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Prostate Cancer

Active Surveillance Magnetic Resonance Imaging Study (ASIST): Results of a Randomized Multicenter Prospective Trial

Laurence Klotz[a,], Andrew Loblaw[a], Linda Sugar[b], Madeline Moussa[c], David M. Berman[d], Theo Van der Kwast[e], Danny Vesprini[a], Laurent Milot[b], Marlene Kebabdjian[b], Neil Fleshner[f], Sangeet Ghai[f], Joe Chin[c], Gregory R. Pond[g], Masoom Haider[b]*

[a] Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [b] Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; [c] University of Western Ontario, London, ON, Canada; [d] Queen's University, Kingston, ON, Canada; [e] University Health Network, Toronto, Canada; [f] Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; [g] McMaster University, Hamilton, ON, Canada

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Abstract

Background and objective: This study aimed to determine, in men recently diagnosed with grade group 1 (GG1) prostate cancer, if magnetic resonance imaging (MRI) with targeted biopsy could identify a greater proportion of men with GG ≥2 cancer on their confirmatory biopsy compared with systematic biopsies. The study was registered with www.clinicaltrials.gov (NCT01354171).
Design, setting, and participants: This study is a prospective, randomized, multicenter, open-label trial. Eligible patients were men diagnosed with GG1 cancer within 1 yr prior to study entry in whom a confirmatory biopsy was indicated. Patients were randomized to 12-core systematic biopsy or MRI with systematic and targeted biopsy using the Artemis fusion targeting system. The primary end point was the proportion upgraded to GG ≥2 in each arm.
Results and limitations: In total, 296 men were registered and 273 randomized. Of the MRI group, 64% had a region of interest. No difference was observed in the rate of GG ≥2 upgrading (the intent-to-treat population, $p = 0.7$, and per-protocol [PP] population, $p = 0.4$), GG ≥2 upgrading within each stratum separately, or GG ≥3. After central pathology review, upgrading was observed in 36/132 (27%) men in the systematic biopsy arm and 42/127 (33%) men in the MRI arm ($p = 0.3$). Upgrading was seen in 19/137 (14%) patients in the MRI arm on targeted biopsy alone (median, 2 cores) compared with 31/136 (23%) in the systematic biopsy arm (median, 12 cores; $p = 0.09$). In the MRI arm, 8/127 (6.5%) patients had GG ≥2 disease identified on targeted biopsy, but ≤GG1 on the systematic biopsy, and 10/127 (7.9%) patients had GG ≥2 disease identified by systematic biopsy but ≤GG1 on targeted biopsy. Significant differences in upgrading on targeted biopsies were seen between sites, likely reflecting different levels of expertise with the targeted biopsy technique.
Conclusions: The addition of MRI with targeted biopsies to systematic biopsies did not significantly increase the upgrading rate compared with systematic biopsy alone. Furthermore, 2-core targeted biopsies alone resulted in a nonsignificant trend to less upgrading than 12-core systematic biopsy ($p = 0.09$). In men on active surveillance, targeted biopsies identify most, but not all, clinically significant cancers.

* Corresponding author. Sunnybrook Health Sciences Centre, 2075 Bayview Avenue #MG408, Toronto, Ontario M4N 3M5, Canada. Tel. +416 480 4673; Fax: +416 480 6121.
E-mail address: laurence.klotz@sunnybrook.ca (L. Klotz).

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1. Introduction

Active surveillance is now considered the standard of care for most men with low-grade prostate cancer, as reflected in many national guidelines [1,2]. A concern with surveillance is that a small but important subset of patients with biologically aggressive but potentially curable disease are denied the benefits of radical therapy in a timely fashion [3–5].

Studies of radical prostatectomy pathology in men who are surveillance candidates indicate that approximately 25% will harbor occult large cancers usually located anteriorly [6,7]. The anterior location of these cancers is predictable as the transrectal ultrasound (TRUS)-guided approach tends to target the posterior, peripheral zone. Early identification of these occult cancers by magnetic resonance imaging (MRI) has the promise of significantly improving the outcome of surveillance by allowing those with co-existent aggressive disease to be identified and treated in a more timely fashion [8]. An additional potential benefit of incorporating MRI would be the avoidance of frequent systematic biopsies if the MRI is negative and has a sufficiently high negative predictive value (NPV) for significant cancer [9,10].

An area of uncertainty in the field is the reliability of MRI for excluding higher-grade prostate cancer in men on surveillance. A recent European Association of Urology panel emphasized that the NPV of MRI was a function of the patient's underlying risk and varied between 67% and 89%. This suggests that systematic biopsies may still be required in many patients to reliably exclude the presence of higher-grade cancer in low-risk surveillance candidates.

This study was undertaken to evaluate the effectiveness of MRI-targeted biopsies versus conventional systematic biopsies in identifying higher-grade prostate cancer on active surveillance. The primary objective was to compare the proportion of patients whose confirmatory biopsy was upgraded to grade group (GG) $\geq$2 in targeted versus systematic biopsies. The hypothesis was that targeted biopsies would identify as many or more men with GG $\geq$2 cancer than systematic biopsies.

