

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

Amin Hayee, MD; Isabella Lugo, MPH; Oleksii A. Iakymenko, MD; Deukwoo Kwon, PhD; Laurence M. Briski, MD; Wei Zhao, MS; Ivan Nemov, MD; Sanoj Punnen, MD; Chad R. Ritch, MD; Alan Pollack, MD; Merce Jorda, MD, PhD, MBA; Radka Stoyanova, PhD; Dipen J. Parekh, MD; Mark L. Gonzalgo, MD, PhD; Oleksandr N. Kryvenko, MD

• **Context.**—Effect of tumor nodule (TN) location in the prostate on adverse radical prostatectomy (RP) outcomes is not well studied in contemporary cohorts.

Objective.—To investigate the significance of TN location with respect to extraprostatic extension (EPE), seminal vesicle invasion (SVI), and positive surgical margin (SM+) in 1388 RPs.

Design.—Each TN at RP was independently graded, staged, and volumetrically assessed. TNs with at least 80% of their volume occupying either the anterior or posterior part of the prostate were categorized accordingly and included in our study, while all other TNs were excluded.

Results.—A total of 3570 separate TNs (median = 3 per RP; range = 1–7 per RP) were scored. There were 1320 of 3570 (37%) anterior TNs and 2250 of 3570 (63%) posterior TNs. Posterior TNs were more likely to be higher

grade, and exhibit EPE (18% versus 9.4%) and SVI (4% versus 0.15%), all $P < .001$. Anterior TNs with EPE were more likely to exhibit SM+ than posterior TNs with EPE (62% versus 30.8%, $P < .001$). TN location, grade, and volume were significant factors associated with adverse RP outcomes in our univariable analysis. When we controlled for grade and tumor volume in a multivariable analysis using anterior TN location as a reference, posterior TN location was an independent predictor of EPE and SVI and was less likely to be associated with SM+ (odds ratio = 3.1, 81.5, and 0.7, respectively).

Conclusions.—These associations may be useful in preoperative surgical planning, particularly with respect to improving radiographic analysis of prostate cancer.

(*Arch Pathol Lab Med.* 2022;146:833–839; doi: 10.5858/arpa.2021-0104-OA)

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 (SVI), positive surgical margin (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) findings, such as EPE, SVI, and SM+.^{11–14} While there are a few noteworthy publications that have previously compared anterior and posterior TNs in terms of BCR, SVI, 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

Accepted for publication June 15, 2021.

Published online October 20, 2021.

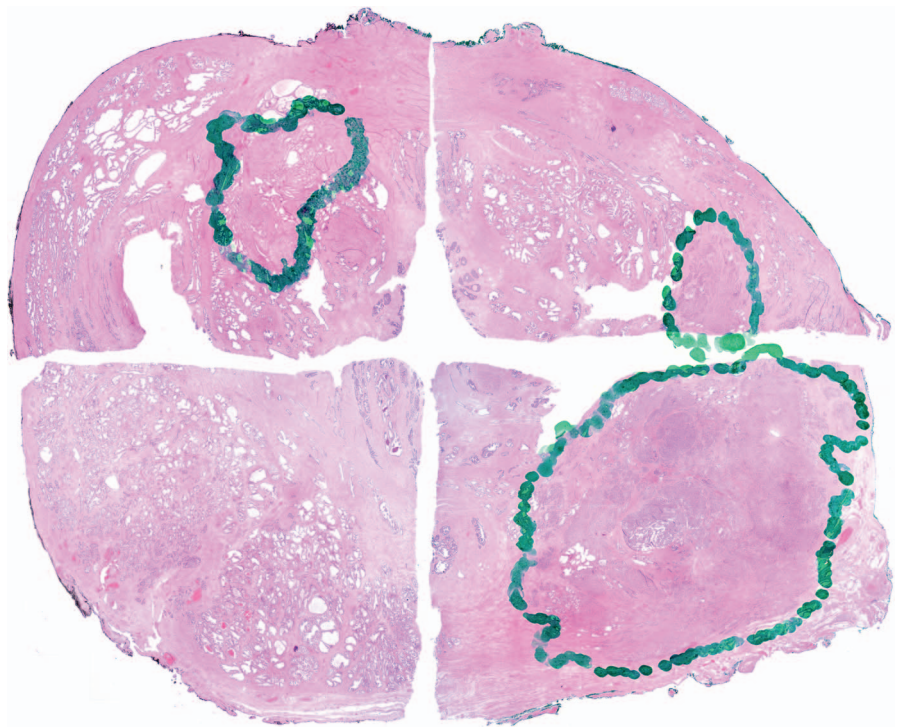
From the Departments of Pathology and Laboratory Medicine (Hayee, Lugo, Iakymenko, Briski, Nemov, Jorda, Kryvenko), Public Health Sciences (Kwon), Desai Sethi Urology Institute (Punnen, Ritch, Jorda, Parekh, Gonzalgo, Kryvenko), Radiation Oncology (Pollack, Stoyanova, Kryvenko), and Sylvester Comprehensive Cancer Center (Kwon, Zhao, Punnen, Ritch, Pollack, Jorda, Parekh, Gonzalgo, Kryvenko), at the University of Miami Miller School of Medicine, Miami, Florida.

