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Multi-parametric MRI-targeted biopsy compared to systematic TRUS biopsy for biopsy-naïve men at risk for prostate cancer. A phase 3 randomized clinical trial

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Laurence.klotz@sunnybrook.caKey Points:

Question:,Is MRI with targeted biopsy only non-inferior to systematic biopsy in all for the diagnosis of clinically significant Pca ?

Findings: A prospective phase 3 randomized clinical trial in 453 men. Clinically significant cancer was found in 35% vs 30% in the MRI and systematic biopsy arms respectively. demonstrating non-inferiority. 37% on the MRI arm avoided a biopsy. . Diagnosis of GG1 PCa was reduced by > 50%.

Meaning: MRI with targeted biopsy alone resulted in similar detection rates of clinically significant PCa while avoiding biopsy in over 1/3rd of men and reducing the diagnosis of clinically insignificant cancer.

Abstract:

Importance: : MRI with targeted biopsy is an appealing alternative to systematic 12 core TRUS biopsy for prostate cancer diagnosis but has yet to be widely adopted.

Objectives: We sought to determine whether MRI with only targeted biopsy was non-inferior (NI) to systematic trans-rectal ultrasound (TRUS) biopsies in the detection of ISUP GG) ≥2 prostate cancer.

Design: A multicenter, prospective randomized trial.

Setting: 5 Canadian academic Health Sciences Centres

Participants: Biopsy-naïve men with a clinical suspicion of prostate cancer. advised to have a prostate biopsy. Clinical suspicion was defined as a: ≥5% chance of ≥ GG2 prostate cancer using the PCPT Risk Calculator version 2. Additional criteria were serum PSA ≤ 20ng/ml, and no contraindication to MRI.

Intervention: MRI,targeted biopsy only if a PI-RADSv2.0 ≥ 3 lesion was identified, , vs 12 core systematic TRUS-Biopsy.

Main Outcome and Measures: The proportion of men diagnosed with GG ≥ 2 cancer. Secondary outcomes included the proportions diagnosed with GG1 PCa; with GG≥3 cancer; no significant cancer but subsequent positive MRI and/or GG≥2 cancer detected on a repeat biopsy by 2 years; and adverse events.

Results: The intention-to-treat (ITT) population consisted of 453 patients randomized to TRUSBx (n=226) or MRI-TB (n=227), of which 421 were evaluable per protocol. A PI-RADS ≥3 lesion was detected in 138/221 (62.4%) men having MRI, with 26 (12.1%), 82 (38.1%) and 30 (14.0%) having maximum PI-RADS scores of 3, 4 and 5, respectively. Eighty-three of 221 (37%) MRI-TB men had a negative MRI and avoided biopsy. GG ≥2 cancers were identified in 67 of 225 (30%) men allocated to TRUSBx versus 79 of 227 (35%) allocated to MRI-TB (absolute difference 5%, 97.5% one-sided CI=-3.4% to ∞, NI margin was -5%)). Adverse events were less common in the MRI-TB arm. GG1 cancer detection was reduced by over half in the MRI arm (from 22 to 10%, risk difference = -11.6%, 95% CI=-18.2% to -4.9%).

Conclusions and Relevance: MRI followed by selected targeted biopsy is non-inferior to initial systematic biopsy in men at risk for prostate cancer in detecting GG ≥2 cancers.

Registration: ClinicalTrials.gov Identifier: NCT02936258

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Laurence Klotz and Masoom Haider had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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Acronyms:

TRUS: Trans-Rectal UltraSound

TRUSBx: Systematic TRUS-guided biopsy

MRI: Multi-parametric Magnetic Resonance Imaging

MRI-TB: MRI Targeted biopsy

ROI: Region of Interest

NPV: Negative predictive value

DSMC: Data Safety Monitoring Committee

ITT: Intention to Treat

CDR: Cancer Diagnosis Rate

GG: International Society of Urological Pathology (ISUP) Grade GroupDWI: Diffusion Weighted Image