2. Patients and methods

This was a prospective, multicenter, randomized open-label trial for men with a diagnosis of low-risk prostate cancer within the past year being managed with active surveillance. Patients were stratified by center, serum prostate-specific antigen (PSA) at study entry (<5.0 or >5.0 to <10.0), and age at study entry (<65 vs >65). After stratification, patients were randomized to systematic biopsy performed or to MRI with both targeted and systematic biopsy in an approximate 1:1 ratio between the two arms using a dynamic allocation method with a random component via a web-based registration system. Patients were registered following diagnostic biopsy or at initial cancer center visit, and randomization occurred just prior to confirmatory biopsy, set to occur 9–13 mo after diagnostic biopsy, after eligibility criteria was reconfirmed.

Eligible patients were men diagnosed with GG1 cancer within 1 yr prior to study entry in whom a confirmatory biopsy was indicated and had not yet been performed. Inclusion criteria included clinical stage < = T2b, GG 1 (Gleason sum <6), and PSA <10.0 ng/ml. Patients had to be candidates for multiparametric (mp) MRI. The research ethics board-approved informed consent was obtained from all patients. The study was registered with www.clinicaltrials.gov (NCT01354171).

Standard biopsy consisted of 12 systematic cores following a zonal biopsy scheme. In the MRI arm, MRI was performed no sooner than 6 mo following the initial diagnostic biopsy. mpMRI was performed on a 3T MRI system with endorectal coil. Slice thickness was 3 mm for all axial sequences. For T2, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE), sequences in plane voxel dimensions were 0.43–0.5 × 0.73–0.83 mm, 1.1–1.25 × 1.1–1.25 mm, and 1.1–1.25 × 1.1–1.25 mm, respectively. The temporal resolution for DCE imaging was 7–8 s for 5 min. DWI b values were 100, 400, and 1000 s/mm^2. Apparent diffusion coefficient (ADC) maps were calculated using all b values. Exams were interpreted by a single central reader who was a uroradiologist with 10 yr of experience reading prostate mpMRI. Interpretation criteria are noted in Supplementary Table 1. ADC values <1000 mm^2/sx10^{-6} were considered low.

The interpretation criteria were developed prior to the publication of the Prostate Imaging Reporting and Data system (PI-RADS) versions 1 and 2. The nature of the criteria used in this study could lead to classification of more lesions as 3, 4, or 5 compared with PI-RADS version 2 given that abnormal enhancement in the peripheral zone was given more weight in the scoring scheme and a size threshold of 15 mm was not used to distinguish score 4 versus 5.

The following pulse sequences were performed:

1. Anatomic T2 imaging in axial, sagittal, and coronal planes.
2. DWI processed to derive ADC maps.
3. DCE T1-weighted imaging with a temporal resolution of <10 s, processed to derive permeability maps using a modified Toft's model.

MRIs were reviewed centrally. As the protocol was initiated prior to the advent of the currently accepted PI-RADS 2 scoring scheme for mpMRI, lesions were graded on a 5-point Likert scale. The interpretation criteria were developed prior to the publication of PI-RADS versions 1 and 2. The nature of the criteria used in this study may have led to the classification of more lesions as 3, 4, or 5 compared with PI-RADS version 2 given that abnormal enhancement in the peripheral zone was given more weight in the scoring scheme and a size threshold of 15 mm was not used to distinguish score 4 versus 5.

All cancer foci were graded as 3, 4, or 5. All foci were traced using ProFuse software (Eigen) to define targets for biopsy. Targeted TRUS/MRI fused-guided biopsies were obtained with a minimum of two and maximum of three biopsies allowed for the first target and one to two biopsies allowed for any additional targets. Total number of targets and targeted cores were recorded. A systematic set of 12-core biopsies was then obtained using the Artemis system.

Systematic biopsies (12-core) were performed using a standard template, targeting the peripheral zone. Transition zone (TZ) biopsies were not mandated.

To avoid oversampling bias in the MRI arm, MRI target-identified biopsies were substituted for the corresponding systematic core in the same zone. Thus, both arms had the same number of biopsy sites. Patients were followed for 2 yr following the confirmatory biopsy. Subsequent intervention was at the discretion of the investigator.

2.1. *Statistics*

The probability of biopsy upgrading in the non-MRI (control) arm (from GG1 to GG2 or higher) was assumed to be 25%. Assuming a 15% absolute difference (25% vs 40%) would be clinically meaningful and setting $\alpha = 0.05$ and $\beta = 0.20$; 133 patients per arm (266 total) would be required using a one-sided Fisher's exact test. Allowing for a non-compliance rate of 3%, 275 patients were targeted. The use of a one-sided statistical test was justified due to the asymmetric nature of the two arms since both groups received systematic biopsies.

Secondary outcomes included the proportion of patients upgraded to ≥GG 3, progression-free survival (PFS), treatments received in the follow-up period, and safety outcomes including the frequency of adverse events.

