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DO PROSTATIC TRANSITION ZONE TUMORS HAVE A DISTINCT MORPHOLOGY?

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Abstract

Previous studies have proposed that the morphologic spectrum of prostatic glands of variable size with tall columnar cells displaying basally-oriented nuclei and clear to pale pink cytoplasm (TZ-LOOK) is characteristic of the well- to moderately-differentiated component of transition zone (TZ) tumors. However, the specificity of these findings has not been well studied. In a recent report, we identified dominant peripheral zone (PZ) and TZ tumors situated anterior to the prostatic urethra. Currently, we evaluate the histopathologic features of 215 dominant tumors, including 63 TZ and 73 anterior PZ lesions and an additional cohort of 79 posterior PZ tumors, in radical prostatectomy specimens, to identify the prevalence of this morphology in tumors of different zonal origin. Each dominant tumor was assigned a TZ-LOOK extent score of 0 to 4, with 0 = no such morphology, 1 = 1-25%, 2 = 26-50%, 3 = 51-75%, and 4 = >75%. Overall, 121/215 (56%) tumors showed some degree of this histology, including 56 of 63 (89%) TZ tumors and 65 of 152 (43%) PZ tumors ($p < 0.0001$). 37 of 215 (17%) lesions had scores of 3-4, with 31 (84%) of these being of TZ origin. However, only 31/63 (49%) TZ tumors had >50% TZ-LOOK. Among PZ tumors, 6/152 (4%) had predominant (>50%) TZ-LOOK morphology, yet 23/152 (15%) of all PZ tumors and 23/65 (35%) of PZ tumors displaying any degree of TZ-LOOK had scores of 2-3 (>25%; non-focal). In tumors of both zones with predominant (scores 3-4; > 50%) TZ-LOOK histology, darker glands of usual acinar adenocarcinoma were often seen at the periphery. Conversely, in tumors with non-predominant TZ-LOOK (scores 1-2; $\leq 50\%$), these glands were frequently admixed with small glands bearing dark cytoplasm. In this series, we demonstrate that some degree of TZ-LOOK morphology is twice as frequent in dominant TZ tumors than in PZ tumors. Tumors demonstrating > 50% of this histology are very likely of TZ origin, but this scenario occurs in only half of TZ tumors. Importantly, the TZ-LOOK is non-focal in up to 35% of PZ tumors exhibiting any degree of this morphology. Given this lack of specificity, caution should be exercised in assigning zone of origin based on this histologic appearance, especially in limited samples such as prostate needle biopsy.

Keywords

prostate; transition zone; peripheral zone; radical prostatectomy

INTRODUCTION

The current model of prostatic anatomy is based on the work of McNeal and colleagues who divided the prostate into three glandular zones: the peripheral zone (PZ), comprising 70% of the glandular mass of the prostate, the central zone, comprising 25%, and the transition zone (TZ), normally comprising approximately 5% (34-35). It is well known that the transition zone is frequently expanded by benign prostatic hyperplasia (BPH) and may account for a greater amount of prostatic bulk (33). Subsequent studies have characterized the prevalence and nature of cancer arising in these zones (40), with nearly 75% occurring in the PZ as opposed to approximately 20% in the TZ. Furthermore, multiple investigators have argued that there is significant variation between the pathologic features and clinical outcomes of tumors arising in different zones. More specifically, most have reported associations between tumors of TZ origin and lower Gleason scores (GS), as well as lower rates of extraprostatic extension, seminal vesicle invasion, and biochemical recurrence (19-20,36,39-40,42,44-45).

As a corollary to these findings, a number of authors have ascribed distinctive morphologic features to TZ-derived tumors (17,21,36,40). This “clear cell” histologic pattern (40) encompasses columnar cells with clear to pale pink cytoplasm lining glands of widely variable size and contour which may occasionally contain granular pink secretions and/or crystalloids. McNeal and others noted that this appearance was typically associated with well-differentiated, Gleason pattern 1, 2, and 3 tumors, often resembling glands of BPH (17,19-21,36,40), and concluded that ‘clear cell carcinoma appears to represent a distinctive class of carcinoma that originates in the transition zone’ (40). Whether this morphology is specific for tumors of TZ origin or simply more often associated with tumors of this zone has not been well studied. In a recent report detailing the pathologic attributes of anterior-predominant prostatic tumors, we identified a large number of dominant TZ and anterior PZ tumors from our institutional series (1). In this report, we utilized that group of well-characterized tumors and an additional cohort of posterior-dominant PZ lesions to determine the specificity of these morphologic features for TZ tumors, by quantitating its presence in dominant tumors developing in both zones.