DCE: Dynamic Contrast Enhancement

CSPCa: Clinically significant prostate cancer

PCPT: Prostate Cancer Prevention Trial

Multi-parametric MRI-targeted biopsy compared to systematic TRUS biopsy for biopsy-naïve men at risk for prostate cancer. A phase 3 randomized clinical trial

Introduction:

For 35 years, the standard pathway for prostate cancer diagnosis has been systematic TRUSBx of the prostate in patients with elevated PSA. TRUS is used primarily for anatomic guidance, as traditional ultrasound discriminates poorly between cancerous and non-cancerous tissue. [1]

With mpMRI, the additional conspicuity of cancer offered by DWI and DCE has improved the diagnostic accuracy of MRI for cancer detection [2]. In studies correlating MRI with radical prostatectomy specimens, the sensitivity, specificity, positive predictive value and negative predictive value were 45-90%, 40-88%, 77-81% and 67-95% respectively for the identification of prostate tumors greater than 0.5ml.[3,4,5] or clinically significant disease [7-11]. These metrics are also a function of grade, insofar as MRI is more sensitive for higher grade cancers.[3,6,] The evidence is less clear in active surveillance. [12,13,14]

There is a major unmet need for a test that identifies CSPCa without overdiagnosing insignificant cancer. This study was to determine if MRI with only targeted biopsy is non-inferior to 12 core systematic biopsies for the diagnosis of CSPCa.

This study was designed independently but in coordination with the PRECISION study, a recent European based, prospective randomized multicenter study that compared MRI TB alone to systematic biopsy [15]. Achieving funding, implementation, and accrual was a more prolonged process for PRECISE. Despite the encouraging results of MRI-TB reported by multiple high quality studies: PRECISION [15], PROMIS [16], MRI-FIRST [17], 4M [18] and a Cochrane meta-analysis[19], in many jurisdictions MRI prior to biopsy is not yet part of routine clinical practice.[20]

In contrast to PRECISION, the PRECISE trial included risk-based eligibility, systematic follow-up of all patients for two years including a repeat MRI in all untreated patients, the investigation of fluid and tissue-based biomarkers in the cohort, and an economic analysis.

Methods:

This was a multicenter, randomized, non-inferiority trial at 5 centers in Canada. Following acquisition of informed consent, men were randomized in a 1:1 ratio to either systematic 12 core TRUSBx or MRI, with targeted biopsy of PI-RADS (version 2.0) $\geq$ 3 lesions. In the absence of

PI-RADS ≥ 3 lesions (a negative MRI), no biopsy was performed. The protocol was approved by the research ethics board at each participating institution, monitored by the trial steering committee and an independent data safety monitoring committee (DSMC).

The primary outcome was the proportion of men with clinically significant cancer (GG≥2) diagnosed in each arm.. Secondary outcomes included the proportion of men in the two arms who were found to have: clinically insignificant cancer (GG1); GG≥3 cancer; no significant cancer but subsequent positive MRI and/or GG≥2 cancer detected on a repeat biopsy by 2 years; post-biopsy adverse events; and definitive local treatment (e.g. radical prostatectomy, external beam radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy). In the MRI arm, we evaluated the proportion of men who avoided biopsy, and the number of men with PI-RADS 3, 4 or 5 lesions but no detection of clinically significant cancer. Health-related quality of life scores were also assessed using the EQ5D validated questionnaire.

