Accuracy of Primary Systematic Template Guided Transperineal Biopsy of the Prostate for Locating Prostate Cancer: A Comparison With Radical Prostatectomy Specimens

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Abbreviations and Acronyms

AA = anterior apex
GS = Gleason score
L = lateral
NPV = negative predictive value
P = posterior
PA = posterior apex
PC = prostate cancer
PL = posterolateral
PPV = positive predictive value
PSA = prostate specific antigen
RP = radical prostatectomy
TP = transperineal
TR = transrectal
TZ = transition zone

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Purpose: We determined whether systematic template guided transperineal biopsies can accurately locate and sensitively detect prostate cancer. In addition, we reported discrepancies between diagnostic and pathological Gleason scores, and investigated whether prostate size had an effect on the cancer detection rate.
Materials and Methods: This retrospective diagnostic accuracy study compares the results of primary transperineal biopsies with the radical prostatectomy pathology of 414 consecutive patients treated at a single institution between November 2002 and August 2010.
Results: The average sensitivity and specificity for the detection of cancer in all prostates across all biopsy zones was 48% (95% CI 42.6–53.4) and 84.1% (95% CI 80–88.2), respectively. There was a statistically significant decrease in the sensitivity of transperineal biopsy in larger prostates ($t_{11} = 4.687$, $p = 0.001$). The overall Kappa value was 0.255 (95% CI 0.212–0.298). Grading concordance between biopsy and pathology specimens was achieved in 65.7% of patients. Upgrading of Gleason scores occurred in 25.6% of patients and downgrading occurred in 8.8%.
Conclusions: Our current transperineal biopsy method has only demonstrated fair agreement with the histopathology findings of the corresponding radical prostatectomy specimens. This finding is most likely due to the small, multifocal nature of prostate cancer in the patient series. The cancer detection rate was lower in larger prostates. Thus, clinicians may consider increasing the number of cores in larger prostates as a strategy to improve cancer detection.

Key Words: prostate, biopsy, organ size

VARIOUS TR biopsy schemes have failed to diagnose between 13% and 35% of tumors compared to the extensive biopsy schemes that have been in use recently.[1–6] Perhaps this is not unexpected given that standard TR biopsies neglect the sampling of some areas of the prostate that could harbor cancer. Since 25% to 55% of patients have disease in the TZ,[7,8] it is increasingly acknowledged that additional sampling of this area may further increase the yield of cancer detection. In addition, patients who have had TR biopsies frequently have more advanced cancer on the examination of RP specimens in terms of stage and grade.[9]

Clinicians need to be able to confidently identify patients who are suitable for active surveillance, focally targeted therapies or definitive treatments. Thus, there is a need to develop better methods of biopsy that can accurately localize and grade PC

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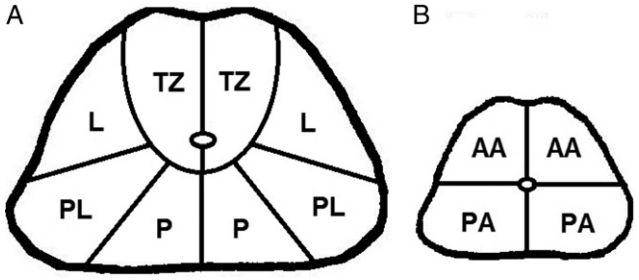

Figure 1. Axial views of 8 biopsy regions at base or proximal half of prostate (*A*) and 4 biopsy locations at apex or distal half of prostate (*B*).

while providing better estimates of tumor size and extent. While currently the most successful imaging modality is magnetic resonance imaging, there are particular challenges in detecting cancers in the transition zone.[10–18] In theory a systematic, template guided TP biopsy approach that allows sampling of all aggregate zones of the prostate should improve diagnostic accuracy with the previously mentioned requirements. However, this is yet to be measured against the gold standard histopathological examination of the entire prostate specimen. We address this issue directly in a retrospective analysis of patients treated at a high volume tertiary referral center.

