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Biologic Differences Between Peripheral and Transition Zone Prostate Cancer

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Abstract

Background—Prostate cancer arises in the transition zone (TZ) in approximately 20-25% of cases. Modern biopsy and surveillance protocols, and advances in prostate cancer imaging, have renewed interest in TZ prostate cancers. We compared TZ and PZ prostate cancer to determine if cancer location is independently associated with better outcomes.

Methods—We evaluated an expanded cohort of 1534 men who underwent radical prostatectomy between 1983 and 2003 with updated long-term clinical follow-up. Regression models were used to compare the volume of high-grade (Gleason 4 or 5) cancer and total cancer volume by location. Uni- and multi-variable logistic regression models tested the associations between cancer location and adverse pathologic features. Multivariable proportional hazard models were fit to examine cancer recurrence.

Results—Patients with TZ cancer presented with higher pre-operative serum PSA values (11.07 *versus* 7.86 ng/mL) and larger total cancer volume (7.1 *versus* 3.8 cc). Patients with TZ cancer had decreased odds of seminal vesicle invasion (OR 0.08, 95%CI 0.03, 0.21), extra-capsular extension (OR 0.56, 95%CI 0.35,0.92), and lymphovascular invasion (OR 0.48, 95%CI 0.27, 0.87) in multivariable models. TZ cancers were independently associated with decreased hazard of tumor recurrence (HR 0.62, 95%CI 0.43, 0.90).

Conclusions—TZ cancer prostate is associated with favorable pathologic features and better recurrence-free survival despite being diagnosed with larger cancers and higher PSA values. Tumor location should be taken into account when stratifying patient risk before and after prostatectomy, particularly with the evolving role of imaging in prostate cancer management.

Keywords

Prostate Neoplasms; Prostate Specific Antigen; Prostatectomy; Transition Zone Prostate Cancer; Peripheral Zone Prostate Cancer

Introduction

Prostate cancer arises from the transition zone (TZ) in approximately 20-25% of cases.[1, 2] Prostate cancers arising from the TZ are larger at the time of diagnosis due to their central location, and the decreased likelihood of detection on digital rectal exam or extended prostate needle biopsy schemes.[3-5] Despite their greater total cancer volume at diagnosis, TZ cancers are associated with lower Gleason scores at the time of prostate biopsy and prostatectomy compared with their peripheral zone (PZ) counterparts.[6, 7] TZ prostate cancer is associated with better clinical outcomes, including improved biochemical recurrence-free survival, when compared with peripheral zone (PZ) cancer.[4, 8]

Prostate cancer Gleason score, specifically the relative proportion of high-grade disease (Gleason pattern 4 or 5), is the most important predictor of treatment failure, metastasis and cancer-specific mortality.[9, 10] Increased percentage of Gleason 4 or 5 disease is also associated with an increased risk of biochemical recurrence after surgery in a “dose-dependent” fashion.[10] In PZ prostate cancer, total cancer volume also has been shown to be an independent predictor of biochemical recurrence and mortality, even after adjusting for the Gleason score.[4, 10]

Gleason score, the percentage of high-grade disease (Gleason score 4 or 5), and the total cancer volume appear to be prognostic in both PZ and TZ prostate cancer. However, it is not known if PZ cancers are biologically different than TZ cancers, or if the improved outcomes for patients with TZ cancer can be explained by the higher prevalence of low-grade disease. With the increasing use of imaging in the diagnosis and management of prostate cancer, understanding the impact of tumor location on biological behavior may have significant implications for the selection of various treatment modalities.

We compared TZ and PZ prostate cancers using a registry of patients treated with radical prostatectomy with detailed pathological characterization and long-term clinical outcomes data. We sought to build on the prior work by Noguchi *et al.* by expanding the original cohort, updating the long-term clinical follow-up, and utilizing robust models to adjust for potential confounders.[4] We hypothesized that, after adjusting for total cancer volume, Gleason score, and PSA level, TZ cancers would be independently associated with favorable clinicopathologic outcomes when compared with PZ cancers.

