Success of targeted transperineal biopsy in patients on surveillance for grade group 1 prostate cancer

Kevin Martell[1,2], Hans Chung[1], Gerard Morton[1], Danny Vesprini[1], Chia-Lin Tseng[1], Ewa Szumacher[1], Patrick Cheung[1], Will Chu[1], Stanley Liu[1], Andrew Loblaw[1,3]

[1]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; [2]Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [3]Institute for Health Policy, Measurement and Evaluation, University of Toronto, Toronto, ON, Canada

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Abstract

Introduction: We aimed to determine the minimum cross-sectional ellipsoid area on magnetic resonance (MR) of intraprostatic nodules that best predicts for subsequent targeted biopsies revealing ≥ grade group (GG) 2 disease.

Methods: Forty-six patients previously diagnosed with GG 1 prostate adenocarcinoma who received cognitively fused, MR-guided, transperineal targeted biopsies in addition to six random biopsies were included in this analysis. A Youden cutpoint analysis was used to determine the ellipsoid area in the axial plane best predicting for ≥GG 2 disease within the targeted biopsy cores and logistic regression used to assess the result.

Results: Median time from MR imaging to targeted biopsy was 2.4 (1.4–5.5) months. Forty of 46 (87%) patients had one nodule and 6/46 (13%) had two separate nodules on MR that received targeted biopsy. Of the 52 nodules, five (10%), 33 (63%), and 14 (27%) were Prostate Imaging-Reporting and Data System (PI-RADS) 3, 4, and 5, respectively. Thirteen (25%), six (12%), and 33 (64%) were in the anterior, medial, and posterior regions of the prostate, respectively. Median area was 0.72 (0.49–1.29) cm^2 (average diameter 9.5 mm). Fifteen of 46 (33%) patients had ≥1 random biopsy and 20/52 (38%) nodules had ≥1 targeted biopsy revealing ≥GG 2 disease. The optimal area cutpoint was ≥0.7 cm^2, with an area under the curve of 0.671 (0.510–0.832). On logistic regression, area ≥0.7 cm^2 was solely predictive of targeted biopsy revealing ≥GG 2 disease (odds ratio 6.5, 1.3–32.4, p=0.022).

Conclusions: Nodule area ≥0.7 cm^2 may predict for transperineal-based targeted biopsies being positive for ≥GG 2 disease when 1–2 cores are taken.

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy in North American men.[1] With increasing life expectancy and changes in screening patterns, the incidence of prostate cancer in Canadian men is estimated to double by 2030.[2] Despite recent changes in screening guideline recommendations, over 90% of men are diagnosed with localized disease.[3] Of these, a considerable number of patients are initially diagnosed with low-risk disease after transrectal ultrasound (TRUS)-guided biopsy. In these patients, active surveillance allows for significant delays in times to treatment and treatment-related toxicity without impacting survival outcomes.[4]

The outcomes of active surveillance may be dependent on how representative biopsy specimens are of true disease extent. In this regard, randomly sampled TRUS-guided biopsies have been known to under-quantify the disease when compared to prostatectomy specimens.[5] Magnetic resonance (MR) imaging-guided biopsies have been shown to increase the sensitivity and specificity of TRUS-guided biopsy for pathological disease progression.[6] Because of this, use of MR imaging and targeted biopsies of MR nodule(s) is becoming commonplace in patients on active surveillance.[7] Despite this, little is known about the diagnostic accuracy of MR imaging-guided biopsies as it relates to nodule size or location within the prostate. On the assumption that smaller nodules would have a higher probability of geographic miss at the time of biopsy, this study aimed to determine the minimal ellipsoid cross-sectional area on MR (eA) in the plane perpendicular to the biopsy that would be associated with Gleason grade group (GG) 2 or higher disease on targeted biopsy (TBx) specimens.