PATIENTS AND METHODS

Patients

In August 2010 a retrospective study was conducted to determine the diagnostic accuracy of primary, systematic, template guided TP biopsy of the prostate. A total of 568 consecutive patients who had undergone TP biopsies with subsequent RP between November 2002 and August 2010 at St. Vincent's Hospital, Sydney, were identified in the database at the Garvan Institute of Medical Research. Excluding men who had previously undergone 1 or more biopsies, 414 patients for whom the interval between the primary diagnostic biopsy and prostatectomy was 6 months or less were included in the study. The general indications for primary TP biopsy in this series were based on the clinical suspicion of prostate cancer as guided by an increased PSA level, rising PSA values or abnormal digital rectal examination.

All patients had biopsies performed by 2 urologists (PDS or PB) at St. Vincent's Private Hospital, Sydney. Patients were also excluded from analysis if the standard 12-zone biopsy scheme was not used, or if they had received neoadjuvant radiotherapy or androgen ablation. Occasionally a subset of finger directed TR biopsies of palpable prostate masses was performed in addition to the standard TP biopsies, and these were omitted from the main body of TP biopsy results. Written informed consent was obtained from each patient who had undergone biopsy or RP. Ethics committee approval had been obtained before the commencement of this study (approval number H00-088).

Biopsy Technique

All patients received general anesthesia in an operating room while in a dorsal lithotomy position. A brachytherapy template grid mounted on a cradle which contained an ultrasound probe was placed next to the perineum. Systematic TP biopsies were performed in real time under direct visualization via TR ultrasound and using a brachytherapy template as a guide. An 18 gauge Tru-Cut® biopsy needle was used to obtain biopsies.

Typically 22 cores were taken from the 12 biopsy locations as designated in our standardized biopsy scheme (fig. 1). On each side of the base/proximal half of the prostate 3 biopsy cores were taken from the TZ, 2 from the P region, 2 from the PL region and 1 from the L region. In the apex/distal half of the prostate 2 cores were obtained from the PA and 1 from the AA.

Study Measures

The presence or absence of tumor in the 12 biopsy locations was compared with the corresponding RP specimen locations using the detailed cancer maps in the pathology reports. This information was used to determine whether biopsies were true/false-positive or negative by location. Sensitivity, specificity, PPV and NPV were calculated for each of the 12 zones. The average sensitivity and specificity values across all 12 zones were used to determine the overall accuracy of the biopsy approach.

The secondary end points were diagnostic GS (obtained from biopsies), pathological GS (obtained from histopathology findings of RP specimens) and prostate weight. Subgroup analyses by prostate weight (less than 50 gm vs 50 gm or greater) were performed to investigate the effects of prostate size on the diagnostic accuracy of the biopsy technique. Discrepancies between diagnostic and pathological GS were assessed for each patient (by analysis of the whole prostate rather than by zones). Upgrading of GS

Table 1. *Baseline characteristics*

	All Prostates	Small Prostates	Large Prostates
Age:			
Mean	60.9	59.8	62.2
Median	61.4	60.8	62.7
SD	7.48	7.00	7.74
95% CI	60.2–61.6	58.8–60.7	61.1–63.3
PSA (ng/ml):			
Mean	7.7	7.4	8.0
Median	6.3	5.9	6.7
SD	5.21	5.77	4.55
95% CI	7.2–8.3	6.6–8.2	7.3–8.6
No. of cores taken:			
Mean	23.5	23.4	23.3
Median	22	23	22
SD	5.72	5.29	5.87
95% CI	22.9–24	22.7–24.1	22.5–24.1
Tumor vol (cm^3):			
Mean	1.81	1.87	1.72
Median	1.50	1.60	1.30
SD	1.540	1.338	1.716
95% CI	1.65–1.96	1.68–2.06	1.48–1.97