Methods and Materials

Study Population

We conducted a retrospective analysis of 1588 patients who underwent radical prostatectomy performed by several urologists at Stanford University Medical Center between 1983 and 2003. We obtained Institutional Board Review approval for the retrospective chart review. Patients were excluded from the analysis if the primary cancer location and/or cancer volume were missing (n=26, 1.6%), if they had prior neoadjuvant hormonal treatment (n=86, 5.4%), other prior treatment (n=7, 0.4%), prior transurethral resection (n=7, 0.4%), primarily central zone cancers (n=11, 0.7%), or the presence of two primary tumors (n=97, 6.1%). We defined the presence of two primary tumors if the second

focus was more than 3mm from the larger cancer focus and had a histologic pattern that was distinct from the neighboring area.[11] In total, our final analytic cohort included 1354 patients, including 82 additional patients with TZ prostate cancer not included in prior reports. The clinical follow-up was defined as the time from the date of surgery to the date of last clinical follow-up. Median clinical follow-up was 7.0 years (interquartile range 3.6 to 10.4).

Data Source

We abstracted pre-operative variables including patient data (age), prostate-specific antigen (PSA) levels, physical findings on digital rectal exam, imaging (transrectal ultrasound of the prostate), and clinical staging. All patients underwent prostate needle biopsy, ranging from sextant to extended biopsy schemes.

All pathologic specimens were reviewed by a single expert urologic pathologist (John E. McNeal, MD). Prostatectomy specimens were processed using the previously published Stanford technique with fixation in 10% formalin for 24 hours, followed by serial transverse 3 mm step sections.[4] All areas of cancer were marked on each slide, and outlines were transferred to create a comprehensive map of the entire prostate specimen and location of primary and secondary cancers in relation to the prostate epithelial boundary defining the transition zone. Total cancer volume and the proportional distribution of cancer in each zone was calculated by computer planimetry for index and secondary cancers, and multiplied by a factor of 1.5 to account for tissue shrinkage during processing.[4, 12] The primary zone of cancer origin (PZ or TZ) was assigned according to the zone containing the majority of the total cancer volume.[4]

Due to the time span of the study, serum PSA measurements were made using one of several assays (Tosoh, Yang, or Hybritec). We defined recurrence as a composite of any biochemical recurrence (BCR), local or distant recurrence, or receipt of salvage therapy. We defined BCR as a persistently detectable or rising post-operative serum PSA level > 0.1 ng/mL and/or a rise in serum PSA above nadir for 2 consecutive measurements. Follow-up PSAs were obtained every 3 months for the first year following surgery, every 6 months for the next 2 years, and annually thereafter.

Statistical Analysis

We analyzed baseline patient and tumor characteristics using univariate analysis of variance (ANOVA) and t-tests for differences. We examined temporal trends in total cancer volume, and the volume of high-grade disease by study year. We used Chi-square and Mann-Whitney comparisons for categorical and continuous variables, respectively, to evaluate differences in clinicopathologic outcomes between PZ and TZ cancers. We fit general linear regression models to compare the relationship between high-grade cancer volume and total cancer volume by tumor location. We performed uni- and multivariable logistic regression to examine associations between cancer location and pathologic adverse outcomes (extracapsular extension [ECE], seminal vesicle invasion [SVI]), lymphovascular invasion [LVI], positive lymph nodes at surgery) adjusting for Gleason score, total cancer volume, and serum PSA level. We constructed uni- and multivariable “Cox” proportional hazard

models to examine factors associated with the time to recurrence. Product-limit Kaplan-Meier curves were generated to illustrate recurrence-free survival for PZ *versus* TZ cancer, stratified by total cancer volume, Gleason score, and PSA.