MATERIALS AND METHODS

After approval from our Institutional Review Board, 215 whole-mounted and entirely-submitted radical prostatectomy (RP) specimens, surgically removed between 2001 and 2006 and containing moderately-differentiated prostatic adenocarcinoma (Gleason scores 3+3=6 and 3+4=7) were retrieved from the surgical pathology files of Memorial Sloan-Kettering Cancer Center. In all cases, the prostate was serially sectioned transversely in planes perpendicular to the rectal surface after shaving the superficial fragments of muscular tissue surrounding the proximal urethra (i.e. bladder neck), sectioning and radially segmenting the most apical 3 mm of the gland in a cone-like fashion, and amputating the seminal vesicles at the junction with the prostate. Histologic examination was performed on all whole-mount sections from each case.

On each slide, the outlines of areas containing lower (Gleason patterns ≤ 3) and higher (Gleason patterns 4-5) grade carcinoma were marked differentially by green and blue ink, respectively. These outlines were used to construct tumor maps that delineated the degree of tumor involvement in the TZ and PZ in each plane of section. Briefly, for anterior tumors, designation as TZ or PZ was based on previous studies regarding relationships between glandular zones (34) and our recent work highlighting the variability of anterior prostatic anatomy from apex through base, including the relationship of glandular zones to the anterior fibromuscular stroma (11). Even in cases where multiple tumor nodules were

present, each case had a tumor nodule designated as “dominant” – having the largest diameter and involving the most sections. All in all, sixty-three cases with dominant TZ tumors and 152 cases with dominant PZ tumors (73 anterior from the prior study and 79 posterior) comprised the study cohort.

The presence and extent of the aforementioned morphologic features, namely, glands of irregular shape and size containing tall cells with basally-situated nuclei and clear to pale pink cytoplasm (TZ-LOOK), were assessed in the dominant tumor nodule in each case. These measures were quantitated on a scale of 0-4, as follows: 0 = absent, 1 = 1-25% (focal), 2 = 26-50% (non-focal), 3 = 51-75%, and 4 = >75% (>50% termed predominant). Consideration was given to other benign and cancerous entities that may demonstrate a similar histologic appearance, such as adenosis and pseudohyperplastic carcinoma, as well as to the configuration of TZ-LOOK glands. Statistical analyses employed Fisher’s exact test.

RESULTS

The results of TZ-LOOK [Figure 1] extent scoring are summarized in Table 1. Taken as a group, 56.3% (121/215) of all dominant tumor foci in this series displayed some degree of this histology. When classified by zone of origin, 56 of 63 dominant TZ tumors (88.9%), but only 65 of 152 (42.7%) dominant PZ tumors demonstrated any TZ-LOOK ($p < 0.0001$).

This appearance was the predominant tumor morphology, i.e. >50%, in 37 of 215 (17.2%) lesions. Of these, 31/37 (83.8%) were TZ tumors [Figure 2A-B], which accounted for 49.2% (31/63) of all TZ tumors [Figure 3A-B]. Overall, TZ-LOOK was the predominant tumor histology in a nominal 6/152 (3.9%) of PZ tumors [Figure 4A-B]. However, this morphology was non-focal (>25%) in 15.1% (23/152) of all PZ tumors and in 35.4% (23/65) of PZ tumors having any such appearance.

When observed in the current series, TZ-LOOK glands were consistently discrete and infiltrative in appearance and therefore classified as Gleason pattern 3. Additionally, all cases contained some degree of usual acinar adenocarcinoma histology, i.e. small glands with amphophilic to basophilic cytoplasm and enlarged nuclei with prominent nucleoli. Irrespective of zone of origin, when >50% of the lesion showed TZ-LOOK histology, darker glands of usual adenocarcinoma were typically seen at the periphery [Figure 5]. Conversely, in cases demonstrating more focal (scores 1-2; < 50%) TZ-LOOK, these glands were commonly admixed among small glands bearing dark cytoplasm.

DISCUSSION

In a series of studies from the late 1980’s and early 1990’s examining the zonal origin of prostate cancer, investigators argued that apart from location of a cancer focus, TZ tumors could be identified using distinctive histologic criteria characterized by McNeal and colleagues (17-21,36,40). Descriptions of this “TZ-LOOK” encompass a range of findings, including well-differentiated glands of variable size and contour, composed of tall columnar cells with basally-oriented nuclei and occasional eosinophilic luminal secretions. Some variability was noted in both the cytoplasm (clear to pale pink) and nuclei (minimally anaplastic to enlarged and hyperchromatic with prominent nucleoli) of such glands. In 1988, McNeal et al found that two-thirds of 21 TZ-dominant cancers and nearly 75% of 29 “incidental”, smaller TZ tumors initially diagnosed on transurethral resection (TUR) showed >60% of this morphology, with well over half of these displaying >80% (40). On the basis of these observations, as well as the association of this histology with a higher percentage of

Gleason pattern 1-2 cancer foci, it was concluded that this “clear cell” appearance was a marker of TZ tumors and more globally, of low grade lesions.