Descriptive statistics were used to summarize patient characteristics and outcomes by study arm separately. Differences in outcomes between study arms were estimated along with 95% Pearson-Clopper confidence intervals and tested using Fisher's exact tests. Chi-square and Kruskal-Wallis tests were used to compare differences in baseline characteristics between treatment sites.

Time-to-event outcomes were estimated using the Kaplan-Meier method and defined from the date of randomization. Logistic and Cox regression were used as supportive analyses to investigate the effect of study arm on outcomes after adjusting for stratification (notably, PSA <5 vs 5–10 ng/ml, age <65 vs 65+ yr, and treatment center) to account for possible confounding.

All randomized patients were included in the intent-to-treat (ITT) population. All patients in this population who had confirmatory biopsy as specified were included in the PP population.

3. Results

Between December 2011 and December 2015, 296 patients were registered to the study. Of this, 23 patients were excluded prior to randomization (see CONSORT diagram; Fig. 1), 136 were randomized to systematic biopsy, and 137 to the MRI-guided biopsy arm. Patient baseline characteristics are summarized in Tables 1 and 2. No obvious differences between treatment arms with respect to stratum, demographics, tumor characteristics, or prior treatments were noted. Baseline tumor characteristics are listed in Table 2. MRIs were performed a minimum of 6 mo after the initial diagnostic biopsy, and no patient had evidence of persistent hemorrhage or artifact remaining from the original biopsy. Median follow-up after the study biopsy for patients remaining untreated on protocol was 2 yr in both arms. Compliance with the biopsy schedule was good. Three patients in the systematic arm withdrew, 87% had 12 cores, 8.7% had 11 cores, and one patient each had 10 and 3 cores (Table 8).

In total, 81/126 (64%) patients had a region of interest (ROI); of these, 60 (48%) had a Likert 4 or 5 (suspicious) lesion and 21 (17%) had a Likert 3 (equivocal) lesion. In addition to systematic biopsies in all men, 94% of patients with an ROI in the MRI arm had at least two targeted cores (6.3% had one targeted core).

MRI targets were located in the peripheral zone only in 55, TZ in 12, both in six, and not notated in eight. Furthermore, 32/123 (26%) targets identified on MRI were considered anterior.

Thirty-one (23%) systematic biopsy patients were observed to have GG ≥2 cancer at the time of confirmatory biopsy compared with 29 (21%) patients in the MRI arm (targeted + systematic; Tables 3 and 4). This was not statistically significant based on the primary analysis (one-sided Fisher's exact test, $p = 0.7$) or after adjusted for stratification variables (logistic regression two-sided, $p = 0.9$). After central pathology review, upgrading to GG ≥2 occurred in 27% of systematic and 33% of MRI-targeted + systematic biopsies. The difference between upgrading rates was estimated to be –5.8% (95% confidence interval [CI] = –17% to 5.4%).

To consider the impact of missing data, in the extreme case that all 10 MRI patients who came off study prior to confirmatory biopsy had GG ≥2 cancer and none of the four systematic biopsy patients did, then the rate of upgrading for MRI patients would be 28%, with a difference in proportions of 5.7% (95% CI = –4.7% to 16%). In this unlikely scenario, one would not have evidence to rule out that the addition of MRI-targeted biopsy results in a meaningful increase (previously defined as 15%) in the upgrading rate.

Upgrading was seen in 19/137 (14%) patients in the MRI arm on targeted biopsy alone (median two cores). This did not achieve statistical significance ($p = 0.06$ by two-sided Fisher's exact test) when compared with the 23% upgraded on the systematic biopsy (median, 12 cores) arm. In the PP population, the upgrading in targeted only (MRI arm) versus systematic (control arm) was 19/127 (15%) versus 31/132 (23%), $p = 0.09$.

There were notable differences in the upgrading rates of targeted biopsies between the three sites (interaction $p = 0.009$). At two of the sites, the upgrading rate for patients on the MRI arm was at least 15% lower than that in the systematic biopsy alone arm (10% vs 29%, $p = 0.06$ and 7.7% vs 26%, $p = 0.08$, respectively, by site). However, in the third, most experienced site, the upgrading rate was much higher in the MRI arm (33% vs 20%, $p = 0.07$).

No statistically significant difference was observed in the rate of GG ≥2 upgrading using the PP population ($p = 1$),

