Location and Pathological Characteristics of Cancers in Radical Prostatectomy Specimens Identified by Transperineal Biopsy Compared to Transrectal Biopsy

Tania Hossack,* Manish I. Patel,† Andrew Huo, Phillip Brenner, Carlo Yuen, Daniel Spernat, Jayne Mathews, Anne-Marie Haynes, Rob Sutherland, Warick del Prado and Phillip Stricker

From the Department of Urology, St. Vincent's Hospital (TH), Department of Urology (PB, CY, DS, PS) and Prostate Cancer Centre (JM), St. Vincent's Clinic (JM), Cancer Research Program, Garvan Institute of Medical Research (AH, AMH, RS), Darlinghurst, Urological Cancer Outcomes Centre, University of Sydney (MIP) and Douglass Hanly Moir Pathology (WdP), Sydney, New South Wales, Australia

Purpose: Anterior tumors are estimated to constitute 20% of prostate cancers. Current data indicate that transperineal biopsy is more reliable than transrectal biopsy in identifying these tumors. If correct, this superior reliability should result in an increased proportion of anterior tumors identified by transperineal biopsy. We investigated this hypothesis with reference to prostatectomy specimens.

Materials and Methods: Radical prostatectomy histopathology records were retrospectively examined. Patients were grouped based on primary transperineal or transrectal biopsy as the modality used to identify the initial cancer. After grouping, tumor location and size were recorded and, thus, the proportion of anterior tumors was determined.

Results: A total of 1,132 (414 transperineal and 718 transrectal) prostatectomy specimens were examined. Overall mean tumor size (1.8 and 2.0 cm^3), stage (pT2 63.3% and 61%) and significance (5.1% and 5.1%) for the transperineal and transrectal methods were similar. However, the transperineal method was associated with proportionally more anterior tumors (16.2% vs 12%, $p = 0.046$), and identified them at a smaller size (1.4 vs 2.1 cm^3, $p = 0.03$) and lower stage (extracapsular extension 13% vs 28%, $p = 0.03$) compared to the transrectal method. The pT3 positive surgical margin rate for anterior vs other tumors was 69% vs 34.9%, respectively.

Conclusions: Overall transrectal and transperineal biopsy identify cancers that are similar in size, stage and significance. However, transperineal biopsy detected proportionally more anterior tumors (16.2% vs 12%), and identified them at a smaller size (1.4 vs 2.1 cm^3) and stage (extracapsular extension 13% vs 28%) compared to transrectal biopsy. Identifying anterior tumors early is important because the positive surgical margin rate for anterior pT3 lesions is significantly higher.

Key Words: prostatic neoplasms; pathology; prostatectomy; biopsy, needle; diagnosis

Abbreviations and Acronyms

AS = active surveillance
DRE = digital rectal examination
ECE = extracapsular extension
PSM = positive surgical margin
TP = transperineal
TR = transrectal

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* Correspondence: Department of Urology, Western Hospital, Gordon St., Footscray VIC 3011 Australia (mobile: +613 83456019; FAX: +619 834567111; e-mail: ta_edwards@yahoo.com).

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Of all prostate cancer it is estimated that anterior tumors constitute 20%.[1] Based on current data, transperineal biopsy is more reliable than transrectal biopsy in identifying these tumors.[1,2] However, this evidence is based on the labeling of biopsies as anterior zone without directly correlating them with whole specimens. TP biopsy typically takes more cores than

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TR biopsy. Therefore, it is possible that TP biopsy simply identifies more cancers independent of location.

Huo et al reported that biopsy core accuracy, when correlated with prostatectomy specimens, had an average sensitivity and specificity for location of 48% and 84%, respectively.[3] Rogatsch et al found the positive predictive value of apical cores in correctly identifying cancer in that location in the prostatectomy specimen was only 71.1%.[4] Thus, the concordance between core location and actual location is not particularly reliable.