Although this assertion has rarely been discussed in the past decade, the uniqueness of this histology for TZ tumors has been questioned (9). The results of the current study, focused on dominant lesions in RP specimens, demonstrate that the TZ-LOOK is present in the overwhelming majority of TZ tumors and is more commonly the predominant morphology in TZ tumors than in PZ tumors (ratio > 5:1). However, we observed that the TZ-LOOK occurs as the predominant morphology in only 49% of TZ-dominant tumors, with nearly one-third having 0-25%. Furthermore, a thorough dissection of McNeal’s original work reveals that while only ~ 3% of PZ-dominant tumors showed >60% TZ-LOOK, 34 of 67 (51%) PZ-dominant tumors exhibited some of this morphology and among these 7/34 (21%) showed ≥20% (40). Our findings in PZ tumors, namely, ~ 4% of PZ tumors with >50% TZ-LOOK and 35% of PZ tumors with any such histology showing non-focal TZ-LOOK, are similar enough to those of McNeal et al to conclude that non-focal TZ-LOOK may be a characteristic of up to 25% of PZ tumors.

An important difference between this study and previous reports regards the Gleason grading of tumor elements displaying the TZ-LOOK. Of 14 TZ tumors with “clear cell” histology, McNeal et al reported a primary Gleason pattern of 1 in two cases, 2 in four cases, and 3 in the remaining 8 cases and noted that TZ-LOOK morphology was more typical of Gleason pattern 1-2 than of pattern 3 (40). Similarly, others have reported a higher rate of Gleason scores 2-4 in TZ tumors (19-20,36). In contrast, when observed in the current series, the architecture of TZ-LOOK glands, even when seen as a component of generally circumscribed tumor nodules, was uniformly infiltrative and hence, these glands were assigned a Gleason pattern 3. Possible explanations for this discrepancy include: a) the focus on TUR-diagnosed tumors, which even when sampling the dominant lesion, may only partially represent the overall tumor grade (previous studies) v. RP-detected dominant lesions (present study); b) the shift away from lower Gleason patterns in the past decade (12,28); c) the possibility that some of the Gleason pattern 1-2 areas described in the past may be better classified as adenosis (adenomatous hyperplasia) if encountered today; d) the recognition that even when a tumor nodule is largely circumscribed, significant infiltration of tumor glands between and around benign glands within the nodular configuration should be interpreted as Gleason pattern 3.

Careful attention to the architecture of TZ-LOOK-appearing glands in earlier studies yields two main descriptions. The first is that of glands emerging from benign prostatic hypertrophy (BPH) nodules. Indeed, 14 of 21 TZ tumors originally described by McNeal et al were present in prostates with BPH, with 7 of these tumors appearing to originate within BPH nodules (40), a phenomenon not detected in our cohort. Many such tumors were said to exhibit compact aggregates of glands confined by bands of stroma which mingled freely with benign BPH glands. In light of the lobulated growth described and occasionally depicted (10,35,40) for these lesions, one may question whether a percentage of these tumors would be better labeled as adenosis, a benign nodular lesion exhibiting small to medium-sized crowded glands admixed with larger glands (15-16). It is well known that adenosis preferentially occurs in the TZ, and may display clear to pale pink cytoplasm, moderate size nucleoli, and intraluminal contents that mimic low grade carcinoma (3,15-16). Recently, the International Society of Urologic Pathology (ISUP) Conference on Gleason Grading has asserted that a subset of the cases diagnosed as primary Gleason pattern 1 in the past may actually have represented adenosis (7), a possibility supported by Dr. Gleason (personal communication to VER). As Gleason himself reviewed the 14 cases with TZ-LOOK morphology in the work of McNeal et al and noted the surprisingly increased frequency of low grade patterns (40), some of those lesions may have benefited from

modern immunohistochemical staining with basal cell markers (3,15-16,24) to clarify their true nature.

A second configuration of TZ-LOOK glands recorded in the original study is that of large caliber glands, often arranged in circumscribed nodular masses, closely resembling benign glands of BPH (40). Subsequent studies and images of this histology revealed a spectrum of closely packed glands with papillary infoldings and branching and/or straight luminal borders lined by a single layer of basally-oriented enlarged nuclei often with prominent nucleoli (21,36-37). Interestingly, while these earlier reports viewed prostatic carcinoma resembling BPH as low grade and of TZ origin, more recent studies have established that these “pseudohyperplastic” cancers are nearly always in continuity with usual Gleason pattern 3 small acinar adenocarcinoma, as in our study, and are evenly distributed between TZ and PZ (25,30). It is now known that cancer with these features may also be associated with foci of typical Gleason pattern 4, extraprostatic extension, and rarely, seminal vesicle invasion (25,30) and these developments led the ISUP Conference on Gleason Grading to designate pseudohyperplastic cancer within Gleason pattern 3, rather than as lower grade (7).

