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Anterior or Posterior Prostate Cancer Tumor Nodule Location Predicts Likelihood of Certain Adverse Outcomes at Radical Prostatectomy

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Prostate cancer is a major cause of morbidity and mortality in men around the world. According to The American Cancer Society, there were approximately 191,930 new cases of prostate cancer and 33,330 prostate-cancer-related deaths reported in the United States in the year 2020. Current management options for localized prostate cancer include active surveillance, radical prostatectomy, radiotherapy, hormonal therapy, cryotherapy, and high-intensity focused ultrasound (HIFU) therapy.1,2 Management plans and the treatment strategies are guided by several clinicopathologic features that include patient age, clinical and pathologic tumor stage, histologic grade (ie, Grade Group and Gleason score), and serum prostate-specific antigen levels.3 Biochemical recurrence (BCR) and prostate cancer-specific mortality are influenced by clinical stage, histologic grade, pathologic stage including extraprostatic extension (EPE) and seminal vesicle invasion (SV+), positive surgical margin status (SM+), and lymph node status.3–10

In cases where cancer does not globally involve the prostate, tumor nodule (TN) location can be categorized as anterior or posterior in relation to the prostatic urethra. To date, relatively few studies have examined the significance of TN location with respect to predicting adverse radical prostatectomy (RP) outcomes, such as EPE, SV+, and SM+.11–14 While there are a few noteworthy publications that have previously compared anterior and posterior TNs in terms of BCR, SV+, and magnetic resonance imaging—detection rate,11,12,15,16 a comprehensive contemporary analysis of the relationship between TN location and certain adverse RP outcomes (controlling for histologic grade and tumor volume [TV]) has heretofore not been performed. The impact of TN location within the prostate on the likelihood...
of certain adverse outcomes at RP may be useful in treatment planning with improving radiographic prostate cancer detection and targeted biopsy procedures, allowing better preoperative assessment of cancer grade, extent, and volume. Herein, we report our findings in such an analysis with a contemporary review of radical prostatectomy specimens.17–20

MATERIALS AND METHODS

We reviewed 1629 consecutive robotic-assisted RPs performed at the University of Miami, Miami, FL over a period of 6 years (2014–2020). In each case, a dissection of bilateral pelvic lymph nodes was performed. Each RP was oriented, inked in 2 colors corresponding to left and right and weighed without seminal vesicles.21–23 All prostates were serially sectioned from apex to base at 0.3-cm intervals and entirely submitted for histologic examination as quadrants in regular size cassettes. The bladder neck and apex margins were submitted as perpendicular sections. The entire SV (or its proximal portion if larger than cassette size) was submitted for histologic analysis. After manual dissection for lymph nodes, all adipose tissue was submitted for histologic analysis.24 Every RP was reviewed by a single urologic pathologist (senior author).

We defined separate TNs as those which were at least 0.3 cm apart from each other in a single plane of section, or at least 0.4 cm apart from each other on consecutive adjacent sections.21,22 Each TN was mapped (Figure 1), staged, and graded according to the latest grading recommendations by the Genitourinary Pathology Society.21,22,23 TV was calculated using the following formula: TV = mm² × 3 (tissue thickness) × 1.12 (shrinkage coefficient). In accordance with Genitourinary Pathology Society recommendations, intraductal carcinoma of the prostate was not incorporated into the overall histologic grade.20,26,27 Tertiary patterns were only reported for Grade Group 2 (3 + 4 = 7) and Grade Group 3 (4 + 3 = 7) tumors in which there was a minor component of pattern 5 representing less than 5% of a given TN.20,26,28 For all other TNs with 2 patterns, the higher grade component was always included in the overall composite grade (even if <5% of the TN). For those TNs in which the highest grade component accounted for greater than 95% of the TN, the lower grade component was not included in the overall composite grade. The prostatic urethra was used as an anatomic reference to characterize TN location.11,13,14,21,23,25 TNs with at least 80% of TV confined to either the anterior or posterior portion of the prostate were categorized accordingly and included in our study (Figure 2, A through D). All other TNs that did not meet these parameters were excluded from our statistical analysis. Furthermore, only treatment naïve patients were included in our study. Patients who received hormonal and/or radiotherapy before RP were excluded.

Bladder neck invasion was defined as the presence of carcinoma involving thick muscle bundles in the perpendicularly submitted sections of the prostate base. A positive margin in this location (ie, tumor present at the inked cauterized surgical margin) was also considered to represent nonfocal EPE.4,17 TNs with SM+ at the apex without evidence of adipose tissue invasion, as well as tumors with SM+ in areas of intraprostatic surgical incision (in which case the presence of EPE could not be assessed) were staged as pT2+. SV+ was defined as the presence of carcinoma within the muscular wall of the SV in the portion of the SV outside the prostate gland (ie, carcinoma involving the muscular wall of the SV only in the portion of the SV within the prostate was not considered SV+).