Table 2. *Diagnostic accuracy of transperineal saturation biopsy*

	Rt						Lt					
	AA	PA	L	PL	P	TZ	AA	PA	L	PL	P	TZ
All prostates:												
Sensitivity (%)	42.2	41.1	37.7	59.8	51.1	58.9	35.4	47.4	44.6	60.0	44.8	53.1
Specificity (%)	85.7	89.2	81.6	93.0	87.2	75.0	86.9	81.8	79.0	88.1	90.3	71.5
PPV (%)	79.0	93.0	82.6	97.0	87.7	56.2	76.0	87.8	80.1	95.2	89.6	58.6
NPV (%)	53.8	30.5	36.2	37.7	49.8	77.0	53.5	36.0	43.0	35.9	46.6	66.7
Small prostates:												
Sensitivity (%)	46.2	46.6	37.4	60.3	52.1	65.3	38.2	54.0	56.6	65.5	50.0	57.0
Specificity (%)	83.0	84.6	82.6	93.9	84.8	75.8	84.7	80.0	76.1	88.6	89.1	67.5
PPV (%)	75.4	89.6	80.3	96.8	84.0	60.3	72.2	89.0	81.1	96.4	90.7	57.0
NPV (%)	57.8	35.8	41.0	43.4	53.6	79.5	56.8	36.7	49.1	35.2	45.6	67.5
Large prostates:												
Sensitivity (%)	38.1	36.6	38.1	59.8	49.6	53.7	33.3	39.4	33.6	53.2	37.9	48.2
Specificity (%)	87.7	97.4	80.8	91.4	90.6	73.5	88.2	82.5	80.9	86.7	90.7	74.6
PPV (%)	81.8	98.3	84.8	97.0	91.8	50.7	79.2	84.8	77.2	93.2	87.0	58.6
NPV (%)	49.3	26.6	31.6	32.7	46.0	75.8	49.7	35.3	38.7	35.1	46.9	65.9

in a patient was defined as the pathological GS being higher than the diagnostic GS, with the converse definition for downgrading. Baseline characteristics such as age at prostatectomy, PSA at biopsy, number of biopsy cores taken, tumor volume and pathological stage were also recorded.

All histopathological reviews were conducted by experienced uropathologists with each prostate specimen being 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 on a prostate cancer map. The total tumor volume for each RP specimen was calculated using a 3-dimensional volume estimation method as reported by Chen et al and recommended by the Royal College of Pathologists of Australasia.[19]

Cohen's Kappa statistical test was used to measure the level of agreement between the results of biopsies and RP findings by location. The paired t test was used for comparison of the stratified groups according to prostate weight and $p < 0.05$ was considered significant. Statistical calculations were performed using SPSS® Predictive Analytics Software Statistics GradPack 18 for Microsoft Windows.

RESULTS

A mean of 23.5 biopsy cores (range 13 to 43) was obtained from each patient (median 22, 95% CI 22.9–24). The mean age of all patients at RP was 60.9 years (95% CI 60.2–61.6) with a mean pre-biopsy PSA of 7.7 ng/ml (95% CI 7.2–8.3). Of the men 63.3% were given a pathological stage of T2, while a staging of T3a and T3b occurred in 29% and 7.7%, respectively. Of 414 patients 15 were omitted from the subgroup analysis of prostate size because prostate weights were not recorded in the pathology reports. Mean prostate weight was 52.4 gm (95% CI 50.7–54.1). The small prostate group (defined as less than 50 gm) consisted of 200 patients and the large prostate group (defined as 50 gm or more) included 199 men. The baseline characteristics of age, pre-biopsy PSA, number of biopsy cores taken and tumor volume are presented in table 1.

The average sensitivity and specificity in the detection of tumors across all 12 prostate zones in all prostates was 48% (95% CI 42.6–53.4) and 84.1% (95% CI 80–88.2), respectively. The biopsy location with the greatest accuracy was the PL zone, which had a combined sensitivity of 59.9% bilaterally. The biopsy locations with the lowest accuracy were the AA and L zones with sensitivity of 38.8% and 41.2%, respectively (table 2). For smaller prostates the average sensitivity and specificity was 52.4% (95% CI 46.5–58.3) and 82.5% (95% CI 78.1–87), respectively, compared with larger prostates, for which averages were 43.5% (95% CI 37.8–49.1) and 85.4% (95% CI 80.9–89.9), respectively. The decrease in the sensitivity of biopsy of larger prostates was statistically significant on the paired t test ($t_{11} = 4.687$, $p = 0.001$).

