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European Association of Urology

Prostate Cancer

Primary Gleason Grade 4 at the Positive Margin Is Associated with Metastasis and Death Among Patients with Gleason 7 Prostate Cancer Undergoing Radical Prostatectomy

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Article info

Article history:
Accepted July 3, 2014

Keywords:
Positive surgical margin
Gleason score 7
Prostate cancer
Radical prostatectomy
Systemic progression
Cancer mortality

Abstract

Background: The presence of a positive surgical margin (PSM) at radical prostatectomy (RP) has been linked to an increased risk of biochemical recurrence and receipt of secondary therapy; however, its association with other oncologic end points remains controversial.
Objective: To evaluate the association of primary Gleason grade (GG) at the site of PSM with subsequent clinical progression and mortality among patients with Gleason score (GS) 7 prostate cancer (PCa).
Design, setting, and participants: We identified 1036 patients who underwent RP between 1996 and 2002. A single uropathologist re-reviewed all specimens noted to have a PSM to record GG at the margin.
Outcome measurements and statistical analysis: Survival was estimated using the Kaplan-Meier method. Cox models were used to analyze the association of margin primary GG with outcome.
Results and limitations: Overall, 338 men (33%) had a PSM; of those, 242 had PSM GG3 and 96 had PSM GG4. Median postoperative follow-up was 13 yr. Compared with men with PSM GG3 or a negative SM, we noted that men with PSM GG4 had significantly worse 15-yr systemic progression-free survival (74% vs 90% vs 93%, respectively; $p < 0.001$) and cancer-specific survival (86% vs 96% vs 97%, respectively; $p = 0.002$). On multivariable analysis, the presence of PSM GG4 was associated with increased risks of systemic progression (hazard ratio [HR]: 2.77; $p = 0.003$) and death from PCa (HR: 3.93; $p = 0.02$) among men with a PSM. Limitations include the relatively small rate of disease recurrence.
Conclusions: PSM primary GG4 was independently associated with adverse oncologic outcomes among men with GS7 PCa. Pending external validation, GG at the PSM may be considered for inclusion in pathologic reports and risk stratification following RP.
Patient summary: Among patients with Gleason grade 7 prostate cancer and a positive surgical margin at the time of prostatectomy, we found that higher Gleason grade at the margin was associated with worse oncologic outcomes.

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http://dx.doi.org/10.1016/j.eururo.2014.07.004
0302-2838/

1. Introduction

While radical prostatectomy (RP) remains a standard of care for clinically localized prostate cancer (PCa), positive surgical margins (PSMs) have been identified as an adverse prognostic feature [1] and, therefore, have been incorporated into multiple predictive models of disease recurrence [2,3]. Nevertheless, although PSMs have been reported in 11–40% of patients undergoing RP [1,4,5], disease recurrence has been noted in only 19–48% of men with margin positivity [1,4,6,7], reflecting a lack of consistency in association of margin status with cancer-related outcomes.

Moreover, biochemical recurrence (BCR) has been used as the clinical end point in multiple studies [1,6,8,9]; however, this measure may not accurately predict systemic progression (SP) or PCa-specific death [7,10,11]. Indeed, few studies have evaluated the association of PSMs with clinical end points, and these have met with conflicting findings. That is, PSMs have been associated with local progression [5], metastasis [12], and cancer-specific mortality [7,13] in several series, while other reports have found no independent association with subsequent disease progression [5,14].

Due to ongoing controversy surrounding the significance of PSMs following RP, there has been a call for further subclassification [15]. Prior studies have evaluated the role of PSM location, linear extent, focality, and uniformity, with variable results [15]. Moreover, to date, conflicting data exist regarding the significance of Gleason grade (GG) at the site of the PSMs [9,16–19]. As such, reporting of GG at the PSM remains at the individual pathologist's discretion, due to insufficient evidence for its utility in predicting cancer progression [15]. Therefore, we sought to evaluate the association between GG at the PSM in patients with pathologic Gleason score (GS) 7 PCa and oncologic outcomes following RP.

2. Patients and methods

Following institutional review board approval, we reviewed our prostatectomy registry of 6222 consecutive patients who underwent RP between 1996 and 2002 and identified 1036 patients with pT2–3a GS7 PCa who did not receive neoadjuvant therapy. This time frame was chosen to capture patients in the prostate-specific antigen (PSA) era with an extended duration of follow-up. Of these men, 338 had a PSM and 698 a negative surgical margin (NSM). Patients with positive lymph nodes at surgery ($n = 39$), seminal vesicle invasion ($n = 170$), or tertiary pattern GG5 at the PSM ($n = 2$) were excluded from analysis.