We defined statistical significance as a p value <0.05 with 2-tailed tests. All analyses were performed using SAS version 9.3 (Cary, NC). Publication graphics were generated using JMP 10 Pro (Cary, NC).

Results

A total of 1354 patients comprised the eligible study population. Table I shows the baseline clinical and pathologic characteristics of 1124 (83%) patients with PZ and 230 (17%) patients with TZ prostate cancer. The mean age of patients at the time of surgery was similar between the groups (62.5 [PZ] *versus* 62.6 [TZ], $p=0.68$). 545 (48.5%) patients had clinical stage T1c prostate cancer in the PZ group compared with 173 (75.2%) in the TZ group ($p<0.0001$). Patients with TZ cancer were more likely to be diagnosed with low-grade disease (Gleason score 3+3) on biopsy (63.4% *versus* 52.8%, $p=0.039$), but final pathologic Gleason score was not significantly different between the two groups ($p=0.51$). Patients with TZ cancer presented with higher pre-operative serum PSA values, with 24.4% of patients having PSAs >20 ng/mL compared with only 11.9% of patients with PZ cancers ($p<0.0001$). Patients with TZ cancer also had significantly larger total cancer volume, with a mean volume almost double that of PZ cancers (7.1 *versus* 3.8 cc).

Patients with TZ cancer were less likely to have seminal vesicle invasion (4.8% [TZ] *versus* 13.1% [PZ], $p=0.0003$). There was no difference in rates of extracapsular extension (ECE) (16.1% [TZ] *versus* 20.4% [PZ], $p=0.179$), lymphovascular invasion (LVI) (9.1% [TZ] *versus* 12.7% [PZ], $p=0.17$), or positive lymph nodes at lymphadenectomy (4.8% [TZ] *versus* 6.7% [PZ], $p=0.28$). Despite these similarities, patients with PZ cancer were more likely to experience poor clinical outcomes, including biochemical recurrence (27.6% *versus* 20.3%, $p=0.01$), distant metastasis (4.9% *versus* 1.5%, $p=0.01$), or death from prostate cancer (3.2% *versus* 0.9%, $p=0.05$).

Even though the TZ cancers had larger total cancer volume, the volume of high-grade disease (defined as Gleason score 4 or 5) was similar between TZ and PZ cancers, (mean high-grade volume 1.7 *versus* 2.8 cc in PZ cancers, $p=0.22$). Figure 1 shows the relationship between total cancer volume and the volume of high-grade disease. Although both TZ and PZ cancer demonstrate increasing volume of high-grade disease with increasing total cancer volume, the relationship differed based on tumor location. Notably, TZ cancers had a lower volume of high-grade disease as the total cancer volume increased, and this was evident in the difference in the slope of the line relating total cancer volume to volume of high-grade disease. (Figure 1b) General linear regression demonstrated this difference in slope to be significant ($p<0.0001$). (Supplemental Data) Over the study period, both the total cancer volume (Figure 1c) and the volume of Gleason 4/5 disease decreased for both PZ and TZ cancer.

Table II shows the results of unadjusted and multivariable logistic regression models comparing adverse clinicopathologic outcomes by cancer location. TZ cancer had significantly lower odds of SVI in unadjusted and multivariable models that included Gleason score, the volume of high-grade disease, and the pre-operative serum PSA. There were no differences in the odds of ECE, LVI, or lymph node positivity between TZ and PZ cancers in unadjusted models. However, after adjusting for clinical factors in a stepwise fashion, TZ cancer demonstrated lower odds of ECE, LVI, and lymph node metastasis.