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number P30CA240139. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors have no relevant financial interest in the products or companies described in this article.

The data were presented in part at the 108th Annual Meeting of the United States and Canadian Academy of Pathology (USCAP), March 16–21, 2019, National Harbor, Maryland.

Corresponding author: Oleksandr N. Kryvenko, MD, Department of Pathology and Laboratory Medicine, University of Miami Miller School of Medicine, 1400 NW 12th Avenue, Room 4076, Miami, FL 33136 (email: o.kryvenko@med.miami.edu).

Figure 1. A pseudo-whole mount of the prostate cross section demonstrating 2 separate tumor nodules involving left anterior and right posterolateral portions of the gland (hematoxylin-eosin, scanning magnification).



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, Florida) during 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 submitted in entirety 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 (O.N.K.).

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.^{21,25} Each TN was mapped (Figure 1), staged, and graded according to the latest grading recommendations by the Genitourinary Pathology Society.^{19,21,23,25} TV was calculated using the following formula: $TV = \text{mm}^2 \times 3$ (tissue thickness) $\times 1.12$ (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.^{20,26,28,29} 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+. SVI 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 SVI).

After characterizing and grading each TN, we performed a univariable analysis (UVA) to assess the association of tumor location, grade, and TV with EPE, SVI, 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 χ^2 test, Student *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 $\leq .05$. This study was approved by the University of Miami institutional review board.