Methods

In this quality assurance study, the electronic medical records were retrospectively reviewed from 95 patients eligible for

active surveillance and receiving MR-guided transperineal TBx at a large-volume center with considerable expertise in TRUS-guided procedures between December 2015 and May 2019. Patients were included in review if they had an initial systematic TRUS-guided biopsy positive for GG1 disease and went on to have MR imaging, then transperineal-based MR to TRUS cognitively fused TBx of the MR nodule(s), and additional transperineal systematic biopsies. In lieu of a formal ethics committee, the principles of the Helsinki Declaration were followed.

Active surveillance and MR imaging procedures

Patients with low-risk and selected low-volume GG 2 prostate cancer were recommended active surveillance.[8] Over the study period, patients were often offered multiparametric MR imaging as an alternative to routine repeat biopsy based on previous work from our center.[9] MRs uniformly included T2, T1, and diffusion-weighted imaging (DWI) sets. Reporting was systematic and incorporated information about T2 signal intensity changes, dynamic contrast enhancement, and diffusion restriction, with corresponding DWI and ADC map changes according to the Prostate Imaging and Data Reporting System (PI-RADs).[10] All lesions were measured in the axial plane on T2 image sets for width (left-right dimension) and height (ant-post dimension). Measurements of length (superior-inferior dimension) were not routinely reported but, when available, were based on the sagittal plane on T2 image sets. All nodule(s) were measured independently of one another, and locations were described according to laterality (left gland, right gland), prostate region (apex, mid-gland, base), and relative position to the rectum (anterior gland, medial gland, posterior gland). Patients were recommended TBx when new or changing nodule(s) were identified on MR imaging or nodule(s) were identified that were unlikely to have been sampled at the time of TRUS-guided standard biopsy (e.g., nodules within the anterior prostate gland). Prostate-specific antigen (PSA) changes alone were considered insufficient for recommendation of TBx.

Biopsy procedures

Initial biopsies for all patients were transrectal sextant biopsies using TRUS guidance and procedures that are well-described elsewhere.[11] In brief, patients consenting to biopsy received prophylactic antibiotics and underwent an enema two and four hours prior to procedure. Then, within the interventional radiology suite, the TRUS probe was inserted. With good visualization of the prostate both left and right (bilateral) apex, mid-gland and base were sampled. Biopsies either consisted of six or 12 total cores, with some 12-core samples being combined according to prostate sextant (i.e., 12 cores submitted as six specimens).

For TBx, the institutional standard of transperineal prostate biopsies was adopted.[12,13] In brief, patients were given prophylactic antibiotics and underwent enema at least two hours prior to the procedure. They then presented to the procedure suite, where, with legs raised in stirrups, a TRUS probe was inserted into the rectum. The perineum was sterilized and local anesthetic was infiltrated both into the skin surface, and then into the periprostatic nerve bundles bilaterally under direct ultrasound visualization. Biopsies were then taken systematically from the bilateral anterior, medial, and posterior gland based on both axial and sagittal ultrasound images. TBx were then directed to the region of prostate where MR disease was visualized based on cognitive fusion. Although it varied according to physician practice, most nodules underwent at least two TBx. Physicians performing the biopsies were either radiation oncologists with considerable transperineal-based prostate brachytherapy experience or prostate brachytherapy fellows under their direct supervision.

Pathological reporting

All specimens underwent routine central review by dedicated genitourinary pathologists. Individual reporting for each sample was accompanied by synoptic reporting with overall GG. For each tissue sample, both GG and percentage of core tissue positive for cancer was available. For initial biopsies (transrectally acquired), individual specimens were recorded according to prostate laterality and region (apex, mid-gland, base) in most patients. Some tissue samples were aggregate and only synoptic reporting was available. For random biopsies at the time of transperineal TBx, individual specimens were recorded according to prostate laterality and relative position to the rectum (anterior, medial, or posterior gland). TBx were recorded according to the corresponding MR nodule(s) and sample number (e.g., nodule 1, biopsy 2).