Eligible patients were men recruited from the outpatient clinics with clinical suspicion of prostate cancer and were advised to have a prostate biopsy. Additional eligibility criteria included: ≥5% chance of ≥GG2 prostate cancer as calculated individually using the Prostate Cancer Prevention Trial Risk Calculator version 2 (http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp); serum PSA ≤ 20ng/ml; no prior biopsy or treatment for prostate cancer; suitable candidates for a biopsy; and no contraindication for an MRI. A dynamic allocation process was used for randomization, including stratification factors of 1) individualized risk of ≥GG2 prostate cancer (5% to 25%, >25% as measured by the PCPTRC 2.0 calculator, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp) and 2) treatment centre. A web based interactive system was used. Allocation of the first 20 patients was performed so patients were allocated to each arm with probability 0.5. From patient 21 onwards, if an imbalance was observed based on the two stratification factors, patients were allocated to the treatment arm which minimized the imbalance with probability 0.8. The dynamic allocation process was programmed by individuals who had no patient contact or involvement in patient enrollment or selection. .

Those men on the MRI-TB arm who had a negative MRI, and those on the TRUSBx arm whose biopsy was negative, were scheduled to have a repeat MRI at 2 years. MRI was performed according to PI-RADS v2.0 guidelines [22,23]. All centers used a 3T scanner without an endo-rectal coil. MRI was interpreted according to PI-RADS v2.0 guidelines by the site radiologists, all of

whom were experienced in the interpretation of at least 500 prostate MRI. Men whose MRI showed a score of 3, 4, or 5 underwent MRI- TB using TRUS guidance with 4 cores per lesion. Co-registration was performed using TRUS MRI fusion software at all centers (Artemis or Koelis). The fusion biopsies were performed by experienced radiologists or urologists who had performed at least 50 prior MRI informed fusion targeted biopsies

Statistics

The primary analysis was based on an ITT non-inferiority outcome, defined as the proportion of men in each arm diagnosed with clinically significant prostate cancer (≥GG2). The rate of detection of GG≥2 by targeted-alone biopsy in a population with no prior biopsy was estimated at between 42% [24] and 50% [25], vs 27% with 12 core TRUSBx,[26]. Therefore it was predicted that MRI-TB would identify >15% more GG≥2 cancer than systematic biopsy. For sample size calculations, it was conservatively hypothesized that systematic biopsy would detect clinically significant cancer in 30% of men, and MRI-TB would detect clinically significant cancer in 10% more men (i.e. 40% total). For the non-inferiority hypothesis, using 90% power and a 2.5% one sided-alpha, assuming an MRI-TB detection rate of clinically significant cancer of 40%, and a detection rate for TRUSBx of 30%, and using a margin of clinical unimportance of 5%, 211 men per arm would be required (422 in total). The choice of 5% as the margin of non-inferiority represented a clinically important difference based on expert consensus [22]. If non-inferiority was met, a superiority analysis was to be performed, with superiority met if the bound of the one-sided 97.5% CI exceeded 0%. To account for potential withdrawal / loss to follow up and the effect of stratification, the sample size was inflated by 5%, and a target of **450 men** was established.

Descriptive statistics were used to summarize the patient characteristics and outcomes of interest. Absolute risk differences and 95% CI intervals were constructed using the Wald method. A multivariable logistic regression analysis was performed investigating the effect of treatment arm, adjusted for stratification factors (study centre and baseline risk). Logistic regression was also used to explore effects prognostic of detecting ≥GG2 cancer within each treatment arm separately. A multivariable model was constructed within each treatment arm based on forward stepwise selection using the p-value<0.05 criterion. Linearity assumptions were examined using visual inspection of residuals. Logarithmic transformations of non-linear continuous variables was as appropriate. No interpolation for missing data occurred and patients with missing data were categorized in a separate group for regression analyses. All the statistical analysis were carried out

using SAS version-9 for Windows (Cary, NC) or R version 3.2.2. (www.r-project.org). The plan for the statistical analysis was pre-specified and approved by the DSMC.

Populations

All participants who underwent randomization were included in the intention-to-treat (ITT) analysis. Analyses based on the PP and biopsy population were performed as supportive efficacy analyses, (Supplementary Table A). Safety analyses were performed on the men having a biopsy. .