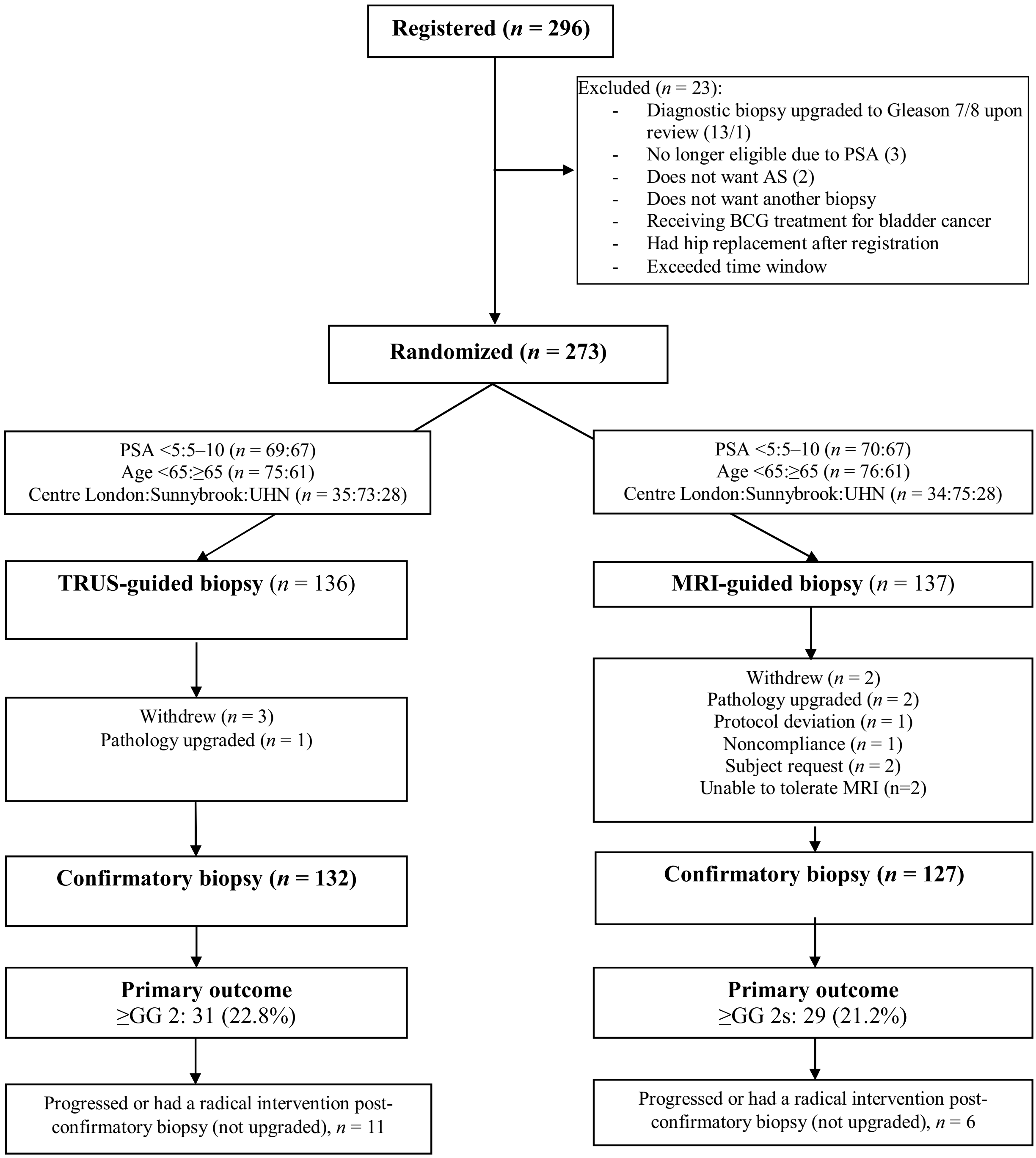

Fig. 1 – Study flow diagram.
AS = active surveillance; BCG = Bacillus Calmette-Guerin; GG = Gleason grade; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; UHN = University Health Network.

GG ≥2 upgrading within each stratum separately, or GG ≥3 (ITT population, $p = 0.5$ and PP population, $p = 0.4$). Moreover, 97 patients who had systematic biopsies and 91 patients who had MRI-guided targeted biopsies had their biopsies randomly selected for independent review, of which five and 13 patients were upgraded from the original pathology interpretation ($p = 0.10$). Combining these results with specimens which were not sent for review, 36/132 (27%) systematic biopsy patients and 42/127 (33%) MRI-guided biopsy patients had an upgraded result, which was not statistically significant ($p = 0.3$).

3.1. *Secondary outcomes*

PFS and time to first radical intervention or progression are described in Table 5. A total of 8/101 and 5/98 of

