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Microultrasonography-Guided vs MRI-Guided Biopsy for Prostate Cancer Diagnosis
The OPTIMUM Randomized Clinical Trial

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IMPORTANCE High-resolution microultrasonography-guided biopsy is an alternative to MRI fusion-guided biopsy for prostate cancer diagnosis.

OBJECTIVE To compare microultrasonography-guided and MRI fusion-guided biopsy.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, international, open-label, randomized, noninferiority trial of biopsy-naive men from 20 centers (8 countries) with clinical suspicion of prostate cancer (elevated prostate-specific antigen [PSA] and/or abnormal digital rectal examination findings) from December 2021 to September 2024.

INTERVENTIONS Participants were assigned to receive either microultrasonography-guided biopsy (n = 121), microultrasonography/MRI fusion-guided biopsy (microultrasonography/MRI; n = 226, in which microultrasonography biopsies were performed prior to unblinding the MRI), or MRI/conventional US fusion-guided biopsy (MRI/conventional ultrasonography; n = 331). All participants received synchronous systematic biopsy.

MAIN OUTCOMES AND MEASURES The primary outcome was the difference in detection of Gleason Grade Group 2 or higher cancers using microultrasonography plus systematic biopsy vs MRI/conventional ultrasonography plus systematic biopsy. The secondary outcome was the difference in detection of Gleason Grade Group 2 or higher cancers found using microultrasonography/MRI plus systematic biopsy vs MRI/conventional ultrasonography plus systematic biopsy. The noninferiority margin was set at 10%.

RESULTS A total of 802 men underwent randomization and 678 underwent biopsy. Median (IQR) age was 65 (59-70) years and prostate-specific antigen level was 6.9 (5.2-9.8) ng/mL; 83% self-identified as White. Gleason Grade Group 2 or higher cancer was detected in 57 participants (47.1%) in the microultrasonography group, in 141 (42.6%) in the MRI/conventional ultrasonography group, and in 106 (46.9%) in the microultrasonography/MRI group. Microultrasonography-guided biopsy was noninferior to MRI fusion-guided biopsy (difference, 3.52% [95% CI, −3.95% to 10.92%]; noninferiority $P < .001$). Combined biopsy with microultrasonography/MRI was also noninferior to MRI/conventional ultrasonography software-assisted MRI fusion biopsy using conventional ultrasonography devices (difference, 4.29% [95% CI, −4.06% to 12.63%]; noninferiority $P < .001$). The rate of Gleason Grade Group 2 or higher cancer diagnosed by targeted biopsy only was 38.0% in the microultrasonography group, 34.1% in the MRI/conventional ultrasonography group, and 40.3% in the microultrasonography/MRI group; these differences were not significant.

CONCLUSIONS AND RELEVANCE The use of microultrasonography-guided biopsy was noninferior to MRI/conventional ultrasonography fusion-guided biopsy for the detection of Gleason Grade Group 2 or higher prostate cancer in biopsy-naive men. Microultrasonography may provide an alternative to MRI for image-guided prostate biopsy.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05220501

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Visual Abstract

Supplemental content

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Prostate cancer diagnosis by biopsy is paramount for risk stratification, treatment planning, and prognostication of men with prostate cancer. The incorporation of multiparametric magnetic resonance imaging (MRI) into the diagnostic workflow of biopsy-naive men has improved detection of clinically significant prostate cancer (defined as Gleason Grade Group ≥2) and reduced overdiagnosis of insignificant disease.[1] MRI with targeted biopsy detects approximately 85% of tumors considered Gleason Grade Group 2 or higher.[2,3] Because MRI is performed at a separate encounter from prostate biopsy, registration errors may be introduced by organ movement, inaccuracies in contouring, distortion from transrectal probe, and other factors.[4] Furthermore, multiparametric MRI is contraindicated in men with ferromagnetic foreign bodies and other medical devices or implants. Access to prebiopsy MRI, which requires sophisticated imaging facilities often not present in low-income nations and rural regions of higher-income nations, has also been limited, with only 36% of urban and 28% of rural residents in the US receiving an MRI prior to biopsy.[5]

A 29-MHz high-resolution microultrasonography device (ExactVu; Exact Imaging) has been specifically designed for prostate imaging and biopsy. Microultrasonography has an imaging resolution of 70 microns (0.07 mm), providing a 300% improvement in resolution to conventional ultrasonography.[6] The increased resolution of microultrasonography allows real-time visualization of prostate cancer, negating registration error. The 70-micron resolution is equivalent to the diameter of a typical prostate duct, permitting visualization of prostate cancer as malignancy alters the ductal architecture. Microultrasonography is scored using the prostate risk identification using microultrasound (PRI-MUS) system, with scores of 1 and 2 considered low-risk; 3, equivocal; and 4 and 5, suspicious for prostate cancer.[7] Previous studies suggest that microultrasonography and multiparametric MRI have similar performance in the detection of clinically significant prostate cancer.[8-19] A software-assisted fusion mode is available on the ExactVu platform that does not require contouring of the prostate to enable MRI/microultrasonography-guided biopsy.

The primary objective of this trial was to determine whether microultrasonography-guided biopsy is noninferior to MRI/conventional ultrasonography fusion-guided biopsy for the detection of clinically significant prostate cancer in biopsy-naive men. As a secondary objective, this trial also sought to determine whether combination MRI/microultrasonography fusion-guided biopsy is noninferior to MRI/conventional ultrasonography fusion-guided biopsy.