The study was registered with ClinicalTrials.gov Identifier: NCT02936258

Results:

Between April 2017 and Nov 2019, 453 patients were accrued, with 226 and 227 men allocated to the TRUSBx arm and MRI arm, respectively. Twenty-four men in the TRUSBx arm came off study prior to the first study intervention, including 15 who withdrew. Six men in the MRI arm came off-study before the MRI (Figure 1).

Patient characteristics are summarized in Table 1.. Patient characteristics were well balanced. .

Primary Outcome

Study outcomes in the ITT population are summarized in Table 2. Of patients who underwent MRI, 138/221 (62.4%) were positive (PI-RADS≥3), with PI-RADS 3, 4 and 5 lesions detected in 26 (12.1%), 82 (38.1%) and 30 (14.0%) men, respectively. Eighty-three of 221 men (36.6% (95% CI=30.3% to 43.2%)) had a negative MRI (PI-RADS≤2) and therefore avoided a biopsy. After undergoing biopsy, 67 (29.7%) men in the TRUSBx arm and 79 (34.8%) men in the MRI arm had GG≥2 cancer detected, resulting in an absolute risk difference of 5.2% (97.5% one-sided CI -3.4% to ∞). The lower bound of this confidence interval exceeded the pre-specified non-inferiority boundary of -5%, thus demonstrating non-inferiority of the MRI-TB approach. A test for superiority was then conducted and observed to be not statistically significant (p-value=0.27).

Results were similar in the per protocol population. However the lower bound of the 95% one-sided confidence interval was slightly below the pre-determined 5% threshold. Of 202 men in the TRUSBx arm, there were 67 (33.2%) with ≥GG2 cancers detected, compared with 79/219 (36.1%) in the MRI-TB arm. The risk difference was 2.9% (95% CI=-6.2% to 12.0%) with the superiority test deemed not statistically significant (p-value=0.54).

Secondary Outcomes

A total of 25 (11.1%) men in the TRUSBx arm and 30 (13.2%) men in the MRI arm had GG≥3 cancer detected, resulting in an absolute risk difference of 2.2% (97.5% CI -3.9% to ∞). The test for superiority was not statistically significant (p-value=0.57). There were fewer diagnoses of GG1 cancer in the MRI-TB arm : 23 (10.1%) vs 49 (21.7%), absolute difference 11.6%, (95% CI=-18.2% to -4.9%, p-value<0.001). PI-RADS score and biopsy grade correlated closely (see Table 3). The rate of diagnosis of GG≥2 for PI-RADS 3, 4 and 5 was 4/24 (16.7%), 49/82 (59.8%), and 26/30 (86.7%) respectively, while for GG≥3 it was 2/24 (8.3%), 16/82 (19.5%), and 12/30 (40.0%). Core number was higher in the TRUSBx arm (mean of 11.4 versus 6.3 per patient) despite having the same number (mean=4.4 in each arm) of positive cores per patient. Across all patients, 36.8% of TRUSBx cores were positive compared with 55.2%of the MRI-TB cores. No substantial differences were observed in the type of treatment received between intervention arms.

A logistic regression analysis demonstrated no significant difference in the detection of ≥GG2 cancer (odds ratio=1.28 for MRI-TB vs TRUSBx, 95% CI=0.86 to 1.93, p-value=0.23) or ≥GG3 cancer (odds ratio=1.23 for MRI-TB vs TRUSBx, 95% CI=0.69 to 2.20, p-value=0.49). In those men who underwent a biopsy, GG≥2 was detected in 79 (58.1%) by MRI-TB and 67 (33.2%) by TRUSBx (P<0.001). This represents an absolute difference of 24.9% (95% CI=14.4% to 35.5%). In the same biopsy population, GG1 was detected in 23 (16.9%) of men in the MRI-TB arm compared with 49 (24.3%) in the TRUSBx arm (p-value=0.14, absolute risk difference of 7.4%, 95% CI=-1.3% to 16.0%).

Results of secondary outcomes on the PP and biopsy only population were similar to that observed in the ITT population and are shown in the Supplemental Appendix A.