Statistical methods

The Shapiro-Wilks test of normality was used to determine normality in all variables. Descriptive statistics were used to describe the cohort. Normally distributed variables were described using the mean and standard deviation, and non-normally distributed variables were described using median and interquartile range (IQR). For binomial and ordinal variables, absolute count and percentages were used. For MR nodules, the ellipsoid formula was used to calculate an eA of the nodule in the axial plan (area = pi*a*b) where "a" is the width/2 and "b" is the height/2 of the lesion. Logistic regression modelling was then employed on the combined cohort of all targets biopsied to determine if prespecified factors, including eA of the nodule (as a continuous variable), number of biopsy cores taken (as a continuous variable),

PI-RADS score (as an ordinal variable), and nodule location (anterior, medial or posterior; a division that determines biopsy difficulty based on the performing center's clinical experience; note: all lesions crossing the medial aspect of the gland were considered as having medial disease for this analysis) were predictive of nodule being positive for GG 2 or higher disease (binomial yes/no). Finally, a Youden-based area under the receiver operator curve analysis was performed on the eA of the dominant intra-prostatic lesion (DIL) on MRI to determine if a specific cutpoint for DIL eA would be more predictive of biopsy positivity for GG 2 or higher disease. The cutpoint found was then used as a binomial variable and the logistic regression analysis repeated.

Results

Between July 2015 and May 2019, a total of 95 patients receiving a total of 101 MRI-guided transperineal TBx procedures were identified. Of these, 14 patients did not have an initial non-TBx and were excluded from the primary analysis. A further 14, six, and one patients had no disease, GG 2, and 3 disease on initial non-TBx, respectively, and were excluded. A further 14 patients did not have complete systematic biopsies at the time of transperineal TBx and were excluded. Finally, one patient remained with two separate TBx procedures. In this case, the first TBx procedure was used. This left a final cohort of 46 patients receiving 46 transperineal TBx procedures. Within this cohort, 26 patients had an initial transrectal biopsy with detailed initial pathological reporting a median of 24 (9–44) months prior to their MR. Their regions of biopsy positivity are described in Table 1.

The median time from MRI to transperineal TBx was 2.4 (1.4–5.5) months. Forty of 46 (87%) had one nodule and 6/46 (13%) patients had two separate nodules identified on MRI that were targeted on transperineal biopsy. Within the 52 nodules that eventually went on to have targeted biopsies, five (10%) were PI-RADS 3, 33 (63%) were PI-RADS 4, and 14 (27%) were PI-RADS 5. Median eA of the nodules was 0.72 (0.49–1.29) cm^2. The nodule locations are described in Table 2.

Random biopsy results at the time of transperineal TBx are described in Table 3. Overall, 21 (46%) patients were diagnosed with higher-grade disease after the transperineal biopsy procedure. Fifteen (32%) patients had at least one random biopsy core positive for GG 2 or higher disease at the time of transperineal TBx (11 [24%] had one core positive and four [9%] had two cores positive).

Three (7%) patients had overall GG 3 disease after the TBx procedure (Table 4). Eighteen (39%), 18 (39%), and seven (15%) had GG 2, 1, and no disease, respectively, based on the TBx procedure. A total of six (13%) patients had TBx cores with GG 2 or higher disease and either GG 1 or no disease on random biopsy cores.

When considering the 52 TBx as individual events, a total of 20 (38%) biopsy targets came back as harboring GG 2 or higher disease. On logistic regression modelling, no factors significantly predicted for TBx coming back as positive for GG 2 or higher disease.

The receiver operator curve analysis revealed a cutpoint of eA >0.69cm^2 as predictive for a DIL biopsy positive for GG 2 or higher disease, with an area under the curve of 0.671 (0.510–0.832) (Supplementary Figure 1; available at *cuaj.ca*). For this cutpoint, sensitivity was 80%, specificity was 63%, and the positive and negative predictive values were 57% and 83%, respectively. Twenty-eight of 52 (54%) targets had eA ≥0.7cm^2. Sixteen of 28 (57%) of targets ≥0.7 cm^2 and four of 24 (17%) of targets <0.7 cm^2 were positive for GG 2 disease (Fisher's p=0.004).