Mean and median follow-up was 7.3 and 7.0 years, respectively. Kaplan-Meier product-limit plots show the recurrence-free survival stratified by total cancer volume, Gleason score, and serum PSA. (Figure 2) TZ cancer had a decreased hazard of recurrence (biochemical, local, or distant metastasis) on unadjusted “Cox” proportional hazards analysis (HR 0.62, 95% CI 0.44-0.86). (Table III) Not surprisingly, many factors (total cancer volume, volume of high-grade disease, Gleason score, stage, and the presence of adverse clinicopathologic factors) were also associated with an increased hazard of recurrence. In a multivariable model including all clinicopathological factors, TZ cancer remained independently associated with a decreased hazard of biochemical recurrence (HR 0.62, 95% CI 0.43-0.90). Gleason score, total cancer volume, the presence of LVI, and lymph node metastasis were also independently associated with recurrence.

Discussion

Since the initial description of TZ prostate cancer, there has been controversy over whether these tumors display differences in biological behavior compared with those that arise in the PZ. We have supplemented a large series of 1354 detailed radical prostate prostatectomy specimens with long-term clinical follow-up to address the question of whether TZ cancers differ from PZ cancers. In many respects, patients with TZ and PZ cancer appear to be similar. We observed no differences in the age at the time of diagnosis, as well as similar unadjusted rates of adverse pathologic findings including extracapsular extension, lymph node involvement, and lymphovascular invasion.[13] For patients with TZ and PZ cancers, Gleason score, pathologic stage and total cancer volume were strong pathological predictors of clinical outcome.

We did, however, identify several important differences between TZ and PZ cancer that suggest differences in their underlying biology. Despite many similarities in clinicopathological features of these cancers, TZ cancers showed better clinical outcomes with respect to biochemical recurrence, local, and distant metastasis. This is notable since TZ cancers are diagnosed at larger cancer volumes and higher serum PSA levels. Importantly, the relationship between total cancer volume and the volume of high-grade disease differs between TZ and PZ cancers (Figure 1b), such that for similarly sized cancers, those arising in the TZ will have a smaller volume of high-grade disease. After adjusting for these differences in total cancer volume and the volume of high-grade disease, TZ cancers continue to demonstrate reduced odds of adverse pathological features such as lymphovascular invasion, lymph node involvement, and extracapsular invasion.

Since increases in tumor volume are associated with worse clinical outcome and more aggressive behavior in many clinical types, including prostate and renal cancer, the difference in the slope of the line describing the relationship between total cancer volume and high-grade tumor volume between TZ and PZ cancers strongly suggests differences in underlying biology. For example, cancer tumor volume may be the product of more rapid proliferation, resulting in more cells at risk to acquire mutations leading to more aggressive behavior. Studies have found that TZ cancers have lower proliferation indices and maintain a diploid DNA status at larger tumor volumes compared with PZ cancers.[14, 15] Given recent reports suggesting that Gleason pattern 4 evolves clonally from pattern 3 based on acquisition of mutations and genomic structural alterations, TZ cancers may be less susceptible to the acquisition of genomic alterations.[16] This could explain the better clinical outcomes observed in TZ cancers, and possibly explains our previous observation of better clinical outcomes in TZ cancers with rapid PSA velocities compared to PZ cancers.[8] On the other hand, if Gleason pattern 3 and pattern 4 are distinct entities with rare transitions from pattern 3 to pattern 4, then the TZ might represent a distinct niche in the prostate in which pattern 3 grows preferentially.[17, 18]

Several reports have examined molecular differences between TZ and PZ cancers. The TMPRSS2-ERG gene rearrangement is thought to be rare or absent in TZ cancers.[19-22] PZ cancers have been shown to have increased expression of Ki-67, MMP-2, MMP-9, p53, and Bcl-2.[14, 23] Whether the presence of the TMPRSS2-ERG gene fusion, or increased expression of these biomarkers is associated with poor clinical outcomes remains to be determined.[24]