There was a statistically significant difference in the level of agreement between small and large prostates ($p = 0.001$), with Kappa values of 0.287 (95% CI 0.241–0.333) and 0.218 (95% CI 0.176–0.260),

Table 3. *Kappa values for each of the 12 biopsy locations*

	AA	PA	L	PL	P	TZ
Rt:						
All prostates	0.263	0.180	0.142	0.343	0.328	0.335
Small prostates	0.285	0.216	0.161	0.389	0.335	0.403
Large prostates	0.230	0.169	0.125	0.300	0.321	0.268
Lt:						
All prostates	0.214	0.208	0.198	0.312	0.288	0.248
Small prostates	0.227	0.244	0.291	0.338	0.312	0.245
Large prostates	0.196	0.156	0.115	0.263	0.241	0.233

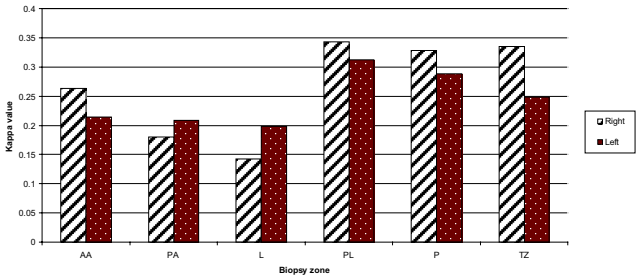

Figure 2. Kappa values of 12 biopsy zones in all prostates

respectively. Across all biopsy zones the overall Kappa value was 0.255 (95% CI 0.212–0.298), demonstrating only a fair level of agreement. Individual Kappa values for each of the 12 biopsy zones are listed in table 3 and figure 2.

The most common pathological Gleason score in all prostates was 3 + 4 at 56.3% (table 4). Grading concordance between biopsy and pathology was achieved in 65.7% of patients (table 5). Upgrading of Gleason scores between the biopsy and RP specimen was observed in 25.6% of patients, while downgrading occurred in 8.8%.

DISCUSSION

Our study is the first to our knowledge to report the sensitivity of in vivo systematic TP biopsies compared to whole mount prostates. When divided into the 12 biopsy zones the accuracy of tumor detection was less than anticipated, with an average sensitivity of 48% and a mean Kappa value of 0.255. The AA and L zones had the lowest correlation. The most likely explanation for this finding is that only 1 biopsy core is routinely taken on each side of the prostate in these regions. However, tiny cancer foci may still be missed even when a large number of biopsy cores is obtained. It is conceivable that any biopsy scheme will be suboptimal compared to whole gland analysis due to inherent errors in sampling. In our observation of the cancer maps of RP specimens, tumors missed on biopsy are often the nondominant, small foci of cancers (fig. 3). Although we did not record the proportion of prostates with unifocal disease, other studies have reported that only 13% to 38% of patients have a single focus of cancer, indicating that a majority of cancers are multifocal.[20–22]

Upgrading and downgrading of biopsy GS occurred in 25.6% and 8.8% of patients, respectively. This appears to be a significant improvement compared to a study by Isariyawongse et al in which 2,963 men had undergone TR biopsies and subsequent RP.[9] In their study upgrading and downgrading for the standard sextant TR biopsy group occurred in 42.9% and 15.7% of men, respectively, and in 39.5% and 9.8% of men in the extended TR biopsy group. The greater grading accuracy in our TP biopsy protocol is likely due to the higher number of biopsy cores and the anterior prostate being examined. This has been demonstrated in a study of staging TP or 3-dimensional mapping biopsies vs TR biopsies by Onik et al.[23] The mean number of cores taken in staging biopsies was 52.17 for TP and 13.19 for TR biopsies, and 17% of TR biopsy GSs were upgraded by the staging biopsies performed in the same patients.