The logistic regression analysis was performed again using an eA cutpoint of ≥0.7 cm^2 or <0.7 cm^2. Within this model, only the eA cutpoint predicted for TBx coming back as positive for GG 2 or higher disease (odds ratio [OR] 6.5, 1.3–32.4, p=0.02). Table 5 shows the regression analyses.

Twenty-eight (51%) of the 55 excluded patients did not have systematic biopsies at the time of TBx. Retrospectively, their MRI and TBx results were reviewed. In these patients, the median time from MRI to transperineal TBx was 1.6 (1.3–2.1) months. Twenty of 28 (71%) patients had one nodule and 8/28 (29%) had two separate nodules identified on MRI that were targeted on transperineal biopsy. Within the 36 nod-

Table 1. Initial (at diagnosis) non-targeted transrectal biopsy characteristics for cohort of 26 patients with detailed pathological reporting in the included cohort and 23 patients with detailed pathological reporting in the excluded cohort

	Number of patients (%) n=26	Median (IQR) of positive patients	Number of excluded patients (%) n=23	Median (IQR) of positive excluded patients
Left apex tissue positive	12 (46%)	5 (4–20)	7 (30%)	15 (5–20)
Left mid-tissue positive	7 (27%)	20 (5–50)	6 (26%)	10 (5–20)
Left base tissue positive	8 (31%)	20 (8–35)	5 (22%)	25 (20–30)
Right apex tissue positive	14 (54%)	9 (5–30)	7 (30%)	20 (15–30)
Right mid-tissue positive	4 (15%)	10 (2–20)	6 (26%)	15 (10–20)
Right base tissue positive	7 (27%)	22 (10–40)	6 (26%)	15 (10–20)

Values are count data (%) for the cohort and median (interquartile range [IQR]) of percentage of positive tissue in those with zone biopsies positive. For example, in the 12 patients with left apex tissue positive, median percentage of core positivity was 5 (4–20)%.

Table 2. Nodule locations on MR imaging

	No/other	AA	AM	AP	MA	MM	MP	BA	BM	BP
AA	4 (8%)	–	–	–	–	–	–	–	–	–
AM	1 (2%)		–	–	–	–	–	–	–	–
AP	10 (20%)			–	–	–	–	–	–	–
MA	2 (4%)	3 (6%)								
MM	2 (4%)					–	–	–	–	–
MP	14 (27%)			3 (6%)		1 (2%)	–	–	–	–
BA	1 (2%)				3 (6%)			–	–	–
BM								1 (2%)	–	–
BP	3 (6%)						3 (6%)		1 (2%)	–

AA: apex anteriorly; AM: apex medially; AP: apex posteriorly; BA: base anteriorly; BM: base medially; BP: base posteriorly; MA: mid-gland anteriorly; MM: mid-gland medially; MP: mid-gland posteriorly; MR: magnetic resonance.

ules that eventually went on to have TBx, eight (22%) were PI-RADS 3, 15 (42%) were PI-RADS4, and 13 (36%) were PI-RADS 5. Median eA of the nodules was 1.02 (0.59–1.52) cm^2 on MRI. Of these targeted biopsies, 11 (31%) specimens were negative for disease, 14 (39%) harbored GG 1 disease, nine (25%) harbored GG 2 disease, and two (6%) harbored GG 3 disease. Within these nodules, median number of cores taken from each target was two (2–3), median number of targeted cores positive was one (0–2), and median percentage of TBx tissue positive was 20 (0–60)%. When considering the 25 (69%) targets within this cohort with eA ≥0.7 cm^2, nine (36%) harbored GG 2 or higher disease. When considering the 11 (31%) targets within this cohort with eA <0.7 cm^2, two (18%) harbored GG 2 or higher disease.

