCR = biochemical recurrence
F-EPE = focal extraprostatic extension
GS = Gleason score
LN = lymph node
NF-EPE = nonfocal extraprostatic extension
OC = organ confined
PM = positive surgical margin
PSA = prostate specific antigen
RP = radical prostatectomy
RT = radiation therapy
SVI = seminal vesicle invasion

Accepted for publication August 6, 2015.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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Editor's Note: This article is the fourth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 530 and 531.

THE significance of positive margins after radical prostatectomy remains controversial. In the modern era of PSA screening, the incidence of PMs has decreased yet it remains an adverse pathological feature.[1] Clear

0022-5347/16/1952-0337/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.08.002
Vol. 195, 337-342, February 2016
Printed in U.S.A.

differences in prostate cancer progression exist between patients who have PMs and those who do not, with 10-year progression-free survival rates of 58% to 74% among patients with PMs vs 81% to 95% among those with negative margins.[2–5] Margin data have been incorporated into nomograms, several of which have high levels of accuracy in predicting postoperative recurrence.[6–9]

Many attempts have been made to understand which features of PMs drive cancer progression. Margin location, extent and associated histopathological characteristics have all been studied as potential prognostic markers that can be used to counsel patients on the risk of progression.[10–12] Prostate cancer is multifocal and can demonstrate grade heterogeneity in the dominant nodule (ie Gleason 7 with a mix of grade 3 and 4) as well as between tumor nodules. A dominant tumor nodule could be 4+4=8 with negative margins but could also have a separate tumor with grade 3+3=6 with a positive margin. Reporting the specific GS at the margin as well as in the dominant nodule potentially gives more specific information compared to merely reporting the dominant nodule with a positive margin without reference to the margin GS. Although tumor grade at the margin has been shown to predict not only biochemical recurrence but also to predict prostate cancer metastases and death, it is still not generally accepted as a routine parameter to report in RP specimens.[13,14]

Since 2010 pathologists at our institution have routinely documented the margin GS and length after a preliminary study demonstrated a high correlation between the margin GS and clinical outcome.[15] The present analysis is a larger followup study with 5 years of comprehensive pathological margin data. Our objective was to evaluate how the GS and length of the positive surgical margin correlate with the GS and adverse pathological characteristics of the final specimen, and whether the PM GS affects the risk of early biochemical recurrence.

METHODS

Patient Cohort

We retrospectively identified 4,082 consecutive patients undergoing radical prostatectomy and pelvic lymph node dissection between 2010 and 2014 for localized prostate cancer. In this cohort 588 patients were identified as having PMs (14.4%), of whom 510 (12.5%) had complete pathological documentation of GS recorded at the margin. From that cohort 405 patients had a GS 7 or greater of the primary nodule and were included in the final analysis.

Pathological Classification

Since 2010 our institution has routinely been recording the length and GS at PMs after prostatectomy. The pathological protocols for this documentation have been previously described in a pilot study at our institution, which confirmed its utility and led to its widespread use.[15] Specimens are serially sectioned and submitted in entirety in routine sections. After fixation RP specimens are inked. To assess for PMs the proximal (bladder neck) margin is removed as 1 mm, thin-shave (en face) margin and the presence of any tumor is considered a positive margin. The distal 5 to 8 mm of the prostate is then sectioned parallel to the urethra and the remaining prostate is sectioned in 2 to 3 mm intervals with tumor at ink a positive margin.

The overall GS at the PM was used instead of merely the Gleason pattern (ie 3 vs 4) to assess differences among Gleason 3+4 and 4+3 tumors, and not merely Gleason 6 and Gleason 8 pattern at the margin. The GS at the PM was assigned independently from the GS for the entire case. In slides with cautery artifact the GS at the PM was assigned based on the noncauterized tissue in continuity with the cauterized PM. A lower grade margin was defined as a GS at the margin that was less than the GS of the dominant nodule (ie GS assigned to the overall case). The largest length of tumor at a margin on a given cross-section of the prostate as well as the largest length of the margin from apex to base were calculated, with the longest distance between these 2 measurements selected for the maximal margin length per case.

Outcomes

Biochemical recurrence was defined as a postoperative serum PSA of 0.2 ng/ml or greater. Secondary variables of interest were other adverse pathological features, including OC disease, F-EPE and NF-EPE, SVI and positive LNs. Receipt of adjuvant RT was determined by the initiation of RT after the date of surgery but before signs of BCR or clinical progression.

Statistical Analysis

Concordance rates between the GS at the margin and the final pathological specimen were documented. Baseline pathological differences between patients with and without downgraded margins were assessed. A linear regression model compared the length at the margin and the GS at the margin. A multivariate logistic regression model controlling for the GS of the dominant nodule as well as preoperative PSA were used to predict the risk of unfavorable pathology. Cox proportional hazards models controlling for tumor stage and adjuvant radiation (immediate RT after surgery and before progression) were used to predict BCR, and Kaplan-Meier estimates of recurrence-free survival were calculated by GS. All statistical analysis was performed using SAS® version 9.1 with $p < 0.05$ considered statistically significant.

RESULTS

Among those patients with PMs, BCR was identified in 22% (vs 5.6% without positive margins) and clinical signs of metastases in 3% (vs 0.5%). In this cohort 30% went on to receive adjuvant radiation