After characterizing and grading each TN, we performed a univariable analysis (UVA) to assess the association of tumor location, grade, and TV with EPE, SV+, and SM+ using a generalized linear mixed model to adjust for the confounding effects of those cases in which there were multiple TNs in the same patient. For each significant association identified in our UVA, we subsequently performed multivariable analysis (MVA) to control for all other potential confounding factors. P values were calculated using standard statistical methods, including the χ² test, Student’s t-test, and analysis of variance with Tukey post hoc test. The normality of distribution was assessed using the Shapiro-Wilk test. Statistical analyses were conducted using SAS version 9.4. All tests were 2-sided. Statistical significance was defined as having a P value ≤ .05. This study was approved by the University of Miami institutional review board.
RESULTS

We reviewed a total of 1629 consecutive robotic-assisted RPs over a 6-year period. Of these, 241 RPs were excluded because they did not meet the criteria we established for our study. These included 107 RPs with extensive bilateral disease, 87 RPs with TNs that contained less than 80% of TV in either the anterior or posterior compartment, 31 RPs status post neoadjuvant hormonal therapy, 8 RPs status after neoadjuvant radiotherapy, 5 RPs with vanishing cancers, 30 1 RP with low-grade neuroendocrine tumor/carcinoid tumor, 1 RP with small cell carcinoma, and 1 RP

Figure 2. A, Posterior-dominant tumor nodule. B, Anterior-dominant tumor nodule. The prostatic urethra (arrow) is the anatomic landmark by which tumors were categorized as anterior or posterior. Although both tumor nodules depicted in (A and B) each demonstrate minor extension into another location compartment, >80% of each tumor was confined to the respective compartment from which its classification was derived. The images below show early enhancing images from dynamic contrast enhanced (DCE)–magnetic resonance imaging (MRI) of the prostate, allowing preoperative visualization of the corresponding posterior (C) and anterior (D) tumor nodules (hematoxylin-eosin, scanning magnification [A and B]).
Abbreviations: EPE, extraprostatic extension; GG, grade group; GS, Gleason score; SM, positive surgical margin; SV, seminal vesicle invasion.

There were 3570 separate TNs, ranging from 1 to 7 per RP, slightly but significantly associated with increasing age. Qualified for our compartmentalization criteria (excludes 161 cases where the dominant tumor nodule was anterior to posterior, but other anterior and/or posterior tumor nodules were included in further analysis).

The findings of our UVA are summarized in Table 4. The results show that posterior TNs were more likely to have EPE (odds ratio [OR] = 2.2; 95% CI = 1.7–2.7; P = .001) and SV+ (OR = 27.4; 95% CI = 6.7–111.7; P = .01). Conversely, posterior location did not significantly correlate with any of the adverse RP findings outlined in our study. EPE, SV+, and SM+ were slightly but significantly associated with increasing age. There were 3570 separate TNs, ranging from 1 to 7 per RP (median = 3 TNs per RP), of which 1320 (37%) were anterior and/or posterior TNs from these cases were included in further analysis. Twenty of 1227 patients (1.6%) with either anterior or posterior dominant TN had regional lymph node metastasis and in all these patients the dominant TN was posteriorly located. Patient age ranged from 38 to 85 years (median = 63 years). Prostate weight did not significantly correlate with any of the adverse RP findings outlined in our study. EPE, SV+, and SM+ were slightly but significantly associated with increased incidence of EPE, SV+, and lymph node status. The objective of our study was specifically to investigate the effect of TN location on the likelihood of EPE, SV+, and SM+ (controlling for the effects of tumor grade and TV). Rather than selecting only a single dominant TN per RP, we used each individual TN as independent variables in our statistical analysis because the highest grade, stage, and TV may not necessarily be represented by a single TN for each RP and adverse findings may also be observed in more than a single TN for each RP (eg, an RP with a small organ-

Table 1. Radical Prostatectomy Characteristics by EPE, SV+, and SM+ in the Dominant Tumor Nodules