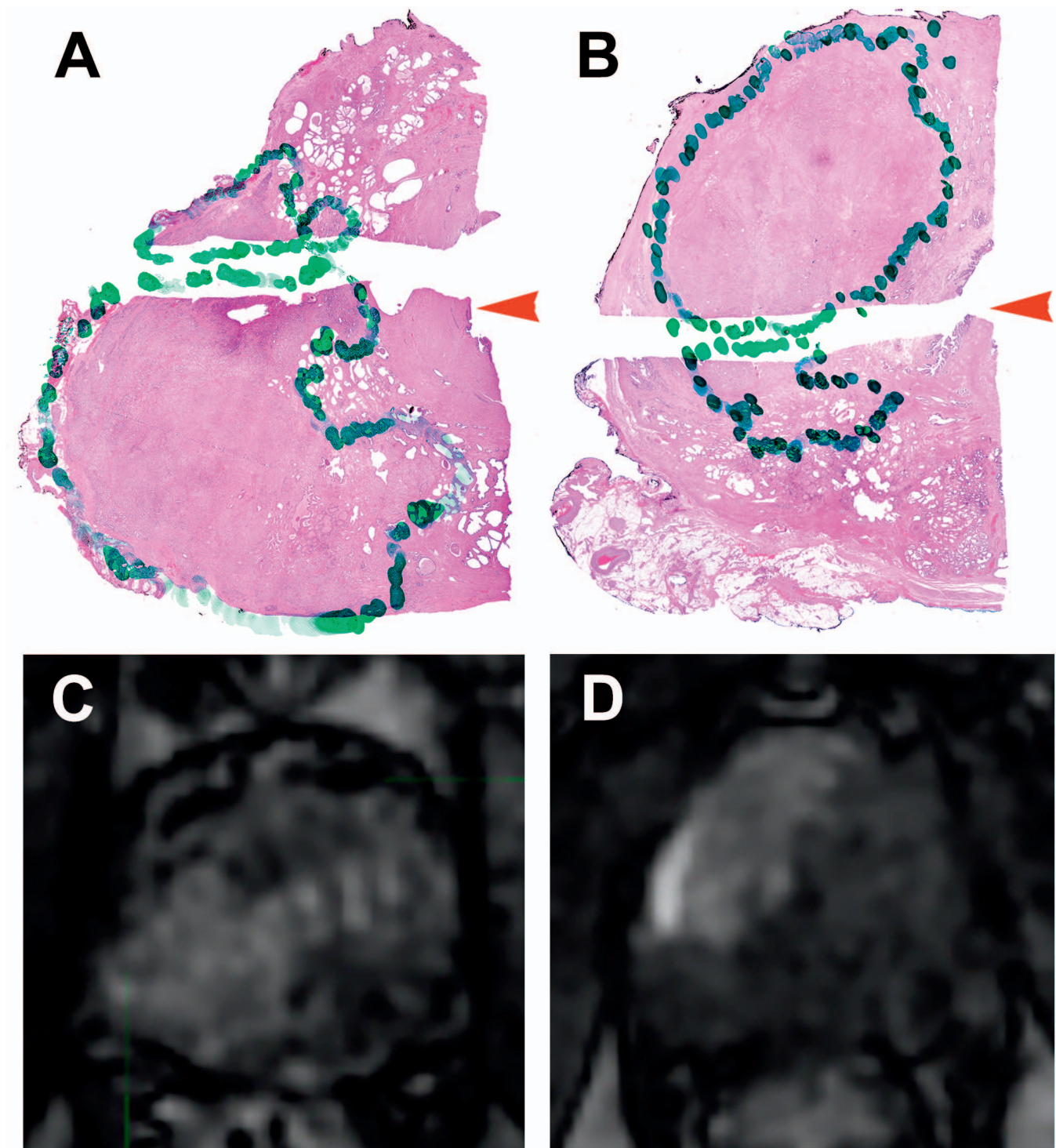


Figure 2. A, Posterior-dominant tumor nodule. B, Anterior-dominant tumor nodule. The prostatic urethra (arrow) is the anatomic landmark by which tumors were categorized as anterior or posterior. Although both tumor nodules depicted in (A and B) each demonstrate minor extension into another location compartment, >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]).

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

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

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

^a Excludes 71 cases with positive surgical margin in the dominant tumor nodule in the area of intraprostatic incision where the presence of EPE cannot be assessed.

^b χ^2 test.

^c 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.

with diffuse adenosis of the peripheral zone.³¹ We therefore only included 1388 cases in our statistical analyses (Tables 1 and 2). Although in 161 RP specimens the dominant TN was anterior-to-posterior (not included in the analysis), the other 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, SVI, 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 2250 (63%) were posterior. None of the TNs that qualified for our compartmentalization criteria (>80% anterior or posterior) had adverse surgical findings in the other part of the prostate where they minimally extended. Overall, in comparison to posterior TNs, anterior TNs tended to be lower grade, less likely to exhibit EPE, and less likely to exhibit SVI. Anterior TNs had a tendency for increased incidence of SM+ compared with posterior TNs but the difference was not significant. Table 3 summarizes the general characteristics of the TNs included in our study.

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 SVI (OR = 27.4; 95% CI = 6.7–111.7; $P = .01$). Conversely, posterior location did not impart a higher likelihood of SM+. TV and cancer grade were significant predictors of all 3 adverse RP outcomes.