The finding that cancers arising in the transition zone have different biologic behavior has important clinical implications. Tumor location was strongly associated with the risk of extracapsular extension, seminal vesicle invasion, lymphovascular invasion, and lymph node metastasis after adjusting for the Gleason score, the volume of high-grade disease, and the serum PSA. In multivariate time-to-event models, tumor location is an important independent predictor of recurrence-free survival along with other known powerful predictors of outcome including total cancer volume. This current study supports the findings of Stamey and Noguchi *et al.* of superior clinical outcomes of TZ cancers, despite larger total cancer volume and higher serum PSA levels.[4, 25] The advent of multiparametric MRI and other novel imaging techniques that allow localization and volume assessment of cancers within the prostate gland open the possibility for adding these clinical variables to pre-treatment predictions of cancer aggressiveness. Reports have suggested inclusion of biopsy templates to identify TZ cancers during the initial diagnostic biopsy, and for surveillance of patients on active surveillance regimens.[26-28] Prediction of cancer aggressiveness is critical in the selection of patients appropriate for active surveillance and for concurrent hormonal therapy in patients receiving radiation for intermediate-risk prostate cancer. Whether tumor location will influence outcomes in these clinical settings is unknown.

There are several limitations to our study. Due to the lengthy nature of follow-up, there was periodic variation in the PSA threshold used to define biochemical recurrence, as well as the specific serum PSA assays used. We attempted to correct for these temporal variations in

PSA assay use by including the year of surgery in the proportional hazards models. The year of surgery was not an independent predictor of recurrence risk in the multivariable model suggesting that variation in PSA assay use had a limited impact on these findings. Information regarding margin status was not uniformly available on all our patients, which could affect overall outcomes such as biochemical recurrence or metastases. Nevertheless, our cohort of 1354 radical prostatectomy patients with detailed pathologic notations and long-term follow-up suggests that there may be distinct biologic differences between TZ and PZ cancer. An improved understanding of prostate cancer location, total cancer volume, and the volume of high-grade disease will have significant diagnostic and prognostic implications, particularly with the evolving role of imaging in the diagnosis of prostate cancer.

Conclusions

Patients diagnosed with prostate cancer arising from the TZ are more likely to have higher PSAs and larger total cancer volume when compared with patients with PZ cancer. However, TZ cancers are associated with decreased odds of adverse pathologic findings and demonstrate improved recurrence-free survival. These favorable outcomes appear to be the result of distinct tumor biology. Prostate cancer location should be taken into account when stratifying patients into risk categories both before and after prostatectomy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Table I

Baseline clinical and pathologic characteristics of patients with peripheral zone (PZ) and transition zone (TZ) prostate cancers

Characteristic	PZ (%)	TZ (%)	p value
Number of patients	1,124 (83.0%)	230 (17.0%)	
Age in years at surgery (mean/median)	62.5 / 63.0	62.6 / 63.0	0.68
Clinical T stage			
T1c	545 (48.5%)	173 (75.2%)	<0.0001
T2	576 (51.3%)	56 (24.4%)	
Pre-op PSA (ng/mL)			
Median (IQR)	7.86 (7.82)	11.07 (12.10)	<0.0001
10	682 (63.1%)	101 (44.9%)	
>10 – 20	269 (24.9%)	69 (30.7%)	
> 20	129 (11.9%)	55 (24.4%)	
Biopsy Gleason Score			
3+3	290 (52.8%)	77 (63.4%)	0.039
3+4	161 (29.3%)	22 (18.2%)	
4+3	43 (7.8%)	13 (10.7%)	
4+4	55 (10.0%)	9 (7.4%)	
Pathologic Gleason Score			
3+3	209 (18.6%)	52 (22.6%)	0.51
3+4	605 (54.0%)	114 (49.6%)	
4+3	291 (26.0%)	61 (26.5%)	
4+4	16 (1.4%)	3 (1.3%)	
Prostate weight (g)			
mean	50.3	53.3	0.021
median	45.0	7.0	
Total cancer volume (cc)			
Mean	3.8	7.1	<0.0001
Median	2.2	4.0	
IQR	3.6	6.7	
Volume of high-grade (Gleason 4 or 5)			
Mean	1.7	2.8	0.22
Median	0.5	0.7	
IQR	1.7	2.2	
Extracapsular extension (ECE)	229 (20.4%)	37 (16.1%)	0.13
Seminal vesicle invasion (SVI)	147 (13.1%)	11 (4.8%)	0.0003
Lymphovascular invasion (LVI)	143 (12.7%)	21 (9.1%)	0.17
LN positive (LN+)	75 (6.7%)	11 (4.8%)	0.28
Distant metastasis	50 (4.9%)	3 (1.5%)	0.01
Biochemical recurrence	284 (27.6%)	42 (20.3%)	0.01
Death due to cancer	36 (3.2%)	2 (0.9%)	0.05