<table>
<thead>
<tr>
<th>Variable</th>
<th>EPE</th>
<th>P Value</th>
<th>SV+</th>
<th>P Value</th>
<th>SM+</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>496/1156 (42.9%)</td>
<td>.01</td>
<td>92/1227 (7.5%)</td>
<td>&lt;.001</td>
<td>269/1227 (21.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Location</td>
<td>.01</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
</tr>
<tr>
<td>Anterior</td>
<td>110/300 (36.7%)</td>
<td>2/326 (0.6%)</td>
<td>98/326 (30.1%)</td>
<td>.909/901 (10%)</td>
<td>171/901 (19%)</td>
<td>.03</td>
</tr>
<tr>
<td>Posterior</td>
<td>386/856 (45.1%)</td>
<td>90/901 (10%)</td>
<td>98/326 (30.1%)</td>
<td>171/901 (19%)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
</tr>
<tr>
<td>GG1 (GS6)</td>
<td>15/238 (6.3%)</td>
<td>0/253 (0%)</td>
<td>22/253 (8.7%)</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
</tr>
<tr>
<td>GG2 (GS 3 + 4)</td>
<td>187/443 (42.2%)</td>
<td>13/478 (2.7%)</td>
<td>101/479 (21.1%)</td>
<td>.03</td>
<td>.03</td>
<td>.03</td>
</tr>
<tr>
<td>GG3 (GS 4 + 3)</td>
<td>116/199 (58.3%)</td>
<td>16/210 (7.6%)</td>
<td>54/209 (25.8%)</td>
<td>.03</td>
<td>.03</td>
<td>.03</td>
</tr>
<tr>
<td>GG4 (GS8)</td>
<td>18/41 (43.9%)</td>
<td>3/43 (7%)</td>
<td>8/43 (18.6%)</td>
<td>.03</td>
<td>.03</td>
<td>.03</td>
</tr>
<tr>
<td>GG5 (GS9-10)</td>
<td>160/235 (68.1%)</td>
<td>60/243 (24.7%)</td>
<td>84/243 (34.6%)</td>
<td>.03</td>
<td>.03</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: EPE, extraprostatic extension; GG, grade group; GS, Gleason score; SM+, positive surgical margin; SV+, seminal vesicle invasion.

Table 2. Radical Prostatectomy Characteristics by EPE, SV+, and SM+ in the Dominant Tumor Nodules

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>No</th>
<th>Yes</th>
<th>P Value</th>
<th>Total</th>
<th>No</th>
<th>Yes</th>
<th>P Value</th>
<th>Total</th>
<th>No</th>
<th>Yes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>62.5</td>
<td>61.6</td>
<td>63.7</td>
<td>&lt;.001</td>
<td>62.5</td>
<td>62.3</td>
<td>64.1</td>
<td>.03</td>
<td>62.5</td>
<td>62.2</td>
<td>63.4</td>
<td>.02</td>
</tr>
<tr>
<td>Tumor volume, mean, cm³</td>
<td>1.38</td>
<td>0.69</td>
<td>2.3</td>
<td>&lt;.001</td>
<td>1.36</td>
<td>1.17</td>
<td>3.78</td>
<td>&lt;.001</td>
<td>1.36</td>
<td>1.04</td>
<td>2.51</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prostate weight, mean, g</td>
<td>49.9</td>
<td>50.5</td>
<td>49.1</td>
<td>.34</td>
<td>49.7</td>
<td>49.5</td>
<td>53.0</td>
<td>.17</td>
<td>49.7</td>
<td>50.0</td>
<td>48.5</td>
<td>.36</td>
</tr>
</tbody>
</table>

Abbreviations: EPE, extraprostatic extension; SM+, positive surgical margin; SV+, seminal vesicle invasion.

DISCUSSION

After RP, BCR and prostate cancer-specific mortality are influenced by several factors, which include cancer grade, EPE, SV+, and lymph node status. The objective of our study was specifically to investigate the effect of TN location on the likelihood of EPE, SV+, and SM+ (controlling for the effects of tumor grade and TV). Rather than selecting only a single dominant TN per RP, we used each individual TN as independent variables in our statistical analysis because the highest grade, stage, and TV may not necessarily be represented by a single TN for each RP and adverse findings may also be observed in more than a single TN for each RP (eg, an RP with a small organ-
confined, higher-grade TN and another larger lower-grade TN with EPE, 2 TNs with EPE in the same RP, etc.). Thus, among all TNs in our cohort, the incidence of anterior TNs was 37% (Table 3). However, to compare this cohort with other studies, one needs to focus on the distribution of dominant TNs in RP (Tables 1 and 2), that is, 26% of anterior-dominant TNs. Although it still may be slightly above the usually reported incidence of anterior-dominant TNs in the range of 10% to 20%, it may be explained because our tri-ethnic cohort is enriched with non-Hispanic black and Hispanic white men who have a described different distribution of significant cancer at RP compared with white non-Hispanic men.\(^{21,23,25}\) We previously used a similar study design with analysis of individual TNs rather than the entire cancer per RP to assess the oncologic significance of other pathologic features in prostate cancer.\(^{23,34}\) Most prostate cancer experts agree that assessment of individual TNs is more informative than assessment of all cancer present in any given RP.\(^{37,19,35}\) For example, Stamey et al\(^{36}\) previously demonstrated that TV per TN was an independently significant variable in both UVA and MVA, while the total TV per prostate gland was significant in UVA, but (more importantly) not in MVA. In addition, Epstein et al\(^{37}\) used a threshold for insignificant TV per TN of 0.5 cm\(^3\) as part of active surveillance criteria in 1994. This threshold was more recently validated using contemporary grading of prostate cancer.\(^{34}\)