Assuming TP biopsy does identify more anterior tumors due to its more direct approach to this region, then the proportion of anterior tumors in prostatectomy specimens should be higher compared to TR identified tumors. More readily identifying anterior tumors should have the potential advantages of identification at a smaller size and lower stage as well as a lower PSM rate. Therefore, we quantified the percentage of anterior tumors in prostatectomy specimens from men in whom cancer was identified by primary TP vs TR prostate biopsy. The secondary study goal was to qualify the size, stage and grade of the anterior tumors.

METHODS

In this retrospective study we examined radical prostatectomy specimens taken between 2004 and 2010 at 2 institutions (Westmead and St. Vincent's Hospitals, Sydney). Patients were grouped by the modality used to identify the initial cancer as primary TP or TR biopsy. There were 6 surgeons who contributed to the database, and the indication for selecting between TR and TP for the initial biopsy was entirely at the discretion of the urologist. Almost all prostate biopsies were done by the surgeon who subsequently performed the surgery.

For the TP group only specimens in which cancer had been identified on initial TP biopsy were included and, thus, men with a prior negative TR biopsy were excluded from study. TP biopsies were performed using ultrasound guidance and a biopsy template. There were 12 zones targeted but additional cores could have been taken for larger prostates. The mean number of cores taken was previously reported as 23 (range 13 to 43).[3] The majority of TR biopsies had 12 cores taken under ultrasound guidance. Additional cores may have been taken if a suspicious area was palpable on DRE. In this study we had access to the mode of biopsy only and not the initial biopsy report. Thus, the number and location of positive cores were not known. DRE information was also not available.

All initial histopathology was reported by experienced uropathologists with each prostate specimen fully embedded for analysis. Sectioning was performed at 3 to 4 mm intervals with each slice divided into 4 quadrants. The anatomical locations of tumor foci were reproduced in a prostate cancer map. The total tumor volume for each radical prostatectomy specimen was calculated using a 3-dimensional volume estimation method as reported by Chen et al[5] and recommended by the Royal College of Pathologists of Australasia. Data were collected from the histopathology reports, and included prostate size, tumor grade, size and stage, and margin status. The prostate was then divided into 4 zones of anterior base, anterior apex, posterior base and posterior apex. Anterior was defined as the portion of prostate above the urethra. A zone was marked positive if it held the main tumor or if more than 20% of the zone was occupied by tumor. Tumors were classified as anterior only if 1 or both of the anterior segments were positive. If a posterior segment was positive it was labeled as other. Data were analyzed with SPSS® using the chi-square or Student t test as appropriate.

RESULTS

TP vs TR Biopsy for All Tumors

A total of 1,132 prostatectomy specimens were examined, with 414 cancers detected by TP biopsy and 718 by TR biopsy. Overall mean prostate volume and tumor size were similar between TP and TR tumors. A higher proportion of lower grade tumors (Gleason 6 or less) was present in the TR vs the TP group (10.8% vs 15.5%, respectively, $p = 0.043$). ECE was present in 149 (36%) of the TP and 274 (38.2%) of the TR specimens. The frequencies of each stage are given in table 1 and are similar between the groups.

The rate of PSMs for pT2 disease was 14.2% and 6.6% for TP and TR, respectively ($p = 0.001$). For pT3 disease the rates were 39% and 36.6% for TP and TR, respectively. Overall the incidence of insignificant cancer (size less than 0.5 cc, Gleason 6 or less, organ confined[6]) was 5.1% for the TP and TR biopsy groups.

TP vs TR Biopsy for Anterior Only Tumors

For TP biopsy 67 (16.2%) cancers were anterior only compared to 86 (12%) for TR biopsy ($p = 0.046$, table 2). For anterior only tumors mean size was 1.4 cm^3 for TP detected vs 2.1 cm^3 for TR detected