Table 4 also summarizes the findings of our MVA. When we controlled for cancer grade and TV, the correlations between posterior location and EPE (OR = 3.1; 95% CI = 2.2–4.5; $P = .001$) as well as between posterior location and SVI (OR = 75.2; 95% CI = 15.4–366.8; $P = .001$) both significantly increased. Of note, posterior location was associated with a significant decreased likelihood of SM+ (OR = 0.7; 95% CI = 0.5–0.95, $P = .02$). Both TV and grade remained strong statistically significant predictors of all adverse RP outcomes in MVA.

Finally, we compared the incidence of SM+ between anterior TNs with EPE and posterior TNs with EPE. Although the incidence of EPE was significantly higher for posterior TNs (9.4% versus 18%, $P < .001$), the incidence of SM+ for anterior TNs with EPE was more than twice that observed in posterior TNs with EPE (77 of 124 [62%] versus 127 of 413 [30.8%], $P < .001$).

DISCUSSION

After RP, BCR and prostate cancer-specific mortality are influenced by several factors, which include cancer grade, EPE, SVI, SM+, and lymph node status.^{3–10} The objective of our study was specifically to investigate the effect of TN location on the likelihood of EPE, SVI, 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,

Variable	EPE				SVI				SM+			
	Total (1156)	No (660)	Yes (495)	P Value ^a	Total (1227)	No (1134)	Yes (92)	P Value ^a	Total (1227)	No (957)	Yes (269)	P Value ^a
Age, mean, y	62.5	61.6	63.7	<.001	62.5	62.3	64.1	.03	62.5	62.2	63.4	.02
Tumor volume, mean, cm ³	1.38	0.69	2.3	<.001	1.36	1.17	3.78	<.001	1.36	1.04	2.51	<.001
Prostate weight, mean, g	49.9	50.5	49.1	.34	49.7	49.5	53.0	.17	49.7	50.0	48.5	.36

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

^a *t*-test.

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

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

^a Analysis of variance and Tukey post hoc.

^b χ^2 test.

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%,³² it may be explained because our triethnic 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.^{21,33,34} Most prostate cancer experts agree that assessment of individual TNs is more informative than assessment of all cancer present in any given RP.^{17,19,35} For example, Stamey et al³⁶ 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 al³⁷ used a threshold for insignificant TV per TN of 0.5 cm³ 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 SVI 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

Outcome	Variable	Measure	No.	UVA		MVA	
				OR (95% CI)	P Value	OR (95% CI)	P Value
EPE ^a	Location	Anterior	1283	Reference		Reference	
		Posterior	2200	2.2 (1.7–2.7)	.001	3.1 (2.2–4.5)	.001
	Grade	GG1 (GS6)	2,232	Reference		Reference	
		GG2 (GS 3 + 4)	723	35.9 (23.6–54.8)	.001	5.0 (3.1–8.1)	.001
		GG3 (GS 4 + 3)	237	93.4 (58.6–148.9)	.001	11.3 (6.6–19.3)	.001
		GG4 (GS8)	49	55.7 (27.5–112.8)	.001	8.7 (3.4–22.1)	.001
GG5 (GS9-10)	242	174.7 (108.5–281.2)	.001	13.6 (8.0–23.1)	.001		
Tumor volume	cm ³	3483	4.9 (4.3–5.6)	.001	4.1 (3.5–4.9)	.001	
Prostate weight	g	3482	0.8 (0.7–1.0)	.09	0.9 (0.6–1.2)	.35	
SVI ^b	Location	Anterior	1320	Reference		Reference	
		Posterior	2250	27.4 (6.7–111.7)	.001	75.2 (15.4–366.8)	.001
	Tumor volume	cm ³	3570	4.4 (3.5–5.4)	.001	6.2 (4.5–8.5)	.001
	Prostate weight	g	3569	1.3 (0.8–2.3)	.34	1.0 (0.5–1.7)	.86
SM+	Location	Anterior	1320	Reference		Reference	
		Posterior	2250	0.9 (0.7–1.2)	.53	0.7 (0.5–0.95)	.02
	Grade	GG1 (GS6)	2255	Reference		Reference	
		GG2 (GS 3 + 4)	766	12.2 (8.1–18.3)	.001	2.6 (1.6–4.2)	.001
		GG3 (GS 4 + 3)	248	21.1 (13.2–33.6)	.001	4.1 (2.3–7.2)	.001
		GG4 (GS8)	51	15.4 (6.9–34.5)	.001	3.1 (1.1–8.2)	.03
	GG5 (GS9-10)	250	36.3 (23.4–56.4)	.001	4.8 (2.7–8.5)	.001	
	Tumor volume	cm ³	3570	3.0 (2.7–3.3)	.001	2.4 (2.1–2.8)	.001
Prostate weight	gram	3569	0.7 (0.5–1.0)	.07	0.7 (0.5–0.99)	.05	