Discussion

This retrospective analysis of targeted transperineal biopsies based on cognitive fusion between MR imaging and real-time ultrasound at the time of biopsy confirmed a positive association between the area of nodule calculated as an ellipsoid in the plane perpendicular to biopsy and the likelihood of biopsy specimens harboring GG 2 or higher disease. The finding that nodules ≥0.7 cm^2 were more likely to harbor clinically significant disease is novel and, if validated in future studies performed at other centers, would guide clinical practice.

With an increasing role for MRI with or without MR TBx in the active surveillance based management of prostate cancer, there will be an increasing emphasis on defining MR features that predict for clinically relevant disease.[7,14,15] Despite its intuitive nature, as smaller nodules would theoretically be less likely to be accurately targeted on biopsy, to date, this is the first study that correlates MR nodule size with TBx results. Of note, several studies have examined the relationship between prostatectomy specimens and MR findings.[16,17] In one notable study, Kim et al found that both tumors >1 cm^3 and tumors harboring GG 2 or higher disease were more likely to correlate with abnormal MR imaging.[16] Although it is difficult to compare with the present study, given the difference in approach and methodology, there is agreement in nodule size correlating with clinically significant disease, with ≥0.7 cm^2 eA having higher rates of disease. Furthermore, within the present study, the overall detection rate of disease that would change management recommendations (≥GG 2 disease) was not insignificant.

Table 3. Overall biopsy (random biopsy and targeted biopsy) and random biopsy (RBx) results at the time of targeted biopsy (TBx) for 46 patients receiving targeted transperineal biopsies

	Number of patients (%) n=46	Median (IQR) of positive patients	GG 1 n (%)	GG 2 n (%)	GG 3 n (%)	GG 4 n (%)
Any RBx or TBx positive	39 (85%)	8 (5–15)	18 (39%)	18 (39%)	3 (7%)	0 (0%)
Any ant RBx positive	22 (48%)	3 (1–8)	15 (33%)	5 (11%)	1 (2%)	1 (2%)
Any med RBx positive	20 (43%)	5 (2–7)	14 (30%)	3 (7%)	3 (7%)	0 (0%)
Any post-RBx positive	20 (43%)	5 (2–8)	14 (30%)	5 (11%)	1 (2%)	0 (0%)
Left ant RBx positive	13 (28%)	20 (10–40)	10 (22%)	2 (4%)	1 (2%)	0 (0%)
Left med RBx positive	12 (26%)	20 (7–30)	7 (15%)	3 (7%)	2 (4%)	0 (0%)
Left post-RBx positive	11 (24%)	10 (5–50)	7 (15%)	3 (7%)	1 (2%)	0 (0%)
Right ant RBx positive	16 (35%)	10 (5–40)	12 (26%)	3 (7%)	0 (0%)	1 (2%)
Right med RBx positive	14 (30%)	13 (5–40)	13 (28%)	0 (0%)	1 (2%)	0 (0%)
Right post-RBx positive	16 (35%)	30 (10–50)	14 (30%)	2 (4%)	0 (0%)	0 (0%)

Table 4. Targeted biopsy results for 46 patients receiving targeted transperineal biopsies

	First target n=46	Second target n=6
Number of cores taken within target	2 (1–2)	1 (1–2)
Number of targeted cores positive	1 (1–2)	1 (0–1)
Percentage of biopsy tissue positive, %	35 (5–60)	5 (0–50)
Grade group of targeted biopsies		
No disease	11 (24%)	2 (33%)
1	17 (37%)	2 (33%)
2	17 (37%)	2 (33%)
3	1 (2%)	0 (0%)

Values are given as median (interquartile range) or number (%) as appropriate.