Table 1 – Baseline characteristics

Baseline characteristics		Systematic biopsy (*n* = 136)	MRI-guided biopsy (*n* = 137)
Eligibility and stratum, n (%)			
PSA stratification	<5	69 (51)	70 (51)
	5–10	67 (49)	67 (49)
Age stratification	<65	75 (55)	76 (55)
	≥65	61 (45)	61 (44)
Study center	London	35 (26)	34 (25)
	Sunnybrook	73 (54)	75 (55)
	UHN	28 (21)	28 (20)
Demographics			
Age at diagnosis, yr	Median (IQR)	63.1 (57.8–68.8)	62.6 (57.5–67.6)
Age at registration, yr	Median (IQR)	63.7 (58.6–69.5)	63.1 (58.2–68.3)
Diagnosis to registration, mo	Median (IQR)	8.5 (7.1–9.9)	8.2 (6.9–10.2)
Race	*n* (%) Caucasian	106 (80)	99 (72)
ECOG performance status	*n* (%) 0	135 (99)	136 (99)
	1	1 (0.7)	1 (0.7)
Height, cm	Median (IQR)	175 (170–178)	176 (170–180)
Weight, kg	Median (IQR)	84.0 (77.4–91.4)	84.0 (75.3–95.2)
Body mass index [a]	Median (IQR)	27.9 (25.3–30.7)	27.7 (24.8–30.3)
Body surface area [b]	Median (IQR)	2.0 (1.9–2.1)	2.0 (1.9–2.1)
Blood pressure	Systolic median (IQR)	133 (122–143)	135 (124–141)
	Diastolic median (IQR)	82 (77–87)	82 (75–88)
Heart rate	Median (IQR)	66 (61–75)	66 (60–77)
Tumor characteristics			
PSA at registration	Median (IQR)	4.99 (4.05–6.30)	4.75 (3.80–6.30)
DRE results	*n* (%) Abnormal	14/97 (14)	9/90 (10)
T stage at initial diagnosis	1b	2	2
	1c	93	99
	2a	8	10
	2b	1	0
	NA	32	26

DRE = digital rectal examination; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; UHN = University health network.
[a] Calculated as weight (kg)/(height[m])^2.
[b] Dubois & Dubois method.

the systematic and MRI groups, respectively, in whom no upgrading was seen on confirmatory biopsy were deemed to progress subsequent to the biopsy. There were no significant difference in PFS (multivariable Cox regression adjusted for stratum, $p = 0.7$) or time to radical intervention, or progression between groups (multivariable Cox regression adjusted for stratum, $p = 0.6$).

Table 2 – Stratification of baseline characteristics by site

Baseline characteristics		London	Sunnybrook	UHN
Eligibility and stratum and treatment				
n		69	148	56
PSA stratification	<5 *	26 (38)	81 (55)	32 (57)
	5–10	43 (62)	67 (45)	24 (43)
Age stratification	<65	32 (46)	87 (59)	32 (57)
	≥65	37 (54)	61 (41)	24 (43)
Demographics				
Age at diagnosis	Median (IQR)	64.7 (59.9–69.3)	62.1 (56.2–68.0)	62.5 (57.8–67.7)
Race	Caucasian *, *n*	66	97	44
Body mass index [a]	Median (IQR) *	29.1 (26.0–32.0)	27.0 (24.2–29.1)	27.9 (25.5–31.3)
Tumor characteristics				
PSA at registration	Median (IQR)	5.2 (4.3–6.5)	4.8 (3.5–6.4)	4.7 (3.9–5.6)
DRE results	Abnormal *, *n*	17/67	3/66	3/54
T stage at initial diagnosis	1b *	0	0	4
	1c	60	83	49
	2a	8	7	3
	2b	1	0	0
	NA	0	58	0

DRE = digital rectal examination; IQR = interquartile range; PSA = prostate-specific antigen; UHN = University health network.
* Statistically significant differences ($p < 0.05$) were observed between centers in the rates of patients with low PSA strata, Caucasian race, weight, body mass index, body surface area, abnormal DRE, and prior therapy using Kruskal-Wallis test (continuous values) or χ^2 tests (categorical values).
[a] Calculated as weight (kg)/(height[m])^2.

Table 3 – Gleason grade upgrading of pre-study diagnostic biopsy

		Systematic biopsy (n = 136)	MRI-guided biopsy (n = 137)	p value
Undergoing confirmatory biopsy	n (%)	132 (97)	127 (93)	
Reasons for no confirmatory biopsy	Withdrew consent	3	4	
	Local path upgraded	1	2	
	Noncompliance	0	1	
	Unable to tolerate MRI	0	3	
Grade group at confirmatory biopsy, n (%)	No confirmatory bx	4 (3.0)	10 (7.3)	
	Negative	35 (26)	37 (27)	
	1	66 (48)	61 (44)	
	2	27 (20)	22 (16)	
	3	4 (2.9)	5 (3.6)	
	4	0 (0.0)	2 (1.5)	
GG2 or higher [a]	n (%)	31/136 (23)	29/137 (21)	0.7[*]
GG3 or higher	n (%)	4 (2.9)	7 (5.1)	0.5
Randomization to confirmatory biopsy, mo	Median (IQR)	2.5 (1.6–3.9)	3.0 (2.1–4.4)	0.019
Diagnosis to confirmatory biopsy, mo	Median (IQR)	11.6 (10.8–12.4)	12.2 (10.7–12.8)	0.010
GG ≥2, by site, n (%)	London	10/34 (29)	3/29 (10)	0.12
	Sunnybrook	14/71 (20)	24/72 (33)	0.09
	UHN	7/27 (26)	2/26 (7.7)	0.14
GG ≥2, by PSA, n (%)	<5	9/68 (13)	11/66 (17)	0.6
	5–10	22/64 (34)	18/61 (29)	0.6
GG ≥2, by age, n (%)	<65	11/72 (15)	16/71 (22)	0.3
	≥65	20/60 (33)	13/56 (23)	0.3
GG ≥3, per protocol, n (%)		4/132 (3.0)	7/127 (5.5)	0.4

Bx = prostate biopsy; GG = Gleason grade; IQR = interquartile range; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; UHN = University health network.
[a] Primary outcome using intent-to-treat population.
[*] One-sided p value. Mantel-Haenszel p = 0.9. Logistic regression p = 0.9 adjusted for strata and center.

