Understanding the Relationship Between Tumor Size, Gland Size, and Disease Aggressiveness in Men With Prostate Cancer

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OBJECTIVE To determine the relationship between prostate gland and tumor volume in men undergoing radical prostatectomy (RP) for prostate cancer. We hypothesized that larger tumors within smaller prostate glands are associated with more aggressive disease characteristics.

METHODS Records of patients undergoing RP from 2000-2008 at a single institution were reviewed retrospectively. The dominant nodule was considered to be the largest focus of cancer within the prostate, and the dominant nodule-to-prostate volume ratio (DNVR) was calculated according to the ratio of the dominant nodule volume to the gland weight. Cox regression was performed to assess the relationship between DNVR and both pathologic outcomes (Cancer of the Prostate Risk Assessment post-Surgical score) and biochemical recurrence (BCR).

RESULTS At a median follow-up of 3.7 years, 174 patients (7.2%) suffered BCR. There was no linear correlation between tumor volume and gland size ($R = -0.09$). DNVR above the median ($\geq$0.033 cc/gm) was closely associated with high clinicopathologic risk as measured by Cancer of the Prostate Risk Assessment post-Surgical score (hazard ratio, 35.53; 95% confidence interval, 14.42-87.55 for high- vs low-risk groups). In the univariable analysis, both tumor diameter and DNVR were associated with increased risk of BCR. However, in the multivariable model, only tumor diameter remained a significant predictor of BCR (hazard ratio, 2.02; 95% confidence interval, 1.04-3.91).

CONCLUSION Increased DNVR appears to be a characteristic of aggressive prostate tumors, although it did not predict BCR in the present study. However, these data support the association between tumor diameter and BCR after RP for prostate cancer independent of other key clinicopathologic features. UROLOGY 84: 373–379, 2014. © 2014 Elsevier Inc.

In the prostate-specific antigen (PSA) era, at least 15% of men will experience biochemical recurrence (BCR) in the first 15 years after radical prostatectomy (RP) for prostate cancer (PCa).[1-5] Predicting which patients will have a recurrence of PCa after RP is critical for patient counseling and postoperative management; however, the natural history of PCa after RP is extremely variable and challenging to predict.[1] As a result, a number of prognostic tools have been developed that rely on clinical and pathologic features to estimate an individual's risk of BCR or PCa-specific mortality.[3,6] Interestingly, none of these nomograms account for tumor or gland size, characteristics that may become more easily assessable for preoperative prognostication with the increasing utilization of multiparametric magnetic resonance imaging.[7]

A number of groups have examined morphometric features in an effort to provide additional predictive power to current postoperative nomograms. Although some reports have demonstrated prognostic importance for tumor volume,[8-10] a number of groups have found that this measure either has no predictive value beyond other known clinicopathologic variables[4,11-13] or has only limited applicability in patients with higher risk

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disease.[14-18] This is in stark contrast to a number of other malignancies, such as breast cancer, where tumor volume is a key variable in commonly used predictive nomograms.[19,20] Although prostate volume has not been found to correlate with post-RP BCR in some reports,[14,21] lower prostate volumes have been associated with increased risk of pathologic upgrading after RP, which itself is linked to faster time to BCR.[22,23] Additionally, there appears to be an independent association between small prostate size and high-grade cancers, suggesting that underlying biological mechanisms impacting gland size may also influence cancer risk.[24]

We evaluated whether larger tumors within smaller prostate glands were associated with BCR in a single institutional cohort of men undergoing RP. We hypothesized that the ratio of tumor size to gland size would be associated with more aggressive disease and predict BCR in an institutional cohort of men after RP.

MATERIALS AND METHODS

With approval from our institutional review board, we performed a retrospective review of the medical records of 2406 consecutive patients who underwent RP as the primary treatment for clinically localized PCa (N0M0) between 2000 and 2008 at a single institution. None of the patients received neoadjuvant or adjuvant hormonal therapy. Preoperative PSA levels were obtained for all patients, and postoperative follow-up included routine PSA monitoring approximately every 3-6 months. Patients whose PSA did not nadir to <0.1 ng/mL were excluded from our analysis. Clinical, pathologic, and outcome data were collected prospectively and were supplemented by medical record review.