The effect of prostate size on the PC detection rate has been previously described by other authors.[6,24,25] For a fixed number of biopsy cores the likelihood of detecting cancer decreases as prostate size increases. Our data have similarly shown that larger prostate size is associated with a lower correlation between biopsy and RP pathology findings. There was a statistically significant difference in the sensitivity of biopsy between small and large prostates (52.4% vs 43.5%, $p = 0.001$). The level of agreement between biopsy and pathology results was also significantly higher in small prostates ($t_{11} = 4.196$, $p < 0.0001$). This finding adds to the consensus views in the literature that increasing the number of biopsy cores is an appropriate strategy for patients with larger prostates.

A major limitation of our study is that the accuracy yields reported here cannot be used in comparison with other published methods of template guided TP biopsies with similar biopsy protocols. In those studies the unaccounted number of patients who had negative biopsies when they actually had

Table 4. *Percentages of prostates categorized by diagnostic and pathological Gleason scores*

	All Prostates (%)		Small Prostates (%)		Large Prostates (%)	
Gleason Scores	Diagnostic	Pathological	Diagnostic	Pathological	Diagnostic	Pathological
3+3	21.0	10.9	15.5	5.5	25.6	16.1
3+4	52.9	56.3	58.0	61.0	49.2	52.8
4+3	18.1	23.7	19.5	24.0	17.6	24.1
4+4	3.6	3.9	3.5	4.0	3.0	3.0
4+5	3.6	4.3	3.5	4.5	3.5	3.5
5+4	0.7	1.0	0	1.0	1.0	0.5

cancer precludes any meaningful comparisons with our data. Another limitation is that our study could not provide information on how the volume of each tumor focus may correlate with the sensitivity of our biopsies. Total tumor volumes were estimated from the combined volumes of the 3 largest tumor foci in each prostate as recommended by local guidelines. Determination of volume in every tumor focus would be labor intensive and this level of detailed data was not available in the pathology reports. Another consideration is the higher cost implications with systematic TP biopsies due to the use of general anesthesia compared to in-office TR biopsies. The increased number of cores for analysis also increases the workload for pathologists.

Although systematic TP biopsy is by no means a perfect method of evaluating PC, it offers the advantage of better grading accuracy compared to standard TR biopsies in other studies.[7] Staging biopsies by greatly increasing the number of biopsy cores to 50 or more is likely to further improve the accuracy of localization and grading of tumors.[6,23,25] However, studies using this extensive biopsy protocol have reported higher complication rates with, most notably, acute urinary retention in up to 38% of patients.[6] In contrast, the urinary retention rate in our study was 4.5%. Another issue with staging biopsies is the potential for extensive fibrosis around the prostate that could be encountered during RP. The subsequent difficulty at surgery may negate any perceived benefit of detailed preoperative cancer mapping. Barzell and Melamed noted that 57% of patients who underwent RP after a staging biopsy had extensive fibrosis and preservation of the neurovascular bundle was not possible in the majority.[25] In contrast, all patients in our series had undergone bilateral nerve sparing RP despite the fibrosis encountered. Thus, staging biopsies should be reserved for patients treated with active surveillance, brachytherapy or cryoablation where detailed cancer maps are most beneficial.

When biopsy locations and the number of biopsy cores can be optimized for a given prostate size, systematic TP biopsies may currently be the best initial diagnostic biopsy strategy available. The TP approach allows better and easier access in sampling the anterior part of the prostate. A systematic biopsy scheme targets all areas of the gland for biopsy and, therefore, is considered a more complete assessment of the prostate compared to standard TR biopsies. The use of a template reduces the sampling error inherent in freehand biopsies. This is particularly relevant when taking large numbers of biopsy cores in smaller prostates. Without the grid it is easy to inadvertently sample the same area as the previous biopsy due to errors in visual recall. Another advantage of the TP approach is the avoidance of potential complications in needling through an irradiated rectum in some patients.