3.2. *Safety*

A listing of all adverse events (AEs) experienced (note some patients experienced multiple AEs) are presented in Table 6. In total, 31% and 35% of patients in the systematic and MRI groups, respectively, experienced any AE, and 6.6% in each group experienced a serious AE. There was no difference in AEs between the two groups and no mortality.

3.3. *Pathology outcome*

There were 127 patients in the MRI group who underwent confirmatory biopsies. Of these patients, 81 (64%) had at least one targeted biopsy and 47 (58% of patients who underwent MRI-guided biopsy) had cancer detected on at least one targeted core. Five patients had two targeted biopsies, four patients had three targets, and one patient had four targeted biopsies. Secondary targets had one or two cores performed. Eighty patients were deemed to have no cancer based on targeted biopsy alone, 28 were GG1, 14 were GG2, four were GG3, and one patient was GG4. Therefore, 19/81 (23%) patients had a GG ≥2 cancer based on the targeted biopsy.

In the MRI arm, systematic biopsy was positive in 71/124, 63 were GG1, 15 were GG2, two were GG3, and four were GG4. Thus, 21/124 (17%) who underwent systematic biopsy had GG ≥2 cancer.

In the MRI arm, eight patients had GG ≥2 disease identified on targeted biopsy, but ≤GG1 on the systematic biopsy. Ten patients had ≥GG2 disease identified by systematic biopsy but missed on targeted (Table 7). Eighteen had MRI scored as 1 or 2 for which a GG ≥2 cancer was observed based on systematic biopsy in that zone, whereas 41 patients had at least one zone which was identified as a

Table 4 – Baseline cancer characteristics of cohort on pre-study diagnostic biopsy

Baseline characteristics		Systematic biopsy (n = 136)	MRI-guided biopsy (n = 137)
Number with ≥1 core submitted	n (%)	120 (88)	120 (88)
Total cores submitted	<10	37	37
	10–11	8	9
	12	54	49
	>12	21	25
% of positive cores/cores submitted, median (IQR)	<10	20 (10–30)	20 (10–30)
	10–11	14 (9–18)	9 (9–27)
	12	17 (8–25)	17 (8–25)
	>12	10 (7–18)	8 (7–31)

IQR = interquartile range; MRI = magnetic resonance imaging.

Table 5 – Secondary outcomes

		Systematic biopsy	MRI-guided biopsy
Progression from randomization			
n		136	137
Progressed	*n*	39	34
Progression-free estimate	1 yr (95% CI)	73.4 (64.9–80.1)	75 (67–82)
Radical interventions or progression	*n*	42	35
Radical intervention or progression-free	1 yr (95% CI)	73 (64–79)	74(66–81)
Progression post-confirmatory biopsy (No upgrading at confirmatory biopsy)			
n		101	98
Progressed	*n*	8	5
Progression-free estimate	1 yr (95% CI)	96 (90–98)	97 (91–99)
Radical interventions or progression	*n*	11	6
Radical intervention or progression-free	1 yr (95% CI)	94 (87–97)	96 (89–98)
Types of interventions	Androgen deprivation	0	0
	Radiotherapy	4	2
	Prostate surgery	7	3
	No intervention	0	1
Reason for intervention	Biochemical Progression	2	1
	Histologic progression	3	0
	Clinical progression	3	1
	Patient choice	3	1
	Clinical judgment	2	3

CI = confidence interval; MRI = magnetic resonance imaging.

Table 6 – Number of patients experiencing adverse events and adverse events affecting 1% of patients

Adverse event	Systematic biopsy, *n* = 136 (%)	MRI-guided biopsy, *n* = 137 (%)
≥1 AE, *n* (%)	42 (31)	48 (35)
≥1 attributable AE, *n* (%)	26 (19)	28 (20)
≥1 serious AE, *n* (%)	9 (6.6)	9 (6.6)
Hematuria, *n* (%)	19 (14)	25 (18)
Hematospermia, *n* (%)	9 (6.6)	6 (4.4)
Hematochezia, *n* (%)	2 (1.5)	3 (2.2)
UTI, *n* (%)	2 (1.5)	2 (1.5)

AE = adverse event; MRI = magnetic resonance imaging; UTI = urinary tract infection.

Table 7 – Pathologic review—patients in MRI-guided biopsy arm: results of targeted versus systematic biopsy (*n* = 127)

		Targeted biopsies (T1–T4)			
		No cancer	GG1	GG2–3	GG4
Systematic biopsies (RBL to LAM)	No cancer	37	3	3	0
	GG1	36	22	5	0
	GG2–3	5	3	9	0
	GG4	2	0	1	1

GG = Gleason grade; LAM = left apex medial; MRI = magnetic resonance imaging; RBL = right base lateral.

target (based on MRI score of 3, 4, or 5), for which the targeted biopsy in that zone was deemed to be ≤GG1.