The results of our UVA and MVA demonstrate that posterior TNs are more likely to exhibit EPE and SV+ compared with anterior TNs. The incidence of SM+ for anterior and posterior TNs did not differ when the entire cohort was considered. However, when only considering those TNs with EPE, anterior TNs with EPE were more than twice as frequently associated with SM+ than posterior TNs with EPE. This particular finding may be due (at least in part) to prostate anatomy. The anterior portion of the gland is composed of thick skeletal muscle bundles and lacks a well-defined prostatic margin (which may make it more challenging to clear the margins), unlike the peripheral zone that comprises the posterior and lateral portions of the gland that has a more well-defined border with the surrounding adipose tissue. The increased likelihood of...

### Table 3. Characteristics of Tumor Nodules Categorized by Location

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anterior (1320)</th>
<th>Posterior (2250)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume, mean, cm(^3)</td>
<td>0.59</td>
<td>0.54</td>
<td>.95(^a)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG1 (GS6)</td>
<td>957 (72.5%)</td>
<td>1,298 (58%)</td>
<td>&lt;.001(^b)</td>
</tr>
<tr>
<td>GG2 (GS 3 + 4)</td>
<td>244 (18.5%)</td>
<td>522 (23%)</td>
<td></td>
</tr>
<tr>
<td>GG3 (GS 4 + 3)</td>
<td>49 (4%)</td>
<td>199 (9%)</td>
<td></td>
</tr>
<tr>
<td>GG4 (GS8)</td>
<td>18 (1%)</td>
<td>33 (1%)</td>
<td></td>
</tr>
<tr>
<td>GG5 (GS9-10)</td>
<td>52 (4%)</td>
<td>198 (9%)</td>
<td></td>
</tr>
<tr>
<td>EPE</td>
<td>124 (9.4%)</td>
<td>413 (18%)</td>
<td>&lt;.001(^b)</td>
</tr>
<tr>
<td>SV+</td>
<td>2 (0.15%)</td>
<td>90 (4%)</td>
<td>&lt;.001(^b)</td>
</tr>
<tr>
<td>SM+</td>
<td>114 (8.6%)</td>
<td>178 (7.9%)</td>
<td>.45(^b)</td>
</tr>
</tbody>
</table>

Abbreviations: EPE, extraprostatic extension; GG, grade group; GS, Gleason score; MVA, multivariable analysis adjusted for age and other variables in the models; SM+, positive surgical margin; SV+, seminal vesicle invasion.

\(^a\) Analysis of variance and Tukey post hoc.

\(^b\) \(\chi^2\) test.
SM+ in anterior TNs with EPE may be an important consideration when deciding upon which surgical approach may be the most appropriate (ie, conventional, hood, or Retzius-sparing).

Our findings coincide with those of a few notable previous studies. In a study of 853 patients published in 2005, Koppie et al11 found an increased likelihood of EPE and SV+ for posterior TNs, while anterior TNs were more likely to have SM+ (12% versus 7%, \( P = .01 \)), higher TV (1.6 versus 0.8, \( P < .001 \)), and a lower grade (\( P = .001 \)). Similar observations regarding TV and grade were reported by Kryvenko et al12 in 2014 in preoperatively low-risk men. However, one important difference in our current study is that our MVA accounts for the confounding variables of TV and cancer grade, both of which have an important impact on adverse RP outcomes. By controlling our MVA for these confounding variables, we show that TN location is a significant independent predictor of EPE, SV+, and SM+. Moreover, we show that anterior TNs with EPE are more than twice as likely as posterior TNs to exhibit SM+ (62% versus 30.8%).