Table 5. *Discrepancies between diagnostic and pathological Gleason scores*

	All Prostates (%)	Small Prostates (%)	Large Prostates (%)
Same	65.7	66.5	64.8
Downgraded	8.8	7.0	10.5
Upgraded	25.6	26.5	24.6

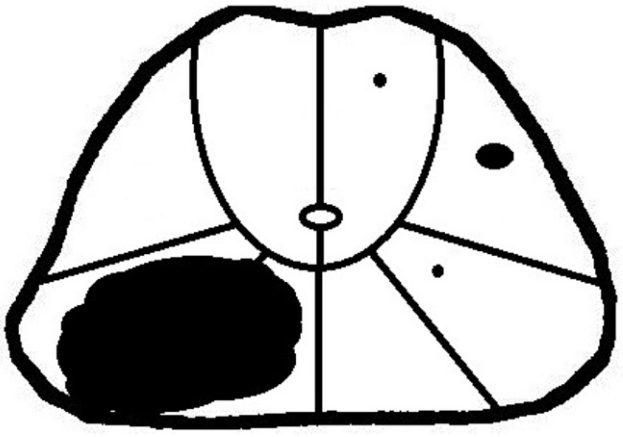

Figure 3. Common appearance of prostate cancer map. Black areas represent locations of tumors found on histopathology of RP specimen.

CONCLUSIONS

Our systematic TP biopsy method has only demonstrated a fair level of agreement with the histopathology findings of RP specimens. This is most likely due to the small, multifocal nature of PC. Optimizing the number of biopsy cores in accordance with prostate size is recommended to improve the diagnostic accuracy in tumor grading and localization. In the selection of patients for active surveillance or focal therapy, a template guided TP staging biopsy may be the best biopsy strategy for excluding patients with clinically significant disease and for localizing cancers.

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EDITORIAL COMMENT

The authors have written an interesting analysis of the accuracy of template guided transperineal prostatic biopsies to diagnose men with prostate cancer. This technique should not be confused with transperineal staging biopsies, which are performed to better select patients for targeted focal therapies or active surveillance.[1]

The number of biopsies taken per prostate volume is an important determinant of biopsy accuracy, whether transrectal or transperineal.[2] Men with larger prostates should be considered candidates for an increased biopsy count.

Does this biopsy scheme demonstrate improved detection of a dominant tumor or highest grade cancer in any single patient? Many lesions prove to be small and clinically insignificant (thus accounting for the lower sensitivity). Future analysis could examine results on a whole patient basis rather than by prostate zones to better inform clinical decision making. Advantages provided by this technique should be appropriately balanced by the need for general anesthesia over the ease of in-office TR biopsies.

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REPLY BY AUTHORS

Rove and Crawford raise a number of issues on which we have additional information that may be of interest. We agree with the statement that "men with larger prostates should be considered candidates for increased biopsy count." In response to the findings of this study, our institution has made adjustments to the biopsy protocol by increasing the number of biopsy cores in larger prostates (with increased sampling in the anterior/transition and lateral peripheral zones in particular).

In terms of dominant tumor detection, we observed that cancers missed by TP biopsies tended to be small and clinically insignificant while dominant tumors were detected. The important clinical question of whether the detection of dominant tumors is improved with our biopsies compared to other techniques requires a different study design. All the patients in this study underwent radical prostatectomy due to the positive result of our biopsies. Analysis on a whole gland basis rather than by prostate zones would produce 100% sensitivity in this study group.

Other merits of our TP biopsy procedure have been demonstrated in other studies yet to be published. For example, when we compared patients who underwent TP vs TR biopsies, the anteriorly located tumors were more prevalent in the TP group. This finding implies that anterior cancers can be detected earlier with TP biopsies. In addition, the septicemia rate was lower in our TP biopsies compared to the average rate in our national audit of TR biopsies (0.2% vs 2.2%).