Adverse events are summarized in Table 3. The MRI arm experienced 25% fewer adverse events. Prostatitis, hematuria, hmatospermia, and incontinence occurred less frequently in the MRI arm Amongst only those men who underwent biopsy, the rate of adverse events remained in favor of the MRI-TB arm, although with a reduced risk difference, (Supplementary Appendix A). The proportion of patients indicating another biopsy would be a major or moderate problem was 15.4%, n=35 vs 6.2%, n=14 (absolute risk difference=9.2%, 95% CI=3.5% to 14.9%,

p=0.002) Further, TRUS-Bx patients were more likely to consider undergoing another biopsy a problem (53%) compared to MRI-TB patients (37%).

No significant differences were observed in the self-reported quality of life as measured by the EQ5D at baseline or at the follow-up visit (Supplementary Table B).

Prognostic Factors

Results of logistic regression analyses evaluating potential prognostic factors of ≥GG2 cancer are presented in Table 4. In the multivariable model baseline risk, PSA, PSA density and palpable tumor were prognostic for diagnosis of ≥GG2 cancer amongst patients who underwent TRUSBx. In the MRI arm, age, PSA density, BMI and palpable tumor were prognostic.

Inter-site Analyses

Supplement Table C shows differences in outcomes of interest amongst participating sites, to explore potential effects due to differences in familiarity with the MRI-fusion software as well as inter-site variability in terms of population / operator / treatment differences. The frequency of detecting cancers (i.e. having PI-RADS >=3 cancer) using MRI was significantly different, ranging from 42% to 83% (p=0.006) as was the number of ≥GG2 (from 50% to 82%, p=0.022) amongst men who underwent a biopsy, however, the number of men with ≥GG3 cancers (from 42% to 76%, p=0.14) detected was not different amongst patients who underwent a biopsy in the MRI arm. . The center with the highest ≥GG2 MRI biopsy cancer detection rate had the lowest TRUSBx rate, and vice versa.

Discussion:

. This study met its primary end point, demonstrating non-inferiority of MRI-TB to conventional systematic biopsy based on the ITT population. Secondary outcomes demonstrated there was a reduction in the rate of men undergoing biopsy of almost 40%, a substantially reduced rate of GG1 cancers or no cancer found in men who undergo biopsy and a decreased adverse event profile. In those having a biopsy, targeted biopsy was superior to systematic biopsy for the detection of GG≥2 cancer. Therefore the strategy of MRI prior to biopsy appears superior to systematic TRUS-Bx.

Performance of the MRI-TB varied between centers, with differences in both positive MRI rates and target biopsy yields. This difference occurred despite the fact that all MRIs were reviewed, and biopsies performed, by experienced radiologists or urologists. This underscores

the need for quality control measures to enable the broad application of MRI. Central review of the MRI images in this study is planned for a subsequent analysis.

This study was designed along similar lines to the PRECISION study[15,19]. The results are similar, albeit with some differences. In this study 38% had a negative MRI and avoided biopsy; in PRECISION, it was 28%. The absolute difference in the finding of clinically significant cancer was 5.2% in PRECISE vs 12% in PRECISION. The diagnosis rate for GG1 in the MRI vs systematic biopsy arms was 10.4 vs 24.3 in PRECISE and 9 vs 22% in PRECISION, which was remarkable similar. Among men who underwent a biopsy, the likelihood of GG≥2 cancer in the MRI arm vs TRUSBx arm was 58 vs 33% in PRECISE and 44 vs 18% in PRECISION (a 25% absolute difference in both studies). There are many potential reasons for these differences including variation in expertise in MRI interpretation and targeted biopsy, differences between the cohorts and variations in systematic biopsy approach. We hope to gain greater insight by central review of the MRI reads as well as follow up MRI at two years.

Multivariable logistic regression analysis identified PSA density and palpable tumor as prognostic factors in both groups. Baseline risk and PSA were prognostic in the TRUS arm only, and age and BMI in the MRI arm only. These parameters are well established prognostic features in men at risk for prostate cancer.