Table 1. *Overall tumor characteristics*

	TP Group	TR Group	p Value
Mean ± SD cm^3 tumor size	1.8 ± 1.5	2.0 ± 1.9	0.12
Mean ± SD cc prostate size	52.4 ± 17.2	50.8 ± 18.4	0.15
No. Gleason score (%):			
6 or Less	45 (10.8)	111 (15.5)	0.043
7	331 (80)	528 (73.5)	
8 or Greater	38 (9.2)	79 (11.0)	
No. stage (%):			
T2	262 (63.3)	437 (61)	0.71
T3a	119 (28.7)	217 (30.2)	
T3b	29 (7.0)	52 (7.2)	
Any T, N1	4 (1)	12 (1.7)	
No. ECE (%)	149 (36)	274 (38.2)	0.47
No. PSM (%):*			
T2	37 (14.2)	29 (6.6)	0.001
T3	59 (39)	98 (36.6)	0.49
Totals	96 (23.2)	127 (17.7)	0.025
No. insignificant Ca (%)†	21 (5.1)	37 (5.1)	0.95

* Percentages taken as a percent of each stage.
† As defined by Epstein criteria.

Table 2. *Characteristics of anterior only tumors*

	TP Group	TR Group	p Value
Mean ± SD cm^3 tumor size	1.4 ± 1.1	2.1 ± 2.2	0.03
Mean ± SD cc prostate size	59 ± 24	53 ± 22	0.06
% Prostate size greater than 80 cc	16	6	0.05
No. Gleason score (%):			
6 or Less	11 (16)	18 (21)	0.52
7	54 (81)	63 (73)	
8 or Greater	2 (3)	5 (6)	
No. stage (%):			
T2	57 (85)	62 (72)	0.055
T3a	9 (13)	23 (27)	
T3b	1 (2)	0	
Any T, N1	0	1 (1)	
No. ECE (%)	9 (13)	24 (28)	0.03
No. PSM (%):*			
T2	12 (21)	1 (2)	0.001
T3	6 (60)	17 (74)	0.42
Totals	18 (27)	18 (21)	0.39
No. insignificant Ca (%)†	7 (10)	7 (8.1)	0.62

* Percentages taken as a percent of each stage.
† As defined by Epstein criteria.

(p = 0.03). Mean prostate volume was not statistically different between the groups. The proportion of larger prostates (greater than 80 cc) was higher in the TP group than in the TR group (16% vs 6%, respectively, p = 0.05). The overall Gleason scores were similar between the groups. ECE was present in 9 (13%) TP specimens and 24 (28%) TR specimens (p = 0.03). The pT2 PSM rate for anterior only tumors in the TP group was higher than in the TR group (21% vs 2%, respectively, p = 0.001). However, the pT3 PSM rate was similar between the TP and TR groups (60% and 74%, respectively).

Anterior Only Tumors vs Other Tumors

Overall 153 anterior tumors were identified with 979 classified as other. Tumor volume was similar between the groups (1.7 vs 1.9 cm^3). Anterior tumors had a lower Gleason score compared to other tumors. Gleason 6 or less was identified in 19% of tumors and Gleason 3 + 4 = 7 in 62.7% of TP cases compared to 13% and 54.1%, respectively, for other tumors (p = 0.01, table 3).

The difference in ECE between anterior and other tumors was 21.6% vs 39.9%, respectively (p = 0.001). The difference in PSM between anterior and other tumors for pT2 was 11% vs 9.1% and for pT3 was 69% vs 34.9%, respectively (p = 0.001). Overall 9.1% of anterior tumors were insignificant compared to 4.5% of other tumors (p = 0.02).

DISCUSSION

All Tumors

In this study we retrospectively compared prostatectomy specimens between those whose initial cancer was identified by primary TP vs TR biopsy. We examined whether there was a difference in the proportion of anterior only tumors. It is useful to begin by reviewing all tumor data of the 2 groups. Overall tumors reported in the TP and TR groups were of a similar size and stage. In addition, the incidence of insignificant cancers was similar for both groups (5.1%).[6] Therefore, despite the higher core numbers inherent in TP biopsy, this method did not appear to result in the over treatment of prostate cancer.