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; SVI, seminal vesicle invasion; UVA, univariable analysis.

^a Excludes cases with SM+ in the area of intraprostatic incision (pT2+).

^b Cancer grading is not included in SVI analysis because there were no observations of SVI by GG1 (GS6) cancer.

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).^{38–40}

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 SVI 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 al²¹ 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, SVI, and SM+. Moreover, we show that anterior TNs with EPE are more than twice as likely than posterior TNs to exhibit SM+ (62% versus 30.8%).

Matsumoto et al¹⁵ 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 al¹⁵ 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 al¹² 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 SVI. However, they found that anterior tumors were smaller than posterior tumors (2.74 versus 3.74 cm³, $P = .0508$) 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 SVI, whereas we reported 2 anterior TNs with SVI. Although (mechanistically) SVI may not be explained by direct invasion for anterior TNs, these cases may represent metastatic SV involvement.^{41,42} Falzarano et al¹⁴ observed no difference in incidence of BCR-free survival between men with anterior-dominant versus 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,⁴³ 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. In other words, it appears that with all other parameters being equal, patients with significant anterior TNs will more frequently have SM+, while those with posterior TNs will be more likely to have EPE and SVI.

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, SVI, 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 al³² observed no difference in the incidence of BCR-free survival between men with anterior and posterior-dominant disease. Although these 3 studies provide 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 that 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, also 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 SVI, 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 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