There was a trend toward lower complications from biopsy in the MRI arm. These patients had fewer cases of prostatitis, sepsis events, visits to the ER, and hospital admissions. In contrast, PRECISION showed no difference in serious adverse events between the two arms (2% in each group). Moderate or major resistance to the prospect of another biopsy was 43% less common (absolute difference 8.9%) amongst MRI arm patients.

There was greater lack of compliance in the TRUSBx arm, with 15 patients withdrawing because they refused TRUS biopsy.

The positive predictive value of PI-RADS 3, 4 and 5 for GG≥2 cancer was 17, 60, and 87%, respectively. These figures are dramatically superior to the predictive value reported by our group in the ASIST trial recently, where the analogous PPV was 13, 24, and 33% [12]. The reported PPV of MRI varies widely.[29,30] A recent overview of 26 centers estimated the PPV for PiRADS ≥ 4 was 49%, CI 40-58%.[30] The PPV results in PRECISE are comparable to those reported in these studies.There are a number of possible explanations for this variability, including different populations (biopsy naïve patients in PRECISE vs low risk active surveillance patients in

ASIST The most compelling explanation is that ASIST results reflected the learning curve of fusion targeted biopsy. Furthermore fewer samples per lesion were mandated in ASIST (1-3 per lesion vs 4).

Several parameters, particularly PSA density, have been identified as predictors for the risk of significant cancer in men with a negative MRI. [23a] Long term follow up on the PRECISE cohort should provide important information on this question.

Limitations of the study

Amongst men who underwent MRI, 40% did not have a biopsy, and a small proportion of these may harbor significant cancer. All of the undiagnosed and GG1 patients on this study will be followed for 2 years, and will have an MRI at the end of that period. Patients who had a concerning change in a clinical parameter suggesting undiagnosed significant prostate cancer were able to have a biopsy off protocol. The outcome of this strategy, including the proportion of patients in each group diagnosed during the period of follow-up, will be evaluated once all patients have reached the 2 year endpoint. The incremental value of systematic biopsies in men having targeted biopsies was not addressed by this study design. The MRI interpretation and biopsies were performed by experienced radiologists, thus limiting the generalizability of the results with respect to less experienced clinicians or residents. It is possible that the disease phenotype of targeted biopsy detected cancers varies from that of systematic biopsy detected cancers [31]; this question may be addressed by long term follow-up studies.

Conclusion: The intervention of MRI followed by MRI-guided biopsy in men at risk results in similar detection rates of clinically significant prostate cancer in the intention-to-treat population compared to systematic biopsy in all men, while avoiding biopsy in over 1/3rd of men and reducing the diagnosis of clinically insignificant cancer. This strategy offers substantial advantages over an initial systematic biopsy.

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Table 1. Baseline Characteristics