When comparing grade the TP biopsy group did have significantly more Gleason 7 or greater cancers than the TR group (89.2% vs 84.5%, respectively, p = 0.043). This result likely reflects selection bias, with surgeons having a lower threshold for offering prostatectomy to patients with Gleason 6 cancer identified on TR vs TP biopsy. In addition, there is increased concern regarding the risk of under staging associated with TR biopsy.[7]

A high pT2 PSM rate was reported in the TP group, most likely due to the learning curve associated with conversion to robotic prostatectomy. Surgeons who converted during the study period also preferentially performed primary TP biopsy and, therefore, the majority of patients on the learning curve were in the TP group. Doumerc et al demonstrated that high PSM rates are seen early in the learning curve and decrease after 200+ cases.[8] Some surgeons may believe that TP biopsy is associated with periprostatic scarring, which obscures planes and makes dissection difficult. However, surgeons in this study stated that they did not find this to be the case.

Table 3. *Characteristics of anterior only tumors compared to other tumors*

	Anterior Only Group	Other Group	p Value
Mean ± SD cm^3 tumor size	1.7 ± 1.8	1.9 ± 1.8	0.24
Mean ± SD cc prostate size	54.4 ± 21.7	51 ± 17.3	0.063
No. Gleason score (%):			
6 or Less	29 (19)	127 (13)	0.01
7 (3+4)	96 (62.7)	530 (54.1)	
7 (4+3)	21 (13.7)	212 (21.7)	
8 or Greater	7 (4.6)	110 (11.2)	
No. stage (%):			
T2	119 (77.8)	580 (59.2)	0.001
T3a	32 (20.9)	304 (31.1)	
T3b	1 (0.7)	80 (8.2)	
Any T, N1	1 (0.7)	15 (1.5)	
No. ECE (%)	33 (21.6)	390 (39.9)	0.001
No. PSM (%):*			
T2	13 (11)	53 (9.1)	0.54
T3	23 (69)	134 (34.9)	0.001
Totals	36 (23.5)	187 (19.1)	0.2
No. insignificant Ca (%)†	14 (9.1)	44 (4.5)	0.02

* Percentages taken as a percent of each stage.
† As defined by Epstein criteria.

Anterior Tumors

Our results support the hypothesis that TP biopsy is superior in identifying anterior tumors compared to TR biopsy. A higher proportion of anterior tumors was found in the TP group (16.2% vs 12%). TP biopsy also identified tumors at a smaller size and stage (1.4 vs 2.1 cm^3 and pT2 85% vs 72%, respectively). The TP group also had a high proportion of large (greater than 80 cc) prostates compared to the TR group (16% vs 6%).

The TP approach has inherently more biopsies compared to the TR approach and, therefore, may potentially identify more cancers. However, it should not alter the proportion of anterior tumors unless it is better at sampling these lesions. The TP approach was used in accordance with a standard template aimed at sampling the whole prostate and not just the anterior zone. Only primary TP biopsy cases were used in the analysis, thereby eliminating selection bias resulting from previously negative TR biopsies. TP biopsy also identified anterior tumors at a lower stage, with ECE in 13% of TP cancers compared to 28% of TR.

Anterior Tumors vs Other Tumors

Despite the higher incidence of ECE in the TR anterior cancer group, the overall incidence of ECE in this group was lower than for cancers at other sites. Overall 77.8% of anterior cancers were organ confined vs only 59.6% of other tumors. Anterior tumors were also more likely to have a low Gleason score, with Gleason 6 in 19% vs 13% for other. This finding is not unique and other studies have reported similar findings.[9] However, this does not indicate that anterior tumors are clinically insignificant. Using Epstein criteria for insignificant, only a minority of cancers was classified as such,[6] with 90.9% otherwise being significant.

Importantly once an anterior tumor is pT3 the ability to achieve a negative margin is significantly decreased. The PSM rate for anterior tumors was significantly higher for pT3 tumors (69% vs 34.9%, respectively, $p = 0.001$). Thus, the ability to identify anterior tumors when they are still organ confined has important clinical implications.

Study Limitations

The main limitation of this study was the lack of DRE data. Previous studies have demonstrated that tumor is more likely to involve the anterior portion in nonpalpable disease.[10] If it had been possible to exclude palpable disease, then the proportion of anterior tumors diagnosed by initial TP biopsy could have been higher. However, in this series the decision to perform TP or TR biopsy was based on surgeon preference rather than clinical findings. Therefore, the incidence of palpable disease was likely similar between the groups.