Two patients had GG4 cancer identified based on systematic biopsy, but no cancer on the targeted biopsy. Upon independent review, one of these two patients was deemed to have GG4 cancer and the other was GG1 cancer (Table 8). The results of targeted biopsy (in the positive MRIs) and systematic biopsy (in the negative MRIs) by grade group in the MRI are in Table 9. Core involvement according to MRI score is listed in Table 10.

The proportion with a negative or GG1 targeted biopsy (Likert 3, 4, and 5) or systematic biopsy (Likert 1 and 2) was 66% for Likert 5, 76% for 4, 83% for 3, 90% for 2, and 83% for 1.

4. Discussion

The question addressed in this study was whether targeted biopsy of MRI ROIs in addition to systematic biopsy of all regions would result in an increased rate of identification of GG ≥2 cancer compared with systematic biopsies.

A total of 64% patients in the MRI arm had an ROI. This is consistent with the published literature. In one recent review article comprising eight studies, 1902/3225 (59%) men on surveillance had an ROI on MRI [10].

In total, 81 patients in the MRI arm had a target with a Likert score of ≥3; 19 of these were ≥GG2 for a positive predictive value (PPV) of 23%. The NPV for a negative MRI (Likert 1–2) was 85%, consistent with the published literature [11,12]. The low PPV compared with other reports [11] has several possible explanations. The Artemis fusion biopsy system was introduced to all three sites at the start of the study; therefore, the results may reflect the learning curve for this technology. The median number of samples per target was relatively low, at two per target. Currently, at least four cores per target are recommended, reflecting the limitations in accurate tumor localization and targeting [9]. The low number of cores per target may have reduced the detection rates of small Gleason pattern 4 components in the targets. The Likert system puts more weight on the DCE MRI than PI-RADS version 2 and does not use a 15-mm size threshold to distinguish score 4 from 5. Despite this, the number of cores required for each significant cancer was dramatically less with the targeted approach (median of two vs 12 cores).

Patients with a Likert 3, 4, or 5 lesion received one to five targeted biopsies (depending on target number). The

Table 8 – Pathologic review of on-study confirmatory biopsy: patients in MRI-guided biopsy arm only

Targeted biopsy (n = 127) (Only performed on Likert 3, 4, and 5 cases)			
Total cohort/*n* (%) number upgraded		127	19 (15)
Number of cores taken, *n* (%)	0		46 (36)
	1		8 (6.3)
	2		34 (27)
	3		24 (19)
	4		7 (5.5)
	5		8 (6.3)
Cancer on at least 1 core, *n* (%)		127	47 (37)
Maximum grade group, *n* (%)	No cancer	127	80 (63)
	1		28 (22)
	2		14 (11)
	3		4 (3.1)
	4		1 (0.8)
Systematic biopsy in men on MRI arm			
Upgraded, *n* (%)		127	21 (17)
Number of cores taken, *n* (%)	0	127	3 (2.4)
	3		1 (0.8)
	10		1 (0.8)
	11		11 (8.7)
	12		111 (87)
Cancer on at least 1 core, *n* (%)		127	84 (66)
Maximum grade group, *n* (%)	No cancer	127	43 (34)
	1		63 (50)
	2		15 (12)
	3		2 (1.6)
	4		4 (3.1)
Target versus systematic biopsy in men on MRI arm			
Upgrade on target biopsy, but not systematic biopsy	*n* (%)	127	8 (6.3)
Upgrade on systematic biopsy, but not target biopsy	*n* (%)	127	10 (7.9)
At least one zone for which MRI score = 4,5, but targeted biopsy for that zone is GG $\leq$1	*n* (%)	127	41 (32)

GG = Gleason grade; MRI = magnetic resonance imaging.

Table 9 – Results of targeted biopsy (Likert score 2, 3, or 4) and systematic biopsy (Likert score 0–1) by grade group in MRI arm (*n* = 126)

MRI Likert score	*n*	No cancer, *n* (%)	GG1, *n* (%)	GG2, *n* (%)	GG 3, *n* (%)	GG4, *n* (%)	GG $\geq$ 2, *n* (%)	PPV targeted, %	PPV targeted + systematic, %
1 (Systematic biopsy)	12	4 (33)	6 (50)	1 (8.3)	0	1 (8.3)	2 (16)		
2 (Systematic biopsy)	33	16 (48)	14 (42)	3 (9.1)	0	0	3 (9.1)		
3 (Targeted)	30	12 (40)	13 (43)	3 (10)	1 (3.3)	0	4 (13)	13	16
4 (Targeted)	21	8 (38)	8 (38)	3 (14)	2 (9.5)	0	5 (24)	29	33
5 (Targeted)	30	4 (13)	16 (53)	8 (26)	1 (3.3)	1 (3.3)	10 (33)	33	40

GG = grade group; MRI = magnetic resonance imaging; PPV = positive predictive value.