Table 5. Rank discrimination indices and OR for each factor explored on logistic regression analysis

	eA used as a continuous variable	eA cutpoint of ≥0.7 cm² used
Somer's D	0.55	0.64
eA, cm² (0.49 vs. 1.27) or (≥0.7 vs. <0.7)	1.3 (0.5–3.2, p=0.64)	6.5 (1.3–32.4, p=0.02)
Number of targeted biopsies (2 vs. 1)	0.5 (0.2–1.4, p=0.19)	0.5 (0.2–1.3, p=0.16)
PI-RADS score (5 vs. 3)	22.3 (0.8–592.5, p=0.06)	9.7 (0.7–138.5, p=0.09)
Nodule location (A vs. P)	0.5 (0.1–3.4, p=0.23)	0.5 (0.1–2.6, p=0.14)
Nodule location (M vs. P)	2.3 (0.4–14.8, p=0.457)	3.0 (0.4–22.4, p=0.4)

Data are presented as either the rank discrimination index or the odds ratio (OR) (95% confidence interval of the estimate, p-value). A: anterior; eA: minimal ellipsoid cross-sectional area; M: mid-gland; PI-RADS: Prostate Imaging-Reporting and Data System; P: posterior.

Overall, 46% of patients had GG 2 or higher disease after transperineal biopsy; 13% of patients had GG 2 or higher disease detected solely on the bases of TBx. These rates are similar to those reported by Recabal et al (35% of men diagnosed with higher-grade disease based on TBx).[18] In the present cohort, it is possible that patients upstaged based on systematic biopsies alone could be due to physicians' adherence to random transperineal biopsy sampling methodology. Specifically, it is possible that regional systematic cores were either consciously or subconsciously focused towards areas nearby the known MR nodules. This possibility seems to be supported by the results of Elkhoury et al, where the detection of ≥GG 2 prostate cancer were 15%, 47%, and 60% in biopsy-naive patients receiving systematic biopsy only, TBx only, or targeted and systematic biopsies, respectively.[19]

Perhaps the largest potential implication for the present study is the potential impact on MR-based active surveillance programs.[20,21] Although the ASIST study was notably negative in finding utility for MR imaging based TBx in addition to systematic biopsy, this was importantly a study of patients who were undergoing repeat biopsy as part of their surveillance protocol.[21] Many clinicians consider MR changes as an indication for repeat biopsy in patients already on active surveillance (as is the practice at the study institution). In this paradigm, the current study holds considerable value, as it suggests that the utility of biopsy is limited when small MR nodules are detected. These findings suggest that MR-based active surveillance protocols that use nodule size and/or other features could be made to maximize the odds of detecting clinically relevant disease. Hence, future study and validation of these results is warranted, as they may allow future patients to avoid unnecessary repeat biopsies.

Limitations

There are several limitations to the present study that necessitate the need for validation and future study. The first of these is the small cohort size (46 patients) and retrospective nature. Furthermore, the study center is a quaternary cancer center that sees a high volume of patients and the physicians performing the biopsy procedures have considerable transperineal prostate procedural experience. The same target positivity rates may not be achieved by physicians with less experience or comfort with transperineal procedures. Beyond this, the use of MR fusion software could lead to differences in targeting accuracy and results that differ from the present study. Otherwise, this study is not translatable to transrectal biopsies, given the nature of the calculated cross-sectional area; however, if calculated in the superior/inferior and left/right dimensions, it may be possible to apply the present result. Finally, as the number of TBx was limited to two samples of most nodules, these results may not be applicable for cases where five or six TBx are obtained.

Conclusions

In this retrospective analysis of transperineal targeted biopsies of MR-identified nodules cognitively fused to real-time ultrasound images, nodules with ellipsoid area ≥ 0.7 cm² in the plane perpendicular to the biopsy (the axial plane) were more likely to be positive for GG 2 or higher disease when 1–2 cores were taken.

This paper has been peer-reviewed.

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Correspondence: Dr. Andrew Loblaw, Sunnybrook Health Sciences Center, Toronto, ON Canada; andrew.loblaw@sunnybrook.ca