Baseline Characteristics		Control (TRUS-Guided Biopsy)	Experimental (MRI-Guided Biopsy)
N		226	227
Eligibility and Stratum			
Risk*	5-25% ≥25%	232 (90) 23 (10)	204 (90) 23 (10)
Study Center	London Sunnybrook Jewish General UHN Vancouver General	52 (23) 49 (22) 30 (13) 53 (23) 42 (10)	52 (23) 50 (22) 30 (13) 51 (22) 44 (19)
Demographics			
Age at Registration	Mean (sd)	64.5 (8.8)	65.3 (7.6)
Race	N (%) Caucasian African-Canadian Asian Hispanic Other Unknown	184 (81) 8 (3.5) 17 (7.5) 4 (1.8) 12 (5.3) 1 (0.4)	183 (81) 11 (4.9) 15 (6.6) 6 (2.6) 12 (5.3) 0
Family History	N (%) No Yes Do not know	133 (59) 74 (33) 19 (8.4)	152 (67) 63 (28) 12 (5.3)
ECOG Performance Status	N (%) ≥1	1 (0.4)	2 (0.9)
Height (in cm)	Mean (sd)	174.8 (7.1)	175.6 (7.0)
Weight (in kg)	Mean (sd)	84.5 (13)	83.6 (14)
Body-Mass Index†	Mean (sd)	27.7 (4.1)	27.1 (4.0)
Body-Surface Area‡	Mean (sd)	2.0 (0.2)	2.0 (0.2)
Prostate Characteristics			
PSA	Mean (sd) Median (range)	6.8 (3.0) 6.2 (1.0, 19)	7.5 (3.6) 6.7 (1.1, 24)
Prostate Volume *	Mean (sd) NA ≤20 cc 21-34 cc 35-49 cc ≥50cc	48 (25) 17 4 (1.9) 67 (32) 101 (48) 37 (18)	60 (45) 11 5 (2.3) 58 (27) 96 (44) 57 (26)
PSA Density	Mean (sd)	0.17 (0.11)	0.16 (0.11)
Palpable Tumor	NA Normal Nodule ≤1.5 cm Nodule > 1.5 cm Both Lobes	2 165 (74) 48 (21) 8 (3.6) 3 (1.3)	6 161 (73) 48 (22) 12 (5.4) 0 (0.0)
Renal Impairment	N (%) Yes	23/76 (30)	26/79 (33)

† Calculated as weight(kg) / [height(m)]^2

* as measured using the PCPTRC 2.0 calculator, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp

Table 2. Outcomes

		TRUS-Guided Biopsy	MRI-Guided Biopsy	
N		226	227	
MRI Result	PI-RADS 1-2/Negative PI-RADS 3-5/Positive 3 4 5		83 (38) 138 (61) 26 (12) 82 (38) 30 (14)	
Did not undergo biopsy	N (%)	24 (11)	91 (40)	
Underwent biopsy	N (%)	202 (89)	136 (60)	
No cancer on biopsy	N (%)	86 (38)	34 (15)	
GG1 or no cancer (including no biopsy)	N (%)	159 (70)	148 (65)	
GG1 cancer	N (%)	49 (22)	23 (10)	
GG2 cancer	N (%)	42 (19)	49 (22)	
GG2 or higher cancer*	N (%)	67 (30)	79 (35)	
GG3 cancer	N (%)	17 (8)	18 (8)	
GG3 or higher cancer	N (%)	25 (11)	30 (13)	
GG4 cancer	N (%)	3 (1)	5 (2)	
GG5 cancer	N (%)	5 (2)	7 (3)	

*** Primary outcome**

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		TRUS-Guided Biopsy	MRI-Guided Biopsy
Days, Randomization to MRI	Median (IQR)	NA	19 (11, 36)
Days, MRI to Biopsy	Median (IQR)	NA	23 (14, 39)
Days, Randomization to Biopsy	Median (IQR)	30 (16, 46)	53 (34, 82)
Further Treatments			
Further Diagnostic Testing	N	92 (41)	92 (40)
	PSA	66 (29)	74 (33)
	MRI	43 (19)	25 (11)
	Biopsy	4 (1.8)	3 (1.3)
Active Surveillance	N	75 (33)	69 (30)
Radical Treatment	N	37 (16)	43 (19)
	Prostatectomy	21 (9.3)	30 (13)
	Radiotherapy	13 (5.8)	13 (5.7)
	Unknown	3 (1.3)	0 (0.0)
Minimally Invasive Therapy (HIFU)	N	3 (1.3)	3 (1.3)
Hormone Therapy	N	6 (2.7)	3 (1.3)
Other Treatment	N	18 (8.0)	22 (9.7)
Deaths During Follow-up	N	0 (0.0)	2 (0.9)
Adverse Events			
Number of Patients with At Least 1 AE	N (%)	145 (64)	89 (40)
Most Frequent AE Experienced	Erectile Dysfunction	8 (4)	10 (4)
	Hematochezia	36 (16)	22 (10)
	Hematospermia	9 (4)	5 (2)
	Hematuria	109 (48)	44 (19)
	Pain	72 (32)	34 (15)
	Prostatitis	9 (4)	1 (1)
	Urinary Incontence	12 (5)	5 (2)
Number of Patients with At Least 1 Grade 3+ AE	N (%)	10 (4.4)	8 (3.5)
Appendicitis		0 (0.0)	1 (0.4)
Arthritis		0 (0.0)	1 (0.4)
Chills		1 (0.4)	0 (0.0)
Erectile Dysfunction		0 (0.0)	1 (0.4)
Fever		1 (0.4)	0 (0.0)
Hematuria		2 (0.9)	0 (0.0)
Hematochezia		0 (0.0)	1 (0.4)
Pain		1 (0.4)	0 (0.0)
Prostatitis		1 (0.4)	0 (0.0)
Sepsis		4 (1.8)	1 (0.4)
Urinary retention		1 (0.4)	0 (0.0)
Urinary tract infection		3 (1.3)	1 (0.4)