Table 10 – Core involvement according to MRI score

Likert score	*n*	Median (IQR), % core involvement	Median (IQR), % positive cores from targeted Bx	Median (IQR), % positive cores from systematic + targeted
1–2	45	NA		
3	30	0 (0–0)	0 (0–0)	0 (0–0)
4	21	30 (0–50)	80 (0–100)	0 (0–100)
5	30	35 (10–70)	100 (75–100)	89 (67–100)

Bx = prostate biopsy; IQR = interquartile range; MRI = magnetic resonance imaging; NA = not applicable.

protocol of two cores per target may have been insufficient to reliably target significant cancers. The 6% of patients who only had one targeted biopsy were at particular risk for pathologic miss despite the fusion targeting technique.

Both systematic and targeted biopsies missed some clinically significant cancers. The likelihood of a positive systematic biopsy for clinically significant cancer was higher if a target was present, even if the targeted biopsy was negative. The likeliest explanation is that the targeted biopsy missed the lesion, and the systematic biopsy hit it. This observation may also reflect a field effect, meaning that the presence of an area of restricted diffusion is associated with an increased likelihood of significant cancer in the adjacent region.

Despite all MRIs being read centrally by the same radiologist (MH), there were major differences in the performance of the targeted biopsies between sites. In particular, the PPV of a target (Likert 3, 4, or 5) for GG $\geq$2 at one site was 33%; at the other two sites, it was 8–10%. This likely reflects differences in the learning curve between sites. At these two sites, the upgrading rate for systematic biopsies alone (29% and 26%) was unexpectedly higher than for systematic + targeted (10% and 8%). In the MRI arm, the targeted + systematic biopsies were performed using the Artemis device, whereas the systematic alone biopsies were performed using the standard TRUS Bx technique. The use of an image fusion biopsy system by the less experienced centers may have reduced the diagnostic yield. The Sunnybrook site had more prior experience and a consistent operator throughout the course of the study; the other centers had less experience, several different operators, and less recruitment, which may have limited their comfort with the Artemis technology. Both MRI and systematic biopsy missed significant cancers; targeted biopsy missed 8% of GG $\geq$2 cancers found on systematic biopsy, and systematic biopsy missed 6% of the significant cancers found on targeted biopsy. Five of 45 patients (11%) with a negative MRI had GG $\geq$2 cancers; four of these five were GG2. Only one (2%) patient with a negative MRI had GG t3 on systematic biopsy. This suggests that GG2 cancers are more likely to be missed or underestimated on MRI compared with higher grade cancers.

The NPV of MRI has been shown to be a function of the underlying risk of co-existent higher grade disease [11]. The NPV in this cohort was 85%, and the overall risk of significant cancer was 22%. Despite the limitations of MRI, based on this data and that of others, we believe that in a patient with favorable parameters (low PSA density and cancer core volume), a negative MRI may replace systematic biopsies with reasonable safety [13]. Several nomograms have been developed to predict the presence of higher grade cancer in surveillance candidates based on clinical and pathological parameters [14–16]. In patients with a higher risk of significant cancer based on clinical parameters, systematic biopsy should be performed even if the MRI is negative. Our data also suggests that high-risk patients with a positive MRI should have both systematic and targeted biopsies.

4.1. Limitations of the study

The investigators' experience with the Artemis fusion targeted biopsy system was modest at the initiation of the study, and the results likely reflect the fusion biopsy learning curve of the operators. Furthermore, 6% and 2% of the MRI and systematic biopsy patients came off study prior to confirmatory biopsy, and there is a small chance that this imbalance could have biased the results.

5. Conclusions

The addition of MRI with targeted biopsies to systematic biopsies did not significantly increase the upgrading rate compared with systematic biopsy alone. Significant differences in upgrading rate were seen between the three sites in the study. At the site with the most experience with the targeted biopsy technique, the upgrading rate on targeted biopsy using two cores was higher than the upgrading rate with 12-core systematic biopsy. Both systematic and targeted biopsies missed significant cancer in 6% and 8% patients, respectively. In patients at high risk for occult higher grade disease, systematic biopsies should be performed regardless of the MRI findings. Experience with the targeted biopsy technique is essential to achieve accurate targeting.

Author contributions: Laurence Klotz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Klotz, Loblaw, Sugar, Moussa, Berman, Van der Kwast, Vesprini, Milot, Fleshner, Ghai, Chin, Pond, Haider.
Acquisition of data: Klotz, Loblaw, Sugar, Moussa, Berman, Van der Kwast, Vesprini, Milot, Kebabdjian, Fleshner, Ghai, Chin, Haider.
Analysis and interpretation of data: Klotz, Loblaw, Pond, Haider.
Drafting of the manuscript: Klotz.
Critical revision of the manuscript for important intellectual content: Klotz, Loblaw, Sugar, Moussa, Berman, Van der Kwast, Vesprini, Milot, Kebabdjian, Fleshner, Ghai, Chin, Pond, Haider.
Statistical analysis: Pond.
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Appendix A. Supplementary data

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