1. Cotter K, Konety B, Ordóñez MA. Contemporary management of prostate cancer. *F1000Res*. 2016;5.

2. Nahar B, Bhat A, Reis IM, et al. Prospective evaluation of focal high intensity focused ultrasound for localized prostate cancer. *J Urol.* 2020;204(3):483–489.
3. Chauh A, Fajardo DA, Gonzalez-Roibon N, et al. High-grade prostatic adenocarcinoma present in a single biopsy core is associated with increased extraprostatic extension, seminal vesicle invasion, and positive surgical margins at prostatectomy. *Urology.* 2012;79(4):863–868.
4. Ball MW, Partin AW, Epstein JI. Extent of extraprostatic extension independently influences biochemical recurrence-free survival: evidence for further pT3 subclassification. *Urology.* 2015;85(1):161–164.
5. Chan SM, Garcia FJ, Chin JL, Moussa M, Gabril MY. The clinical significance of in-depth pathological assessment of extraprostatic extension and margin status in radical prostatectomies for prostate cancer. *Prostate Cancer Prostatic Dis.* 2011;14(4):307–312.
6. Eggner SE, Scardino PT, Walsh PC, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. *J Urol.* 2011;185(3):869–875.
7. Kordan Y, Salem S, Chang SS, et al. Impact of positive apical surgical margins on likelihood of biochemical recurrence after radical prostatectomy. *J Urol.* 2009;182(6):2695–2701.
8. Potter SR, Epstein JI, Partin AW. Seminal vesicle invasion by prostate cancer: prognostic significance and therapeutic implications. *Rev Urol.* 2000;2(3):190–195.
9. Silberstein JL, Eastham JA. Significance and management of positive surgical margins at the time of radical prostatectomy. *Indian J Urol.* 2014;30(4):423–428.
10. Wright JL, Dalkin BL, True LD, et al. Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. *J Urol.* 2010;183(6):2213–2218.
11. Koppie TM, Bianco FJ Jr, Kuroiwa K, et al. The clinical features of anterior prostate cancers. *BJU Int.* 2006;98(6):1167–1171.
12. Sato S, Takahashi H, Kimura T, Egawa S, Furusato B, Ikegami M. Clinicopathological importance of anterior prostate cancer in Japanese men. *Pathol Int.* 2017;67(3):156–162.
13. Al-Ahmadie HA, Tickoo SK, Olgac S, et al. Anterior-predominant prostatic tumors: zone of origin and pathologic outcomes at radical prostatectomy. *Am J Surg Pathol.* 2008;32(2):229–235.
14. Falzarano SM, Nyame YA, McKenney JK, et al. Clinicopathologic features and outcomes of anterior-dominant prostate cancer: implications for diagnosis and treatment. *Prostate Cancer Prostatic Dis.* 2020;23(3):435–440.
15. Matsumoto K, Akita H, Narita K, et al. Prediction of extraprostatic extension by MRI tumor contact length: difference between anterior and posterior prostate cancer. *Prostate Cancer Prostatic Dis.* 2019;22(4):539–545.
16. Magheli A, Rais-Bahrami S, Peck HJ, et al. Importance of tumor location in patients with high preoperative prostate specific antigen levels (greater than 20 ng/mL) treated with radical prostatectomy. *J Urol.* 2007;178(4 Pt 1):1311–1315.
17. Braunhut BL, Punnen S, Kryvenko ON. Updates on grading and staging of prostate cancer. *Surg Pathol Clin.* 2018;11(4):759–774.
18. Epstein JI, Amin MB, Reuter VE, Humphrey PA. Contemporary Gleason grading of prostatic carcinoma: an update with discussion on practical issues to implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol.* 2017;41(4):e1–e7.
19. Kryvenko ON, Epstein JI. Prostate cancer grading: a decade after the 2005 modified Gleason grading system. *Arch Pathol Lab Med.* 2016;140(10):1140–1152.
20. Epstein JI, Amin MB, Fine SW, et al. The 2019 Genitourinary Pathology Society (GUPS) white paper on contemporary grading of prostate cancer. *Arch Pathol Lab Med.* 2021;145(4):461–493.
21. Kryvenko ON, Carter HB, Trock BJ, Epstein JI. Biopsy criteria for determining appropriateness for active surveillance in the modern era. *Urology.* 2014;83(4):869–874.
22. Samaratunga H, Montironi R, True L, et al. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 1: specimen handling. *Mod Pathol.* 2011;24(1):6–15.
23. Sundi D, Kryvenko ON, Carter HB, Ross AE, Epstein JI, Schaeffer EM. Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men. *J Urol.* 2014;191(1):60–67.
24. Yoon JY, Kryvenko ON, Ghani KR, Bertucci C, Menon M, Gupta NS. Characteristics of pelvic lymph node metastases in prostatic adenocarcinoma: a study of 83 cases. *Int J Surg Pathol.* 2012;20(5):449–454.