Table II

Logistic regression model of odds of adverse pathologic outcomes for TZ compared with PZ cancer (referent)

Outcome	TZ versus PZ			
	Univariable	Multivariable Model A	Multivariable Model B	Multivariable Model C
ECE	0.75 (0.51, 1.10)	0.76 (0.49, 1.17)	0.57 (0.35, 0.93)	0.56 (0.35, 0.92)
SVI	0.33 (0.18, 0.62)	0.34 (0.17, 0.70)	0.08 (0.03, 0.25)	0.08 (0.03, 0.21)
LVI	0.71 (0.44, 1.16)	0.69 (0.41, 1.16)	0.50 (0.27, 0.90)	0.48 (0.27, 0.87)
LN+	0.70 (0.37, 1.34)	0.76 (0.38, 1.54)	0.34 (0.14, 0.84)	0.29 (0.12, 0.69)

Model A: adjusted for pathologic Gleason score (3+3, 3+4, 4+3, >=4+4)

Model B: adjusted for pathologic Gleason score + volume of high-grade disease (Gleason 4 or 5)

Model C: adjusted for pathologic Gleason score + volume of high-grade disease (Gleason 4 or 5) + PSA

Odds Ratios are presented in bold if meeting statistical significance of $p < 0.05$.

Table III

Cox proportional hazards model predicting recurrence-free survival in patients with PZ and TZ prostate cancer

Characteristic	Hazard Ratio (95% CI)	
	Univariable	Multivariable
Tumor Location (vs PZ)		
TZ	0.62 (0.44, 0.86)	0.62 (0.43, 0.90)
Volume of high-grade cancer (Gleason 4 or 5) (per cc)	1.07 (1.06, 1.08)	1.02 (1.00, 1.04)
Tumor Volume (vs. <2 cc)		
2-4 cc	2.58 (1.84, 3.60)	1.63 (1.15, 2.31)
>4 cc	5.85 (4.36, 7.83)	2.19 (1.51, 3.18)
Serum PSA (vs <=10)		
>10-20	2.35 (1.82, 3.02)	1.32 (0.99, 1.75)
>20	4.44 (3.40, 7.83)	1.50 (1.05, 2.14)
Extracapsular extension (ECE)		
Yes vs No	2.88 (2.33, 3.57)	1.22 (0.95, 1.56)
Seminal vesicle invasion (SVI)		
Yes vs No	5.42 (4.28, 6.87)	1.30 (0.96, 1.78)
Lymphovascular invasion (LVI)		
Yes vs No	4.31 (3.43, 5.42)	1.94 (1.50, 2.50)
LN positive		
LN+ vs LN-	5.30 (4.04, 6.95)	1.42 (1.01, 1.99)
Clinical Stage		
T2 vs T1c	2.16 (1.72, 2.72)	1.40 (1.08, 1.81)
Gleason Score (vs 3+3)		
3+4	5.64 (3.14, 10.1)	3.14 (1.72, 5.73)
4+3	18.0 (9.96, 32.4)	6.72 (3.61, 12.5)
4+4	25.9 (11.4, 58.9)	5.1 (2.03, 12.8)
Year of Surgery	0.92 (0.90, 0.95)	1.02 (0.99, 1.06)

Hazard Ratios presented in bold if meeting statistical significance of $p < 0.05$.