Furthermore, while TZ-based pseudohyperplastic cancers may well have a nodular appearance, those located in the PZ may display clear infiltration while retaining the contours of BPH glands (25). Although not specifically quantitated, this variation on TZ-LOOK features was also identified in some of our cases, with tumors in the PZ [Figure 4B] exhibiting limited to vague nodularity and an overall invasive appearance. This nuance may help explain the discrepant conclusions regarding TZ-LOOK in PZ-dominant tumors between this study and previous works. Specifically, even though one-fifth of McNeal et al's PZ tumors showed non-focal TZ-LOOK, those authors do not emphasize this finding, as such foci lacked characteristic rounded borders and/or circumscription, less closely mimicking BPH (40). Conversely, no pre-specified architectural qualities impacted our quantitation of TZ-LOOK histology.

The presence of non-focal TZ-LOOK morphology in greater than 20% of all tumors in this series is highly relevant to assignment of zonal origin to some anterior prostatic tumors. Our group has recently highlighted the variability of anterior prostatic anatomy and specifically, the impact of the proportions of PZ and TZ present in this region in determining zone of origin (1,11). Especially in cases where anatomic complexity makes this assessment difficult, the present data suggests that finding 25-50% (non-focal) TZ-LOOK histology in an anterior tumor will not help establish its zonal origin. The same logic may be applied to TUR specimens, in which the TZ is typically sampled, but may well include glandular tissue of the anterior PZ. Furthermore, although TZ-LOOK morphology was detected in Gleason pattern 3 portions of tumors in this study, its presence as a significant component of tumor morphology alone did not imply less adverse pathologic outcomes in our cohort (1).

Finally, these observations are pertinent in assessment of tumor location detected by needle biopsy. Given the difficulties in detecting anterior prostatic tumors on clinical examination, imaging studies and needle biopsy (4,29,46,48), a number of investigators have examined the value of transition zone-directed needle biopsies (NB) in prostate cancer detection, with conflicting results. While some have found utility for such biopsies in patients with previous negative NB sessions or ‘gray-zone’ PSA levels (13-14,22,26,31-32), with few exceptions (5-6), most authors have argued against using TZ-directed NB in routine protocols (2,8,27,41,43,47). Surprisingly however, few studies have correlated the cancer seen in these NB with that seen in RP specimens and/or the clinical relevance of these tumors. McNeal and Noldus determined that TZ-directed NB were useful in identifying tumors > 5.0 cc, but could miss anterior tumors in the 2.0 to 5.0 cc range (38), while Pelzer et al showed that

these biopsies very rarely detected solitary TZ cancer (43). While we have recently found that TZ-directed NB do not sample any TZ tumor or a TZ-dominant cancer in ~ 40% and 80% of cases, respectively (23), the presence of non-focal TZ-LOOK morphology in a significant number of PZ tumors implies that this feature should not be used in determining whether one has actually sampled the TZ on NB. However, given the current finding that TZ-LOOK is more commonly the dominant morphology in TZ tumors, further analysis of matched NB and RP specimens is underway to determine whether the volume of cancer with TZ-LOOK on biopsy can predict for TZ-localized cancer.

In summary, we have shown that while >50% TZ-LOOK morphology is more frequently identified in TZ tumors than in those arising from the PZ, this extent is seen in only half of TZ-dominant cancers. Importantly, we have highlighted the non-focal nature of this histologic appearance in a significant proportion of PZ tumors. In light of these findings, we conclude that the presence of TZ-LOOK alone is not specific for TZ tumors and that caution should be exercised in utilizing this feature in assigning zone of origin, especially in limited samples such as prostate needle biopsy.

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Figure 1.
“TZ-LOOK” – variably shaped glands displaying pale cytoplasm and basally-oriented nuclei.

Figure 2.
(A) Whole-mount section of prostate demonstrating a dominant TZ tumor (B) predominant TZ-LOOK in the same tumor.

Figure 3.
(A) Whole-mount section demonstrating a dominant TZ tumor (B) no TZ-LOOK in the same tumor.

Figure 4.
(A) Whole-mount section showing a dominant posterior PZ tumor (B) predominant TZ-LOOK in the same tumor.

Figure 5.
Darker glands are seen at the edge of a tumor with predominant TZ-LOOK.

Table 1

TZ-LOOK Extent Scores for Tumors by Zone of Origin

	0	1	2	3	4
Transition Zone (n = 63)	7	13	12	24	7
Peripheral Zone (n = 152)	87	42	17	6	0

0: no TZ-LOOK; 1: 1-25%; 2: 26-50%; 3: 51-75%; 4: >75%