25. Kryvenko ON, Lyapichev K, China FM, et al. Radical prostatectomy findings in white Hispanic/Latino men with NCCN very low-risk prostate cancer detected by template biopsy. *Am J Surg Pathol.* 2016;40(8):1125–1132.
26. Epstein JI, Kryvenko ON. A comparison of Genitourinary Society Pathology and International Society of Urological Pathology Prostate Cancer guidelines. *Eur Urol.* 2021;79(1):3–5.
27. Gandhi JS, Smith SC, Paner GP, et al. Reporting practices and resource utilization in the era of intraductal carcinoma of the prostate: a survey of genitourinary subspecialists. *Am J Surg Pathol.* 2020;44(5):673–680.
28. Protocol for the examination of radical prostatectomy specimens from patients with carcinoma of the prostate gland. College of American Pathologists Web site. <https://documents.cap.org/protocols/cp-malegenital-prostate-radicalprostatectomy-20-4101.pdf>. Accessed on May 15, 2021.
29. Kryvenko ON, Epstein JI. Re: clinical significance of prospectively assigned Gleason tertiary pattern 4 in contemporary Gleason score 3 + 3 = 6 prostate cancer. *Prostate.* 2016;76(12):1130–1131.
30. Loeb S, Schaeffer EM, Epstein JI. The vanishing prostate cancer phenomenon. *Urology.* 2010;76(3):605–607.
31. Lotan TL, Epstein JI. Diffuse adenosis of the peripheral zone in prostate needle biopsy and prostatectomy specimens. *Am J Surg Pathol.* 2008;32(9):1360–1366.
32. Mygatt J, Sesterhenn I, Rosner I, et al. Anterior tumors of the prostate: clinicopathological features and outcomes. *Prostate Cancer Prostatic Dis.* 2014;17(1):75–80.
33. Iakymenko OA, Lugo I, Kwon D, et al. Prostatic ductal adenocarcinoma controlled for cancer grade and tumor volume does not have an independent effect on adverse radical prostatectomy outcomes compared to usual acinar prostatic adenocarcinoma. *Urology.* 2020;137:108–114.
34. Kryvenko ON, Epstein JI. Definition of insignificant tumor volume of Gleason score 3 + 3 = 6 (grade group 1) prostate cancer at radical prostatectomy—is it time to increase the threshold? *J Urol.* 2016;196(6):1664–1669.
35. Egevad L, Delahunt B, Srigley JR, Samaratunga H. International Society of Urological Pathology (ISUP) grading of prostate cancer - an ISUP consensus on contemporary grading. *APMIS.* 2016;124(6):433–435.
36. Stamey TA, Freiha FS, McNeal JE, Redwine EA, Whittmore AS, Schmid HP. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer.* 1993;71(3 Suppl):933–938.
37. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA.* 1994;271(5):368–374.
38. Dalela D, Jeong W, Prasad MA, et al. A pragmatic randomized controlled trial examining the impact of the Retzius-sparing approach on early urinary continence recovery after robot-assisted radical prostatectomy. *Eur Urol.* 2017;72(5):677–685.
39. Galfano A, Di Trapani D, Sozzi F, et al. Beyond the learning curve of the Retzius-sparing approach for robot-assisted laparoscopic radical prostatectomy: oncologic and functional results of the first 200 patients with ≥ 1 year of follow-up. *Eur Urol.* 2013;64(6):974–980.
40. Lim SK, Kim KH, Shin TY, et al. Retzius-sparing robot-assisted laparoscopic radical prostatectomy: combining the best of retropubic and perineal approaches. *BJU Int.* 2014;114(2):236–244.
41. Ohori M, Scardino PT, Lapin SL, Seale-Hawkins C, Link J, Wheeler TM. The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. *Am J Surg Pathol.* 1993;17(12):1252–1261.
42. Kryvenko ON, Gupta NS, Virani N, et al. Gleason score 7 adenocarcinoma of the prostate with lymph node metastases: analysis of 184 radical prostatectomy specimens. *Arch Pathol Lab Med.* 2013;137(5):610–617.
43. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging - reporting and data system: 2015, Version 2. *Eur Urol.* 2016;69(1):16–40.
44. Rud E, Klotz D, Rennesund K, et al. Detection of the index tumour and tumour volume in prostate cancer using T2-weighted and diffusion-weighted magnetic resonance imaging (MRI) alone. *BJU Int.* 2014;114(6b):E32–E42.
45. Tschudi Y, Pollack A, Punnen S, et al. Automatic detection of prostate tumor habitats using diffusion MRI. *Sci Rep.* 2018;8(1):16801.
46. Iremashvili V, Pelaez L, Jorda M, Parekh DJ, Punnen S. A comprehensive analysis of the association between gleason score at a positive surgical margin and the risk of biochemical recurrence after radical prostatectomy. *Am J Surg Pathol.* 2019;43(3):369–373.
47. Martini A, Gandaglia G, Fossati N, et al. Defining clinically meaningful positive surgical margins in patients undergoing radical prostatectomy for localised prostate cancer. *Eur Urol Oncol.* 2021;4(1):42–48.