Surgical procedures were performed by different surgeons using standardized techniques. The Mayo Clinic routine sampling protocol for preparing and reporting serially sectioned prostates has been previously reported [20]. Specifically, the RP specimen tissue was microscopically examined and inked by the pathologist after resection and multiple frozen sections were examined. The presence of Gleason pattern 5 within the specimen was reported per protocol as a primary or secondary component of the GS and, therefore, excluded from analysis. Margins included prostate apex/urethra, base, bladder neck, left and right anterior, left and right posterior, and seminal vesicles. All sections were separately examined with routine grading and staging parameters by formalin-fixed, paraffin-embedded sections the following day. A PSM was defined as tumor extension to the inked surface of the resected specimen [21].

PSM cases were re-reviewed by a single urologic pathologist (WRS), and tumor characteristics were classified based on the 2010 American Joint Committee on Cancer staging system [22]. Histopathologic review included PSM focality (multiple vs single), location (bladder neck vs other location), and GG at the margin. When there was a PSM with more than one GG, the highest GG was used for analysis and identified as PSM primary GG3 or PSM primary GG4. In cases with more than one PSM, the primary GG at each margin was recorded, with the highest GG assigned to that specimen.

To capture treatment intent, adjuvant therapy was defined as treatment planned, or received, within 90 d of RP without evidence of disease. Salvage therapy was defined as treatment received for disease progression. Secondary therapies were administered at the discretion of the treating physician. BCR was defined as a post-treatment PSA level $\geq$0.4 ng/ml, which has been associated with a greater likelihood of metastatic progression [23]. SP involved demonstrable metastatic disease on radionuclide bone scan or biopsies outside of the prostatic bed. Postoperative assessments, including physical examinations and serum PSA measurement, were done quarterly for 2 yr, semiannually for an additional 2 yr, and annually thereafter. For patients followed elsewhere, the prostatectomy registry monitors outcomes annually by correspondence. Vital status was identified by death certificate or physician correspondence.

Clinicopathologic features of patients with a NSM were compared to margin-positive men and stratified by the primary GG at the PSM. Differences between groups were analyzed using the chi-square and Kruskal-Wallis tests. Postoperative survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Patients were censored at last follow-up or death if the clinical end point was not obtained. Among men with a PSM, Cox proportional hazard regression models were used to analyze the impact of clinicopathologic variables including PSM primary GG, primary specimen GG, pathologic stage, $\log_2$ preoperative PSA level, and receipt of adjuvant radiation therapy (RT) and/or androgen deprivation therapy (ADT) on BCR and SP. Patients with an event $\leq$90 d (six BCRs, no SPs, one death) and subjects with $<$90 d follow-up were excluded from the Cox models. To account for its skewed distribution, preoperative serum PSA level was transformed using the base-2 logarithm, such that the hazard ratio (HR) represents the increased risk of cancer progression for a doubling of PSA level. To avoid overfitting in the setting of a limited number of events, we restricted our multivariable analysis for cancer-specific survival (CSS) to significant covariates including PSM primary GG, pathologic stage, and primary specimen GG. Similar models were fit adjusting for the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score, a validated, postoperative, predictive model of cancer progression [24,25]. Finally, the prognostic ability of features included in the Cox models were evaluated using the concordance (C) index adjusted for optimism [26]. The net reclassification index was used to assess the impact of PSM primary GG on SP risk classification [27]. All tests were two-sided, with $p \leq 0.05$ considered significant. Statistical analysis was performed with the SAS v.9.1.3 software package (SAS Institute, Cary, NC, USA).

3. Results

We identified PSMs in 338 of 1036 men (33%) undergoing RP with pT2–3a GS7 PCa, of whom 249 (74%) had GS 3 + 4 and 89 (26%) had GS 4 + 3. Of these men, 242 (72%) had GG3 at the PSM and 96 (28%) had GG4 at the PSM. Relative to patients with a NSM and those with PSM GG3, men with PSM GG4 had a higher preoperative PSA level, advanced pathologic tumor stage, and greater estimated tumor