Prostate specimens were submitted in their entirety for fixation and evaluation by our institutional genitourinary pathologists. Fresh prostates removed after surgery were weighed, measured, inked, and fixed in 10% neutral formalin. Seminal vesicles, apex, and base were amputated, and the remaining prostate was serially sectioned at 4- to 5-mm intervals perpendicular to the long axis of the gland from the base to apex and quartered. Tumor maps were generated by tracking each section and reconstructing them as a whole-mount section. A cancer focus was considered spatially separate or multifocal if it was ≥3 mm from the closest cancer in any single section or ≥4 mm from the closest cancer on the adjacent section above or below, as described previously.[25] The largest tumor focus was designated as the index tumor, and additional smaller tumors were labeled as multifocal tumors. Primary and secondary Gleason grades were documented for each specimen, and the presence of extracapsular extension (ECE), seminal vesicle invasion, lymph node involvement, and surgical margin status (SMS) were noted. Stage was reported according to the 2010 American Joint Committee on Cancer guidelines.

The dominant nodule was considered to be the largest focus of cancer within the prostate, based on pathologic evaluation of the RP specimen. The diameter of this nodule was noted and further categorized as ≥1 cm vs <1 cm, a commonly used threshold in specimen evaluation.[26] The volume of the dominant nodule was calculated by assuming a spherical shape of the nodule (computed using the measured dominant nodule diameter within the spherical volume formula), and the dominant nodule-to-prostate volume ratio (DNVR) was calculated according to the ratio of the dominant nodule volume to the measured gland weight in grams. We tested for a relationship between tumor diameter and gland size by Pearson correlation to assess whether these 2 features were interrelated. Clinical and pathologic variables were compared using chi-square tests.

To assess the relevance of DNVR, we first sought to determine if DNVR was significantly correlated with key clinicopathologic outcomes. We used the Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score for this purpose, as it is a validated summary measure of disease aggressiveness and clinicopathologic risk.[3] CAPRA-S score was calculated for all subjects and categorized according to the previously defined risk strata as low (score of 0-2), intermediate (3-5), or high (≥6) risk. The correlation between DNVR and CAPRA-S score was then assessed with generalized logits modeling, with age and race as covariates. Because PSA, grade, stage, and margin status are included in the CAPRA-S score, they cannot be included as covariates in the multivariable model.

The primary outcome measure was BCR, defined as 2 consecutive serum PSA levels >0.2 ng/mL. Cox univariable and multivariable analyses were performed to determine the association between DNVR and BCR. Variables assessed in the univariable Cox model were age, race (white vs nonwhite), PSA before surgery, pathologic Gleason grade, pathologic T stage, SMS, tumor diameter, and DNVR. All of these except race (nonsignificant in univariable analysis) were carried forward to the multivariable models, and separate models were created to evaluate whether tumor diameter or DNVR was more closely associated with BCR. Tumor diameter and DNVR were not included in the same model because of colinearity. Hazard ratios (HRs) are presented along with their 95% confidence intervals (CIs). For the primary analyses, tumor diameter (≥1 vs <1 cm) and DNVR (above/below the median) were assessed as categorical variables; however, secondary analyses were performed with each evaluated as continuous variables. Data analysis was performed with SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

There were 2406 subjects with a median age of 60 years (interquartile range [IQR], 55-65 years) and a median follow-up of 3.7 years (IQR, 2.1-6.2 years). The majority of patients had low-risk features, and high DNVR was associated with worse clinical and pathologic disease features (Table 1).

The median tumor diameter was 1.40 cm (IQR, 0.9-1.9 cm) and median gland size 44.4 gm (IQR, 36.4-55.0 gm). There was no correlation between tumor diameter and gland size ($R = -0.09$). The median DNVR was 0.033 cc/gm (IQR, 0.008-0.083 cc/gm), and tumor diameter was correlated with DNVR, as given in Table 2 ($R = 0.75$). DNVR was also inversely associated with gland size ($R = -0.15$).

To assess the association between DNVR and clinicopathologic risk, patients were categorized according to CAPRA-S risk groups. Within the study cohort, 68% were considered low risk, 27% intermediate risk, and 5% high risk. With age and race as covariates, we assessed the correlation between DNVR and CAPRA-S, with CAPRA-S score categorized as a binary outcome