Matsumoto et al13 found an increased likelihood of EPE associated with posterior TNs compared with anterior TNs. However, they used lower thresholds than we did in our study to define anterior and posterior location (Matsumoto et al13 defined each as having >50% of TV in the respective compartment). They also had a different focus than our study, in which they sought to correlate radiologic tumor contact length with histopathologic findings as opposed to analyzing the differences between anterior and posterior location on adverse RP outcomes.

In a study of 201 RP with anterior and posterior TN location defined as having more than two thirds of TV in the respective compartment, Sato et al13 found that anterior tumors were significantly more likely to have SM+ in the area of intraprostatic incision (pT2+). In their study, anterior TNs were lower grade and lower stage, and none had SV+. However, they found that anterior tumors were smaller than posterior tumors (2.74 versus 3.74 cm\(^3\), \( P = .0508 \)) in their study, a finding which differs from the results of our study.

In another recent study, Falzarano et al14 described 132 cases with anterior-dominant TNs and 352 cases with posterior-dominant TNs matched by tumor grade. The authors reported a higher incidence of EPE (42.4% versus 33.7%) and SM+ (43.9% versus 37.1%) in anterior TNs. Although we too found a greater likelihood of SM+ in anterior-dominant TNs (Table 1), the incidence of EPE in our study was greater for posterior-dominant TNs than anterior-dominant TNs. We believe this is due in large part to the grade-matched design Falzarano et al14 used in their study. None of their anterior TNs had SV+, whereas we reported 2 anterior TNs with SV+. Although (mechanistically) SV+ may not be explained by direct invasion for anterior TNs, these cases may represent metastatic SV involvement.11,42 Falzarano et al13 observed no difference in incidence of BCR-free survival between men with anterior and posterior-dominant disease.

Knowledge of such trends in RP outcomes between anterior and posterior prostate cancer TNs can be used preoperatively. Prostate Imaging Reporting and Data System reliably detects TNs with Grade Group 2 and above that may be subjected to a targeted biopsy procedure,44 and also appears to perform well in the assessment of prostate cancer TV.44,45 Together, radiographic and biopsy specimen data may allow for the precise localization of significant TNs within the prostate. Thus, knowledge of the associations between certain adverse outcomes at RP and TN location that we report can potentially be useful in patient management decision-making and preoperative planning.

To the best of our knowledge, our study presents the largest group of individual TNs with a detailed contemporary pathologic review that controls for previously established variables associated with adverse RP outcomes (specifically, TV and histologic grade). Our study demonstrates that TN location independently influences the likelihood of EPE, SV+, and SM+. We investigated immediate postoperative outcomes but did not include an analysis of TN location on the likelihood of BCR and prostate cancer-specific death after RP. To our knowledge, only 3 studies have assessed the effect of TN location on the likelihood of BCR-free survival after RP. Magheli et al16 analyzed 265 patients with RP whose preoperative prostate-specific antigen was greater than 20 ng/mL. Although a Kaplan-Meier analysis demonstrated that patients with anterior-dominant tumors had significantly better 5-year BCR-free survival in this cohort, tumor location was not an independent predictor of BCR. Similarly, Falzarano et al14 and Mygatt et al12 observed no difference in the incidence of BCR-free survival between men with anterior and posterior-dominant disease. Although these 3 studies provide the significant information, all of them included the patients who underwent RP a decade or more ago. Thus, it is not only the nature of the treated cohorts is different (more robust active surveillance and greater ethnical diversity of the current cohort), the operative approach (all our RPs are endoscopic robotic-assisted), and the surgical technique, particularly a more recent adoption of Retzius-sparing approach altering the resection of the anterior prostate, distinguish our cohort from those previously reported. In a separate upcoming study, we intend to analyze the extent of positive margin (ie, positive margin length) and the cancer grade at margin between anterior and posterior TNs. These factors have been reported to correlate with the likelihood of BCR and may trigger adjuvant radiotherapy by themselves.46,47

**CONCLUSIONS**

Our analysis of a large contemporary cohort of RPs demonstrates that TN location is a statistically significant independent predictor of certain adverse outcomes at RP, even when controlling for important potentially confounding variables, such as cancer grade and TV. Posterior TNs are more likely to exhibit EPE and SV+, while anterior TNs (and particularly those with EPE) are more prone to SM+. However, 3 previous studies on older cohorts have suggested that TN location does not alter the likelihood of BCR-free survival after RP. It is not clear if the same is true for men currently treated by RP with the contemporary surgical techniques. In summary, these associations may be useful in preoperative planning of treatment strategies in conjunction with biopsy specimen results and multiparametric magnetic resonance imaging findings.

**References**