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Table 4. Logistic Regression of Prognostic Factors of GG2 or higher Cancer

		TRUS Bx Arm (n=202)		MRI Arm (n=221)	
Factor	**Comparator**	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Age	/ year	1.06 (1.01, 1.10)	0.009	1.07 (1.03, 1.11)	0.001
Risk	High vs Low Risk	11.13 (3.57, 34.71)	<0.001	1.93 (0.80, 4.67)	0.15
PSA	Log-transform	5.40 (2.41, 12.11)	<0.001	2.76 (1.43, 5.33)	0.003
BMI	/ unit	0.98 (0.91, 1.05)	0.53	1.05 (0.98, 1.13)	0.17
Volume	/ unit	0.97 (0.95, 0.99)	<0.001	1.00 (0.99, 1.00)	0.41
PSA Density	/ 0.1 unit	2.78 (1.88, 4.10)	<0.001	1.68 (1.25, 2.27)	<0.001
Center	LHSC Sunnybrook Jewish General UHN Vancouver	1.77 (0.73, 4.26) 0.50 (0.18, 1.39) 2.86 (1.01, 8.12) 0.75 (0.29, 1.97) Reference	0.009	0.58 (0.24, 1.41) 1.41 (0.60, 3.30) 0.91 (0.34, 2.47) 1.06 (0.45, 2.50) Reference	0.35
Family History	Yes No Do Not Know	Reference 1.06 (0.57, 2.00) 1.87 (0.56, 6.22)	0.59	Reference 1.12 (0.60, 2.09) 1.12 (0.29, 4.25)	0.94
Palpable Tumor	Normal Abnormal ≤1.5cm Abnormal >1.5cm Both lobes	Reference 2.55 (1.27, 5.12) 6.99 (1.30, 37.49) 5.59 (0.49, 63.38)	0.007	Reference 3.04 (1.54, 6.01) 1.74 (0.53, 5.76) -	0.005
Prostate volume	<=20 21-35 36-50 ≥51	7.67 (0.70, 83.74) 1.38 (0.54, 3.51) 1.20 (0.49, 2.91) Reference	0.40	Undefined 1.44 (0.64, 3.24) 1.97 (0.96, 4.06) Reference	0.32
Multivariable Analysis					
Risk	High vs Low Risk	4.98 (1.38, 17.97)	0.014		
Palpable Tumor	Normal Abnormal ≤1.5cm Abnormal >1.5cm Both lobes	Reference 2.51 (1.10, 5.72) 6.05 (0.85, 42.97) 2.36 (0.07, 79.04)	0.065	Reference 4.40 (1.96, 9.89) 1.94 (0.51, 7.45)	0.001
PSA Density	/ 0.1 unit	2.24 (1.59, 3.69)	<0.001	2.16 (1.52, 3.09)	<0.001
Age	/ year			1.08 (1.03, 1.13)	0.001
BMI	/ unit			1.15 (1.05, 1.26)	0.003

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