Clinical Implications

TP and TR identified tumors were of a similar size and stage, and 94.9% could be classified as significant cancers in both groups. In addition, more than 80% of tumors involved the posterior zone, suggesting that both methods are capable of identifying the majority of cancers. The main difference identified between the 2 biopsy approaches was that TP identified proportionally more anterior only tumors, and identified them at a smaller size and lower stage than TR biopsy. The absence of a difference in tumor size and stage in overall cancers is most likely because 80% of cancers involve the posterior zone (979 cancers overall vs 153 anterior only). This study suggests that cancers involving the posterior zone are likely to be detected by either biopsy method. Therefore, the difference between biopsy methods is more likely to be confined to the anterior zone only. This difference may also be more apparent in larger glands because there was a significantly higher proportion (16% vs 6%) of large glands (greater than 80 cc) in the TP biopsy group. This suggests that the ability of TP biopsy to sample the anterior zone may be even better in large glands. Finally, anterior tumors appear to pose a greater surgical challenge, with the ability of a surgeon to achieve clear margins significantly decreasing in cases of pT3 disease.

In men with prior negative biopsies TP biopsy was previously reported as more likely to yield anterior positive cores.[2] However, results have not been correlated with prostatectomy specimens to confirm if the cores labeled anterior were, in fact, from the anterior zone. Independent of location the cancer detection rate for men with 3 or more negative prostate biopsies was 34.4% for TP biopsy[2] compared to 10% to 20% for TR biopsy,[11–13] suggesting there is a difference in cancer detection between the biopsy methods.

There are significant procedural differences between TP and TR biopsy. TR biopsy can be performed in office and is well tolerated with the patient under local anesthesia,[14–16] making it less expensive and readily accessible. However, TR biopsy may be associated with a higher sepsis rate.[16] TP biopsy has a low sepsis rate but requires an operating room, an anesthetist for sedation or general anesthesia and a dedicated biopsy grid,[2,3] making it significantly more expensive.

Therefore, our current recommendation is that TR biopsy can be performed as the initial biopsy in the majority of men. Primary TP biopsy can be considered in men with increased prostate specific antigen and nonpalpable disease, particularly if the prostate is large. Secondary TP biopsy should be considered the first line repeat biopsy method for initial negative TR biopsy in which a high index of suspicion persists and for men on AS.

Lawrentschuk et al reported a reservation about enrolling men in AS was concern that they may harbor more extensive disease than thought on biopsy.[7] While they recommended magnetic resonance imaging as a potential method to identify these evasive anterior tumors, this study shows that TP biopsy may be an alternative and, therefore, may help reassure doctors and patients that the tumors may be safely managed with AS.

CONCLUSIONS

Overall TR and TP biopsy identifies cancers that are similar in size, stage and significance. However, TP biopsy detected proportionally more anterior tumors (16.2% vs 12%), and identified them at a smaller size (1.4 vs 2.1 cm^3) and stage (ECE 13% vs 28%) compared to TR biopsy. Identifying anterior tumors early is important because PSM rates for anterior pT3 lesions are significantly higher.

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EDITORIAL COMMENT

This retrospective analysis supports the notion that transperineal biopsy is superior to transrectal prostate biopsy. Although it is a valuable study, the methodology to demonstrate such a difference is perhaps not quite solid enough to make as strident a conclusion as is made here. Nevertheless, it is a useful guidepost as to where prostate biopsy is heading. Increasingly with transrectal biopsy sepsis is an issue[1] and transperineal biopsy offers fewer such complications. Furthermore, the acceptance that anterior tumors are difficult to locate using current transrectal templates is well recognized with imaging such as magnetic resonance imaging assisting (reference 7 in article). However, can transperineal biopsy replace the need for imaging or, for that matter, transrectal biopsy? Prospective studies with definitive outcomes are required, but on the strength of the available data the future for transperineal biopsy is promising. Costs, access to operative time and urologist acceptance as well as another learning curve remain ahead.[2]

Nathan Lawrentschuk
Department of Surgery
University of Melbourne and
Ludwig Institute for Cancer Research, Austin Hospital
Melbourne, Victoria, Australia

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