Key Points

Question Is high-resolution microultrasonography-guided biopsy noninferior to magnetic resonance imaging (MRI) fusion-guided biopsy in the detection of clinically significant prostate cancer?

Findings In this randomized clinical trial that included 678 participants, microultrasonography-guided biopsy was noninferior to MRI fusion-guided biopsy for detection of Gleason Grade Group 2 or higher prostate cancer (difference, 3.52% [95% CI, −3.95% to 10.92%]; noninferiority $P < .001$).

Meaning Microultrasonography-guided biopsy was noninferior to MRI fusion-guided biopsy and may provide an alternative to MRI for image-guided prostate biopsy.

Methods

Trial Design and Oversight

This was a phase 3, international, multicenter, prospective, open-label, noninferiority, randomized clinical trial conducted at 20 centers in 8 countries (eTable 1 in Supplement 1). Men who provided written informed consent were randomized in a 1:2:3 ratio to undergo microultrasonography-guided biopsy without MRI (microultrasonography group), combined MRI/microultrasonography fusion-guided biopsy (microultrasonography/MRI group), or software-assisted MRI/conventional ultrasonography fusion-guided biopsy (MRI/conventional ultrasonography group) (eFigure 1 in Supplement 1). The operator performing the biopsy in the microultrasonography/MRI group was formally blinded to the results of the MRI until after microultrasonography targeted biopsies were performed. This design permitted combination of data from the microultrasonography and the blinded component of microultrasonography/MRI groups, resulting in 1:1 ratio of patients in the microultrasonography group to MRI/conventional ultrasonography group for analysis. This 3-group structure allowed simultaneous testing of the primary and secondary hypotheses with the same MRI/conventional ultrasonography comparator. To definitively ensure blinding to MRI in the primary outcome measure, we included the microultrasonography group for comparison where no MRI was performed. This also ensured that, in the event that microultrasonography turned out to be inferior, only 1 in 6 patients were exposed to the risk of an inferior diagnostic test. All groups received targeted plus systematic biopsy in the same session. Randomization was performed using an online platform (TrialStat) that randomly permuted blocks of uneven size (6 or 12).

The full trial protocol has been previously published and was approved by human research ethics boards at each institution (Supplement 2).[20] The trial was designed and overseen by a steering committee, supported by Exact Imaging for study infrastructure, including clinical monitoring, with oversight by the study principal investigator. In-person monitoring was completed for all but 4 centers, which were monitored remotely; 64% of the database was monitored against source documentation. Additional risk-based monitoring was completed as required. Statistical analysis was conducted by an independent third-party biostatistician. The trial was registered at ClinicalTrials.gov (NCT05220501). This trial report adheres to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Eligible patients were biopsy-naive males 18 years or older in whom, due to an elevated prostate-specific antigen (PSA) level and/or abnormal digital rectal examination, a prostate biopsy

was deemed indicated by a urologist. Inclusion required the absence of contraindications to MRI or biopsy and absence of a prostate MRI in the past year. No limits were placed on prostate size. A complete list of the inclusion criteria is provided in Supplement 2 and eTable 2 in Supplement 1. All participants provided written informed consent. Ethnicity, a known risk factor for prostate cancer, was self-reported based on fixed categories.

Trial Procedures

After randomization, participants randomized to a group requiring MRI (MRI/conventional ultrasonography group or microultrasonography/MRI group) underwent MRI prior to biopsy, while those randomized to the microultrasonography group proceeded to biopsy without undergoing MRI. In the MRI/conventional ultrasonography group, an ultrasound fusion device was used. Participating centers were permitted to use whichever commercial device they had the most experience with. Cognitive fusion was not permitted. In the microultrasonography/MRI group, the fusion software feature incorporated into the ExactVu device was used to sample MRI targets. The operator performing the biopsy was formally blinded to the results of the MRI until after microultrasonography targeted biopsies were performed. Investigators were reminded repeatedly and for each patient to scrupulously avoid reviewing either the report or the images of the MRI prior to the microultrasonography targeted biopsy. This policy was complied with by all investigators. The biopsy strategy was similar in all groups, starting with 3 targeted samples for each region of interest and finishing with 12 systematic samples. To keep the overall number of samples required similar to standard clinical practice, operators were permitted to reduce the number of systematic samples if they felt an area was already well sampled. In the microultrasonography/MRI group, the operator sampled any microultrasonography regions of interest first while formally blinded to the MRI. After the microultrasonography targeted samples were completed, any MRI regions of interest were revealed and sampled. In the case in which an MRI region of interest overlapped completely with a microultrasonography region of interest, additional targeted samples were not taken. Both transperineal and transrectal approaches were permitted if the approach was consistent for all study groups at each site. Prostate cores were sent for standard histopathological staining and analysis by pathologists at each participating center without central review. The study end point was reached after participants completed a 7-day postbiopsy modified Prostate Biopsy Effects survey.[21]

Outcomes

The primary outcome was the difference in detection of clinically significant prostate cancer (defined as Gleason Grade Group ≥2) found using microultrasonography-guided biopsy, including targeted and systematic samples from the microultrasonography group and MRI-blinded portion of the microultrasonography/MRI group, vs MRI/conventional ultrasonography-guided biopsy, including targeted and systematic samples from the MRI/conventional ultrasonography group. The secondary outcome was the difference in detection of clinically significant prostate cancer found using microultrasonography/MRI-guided biopsy vs MRI/conventional ultrasonography-guided biopsy.

Power Calculation and Statistical Methods

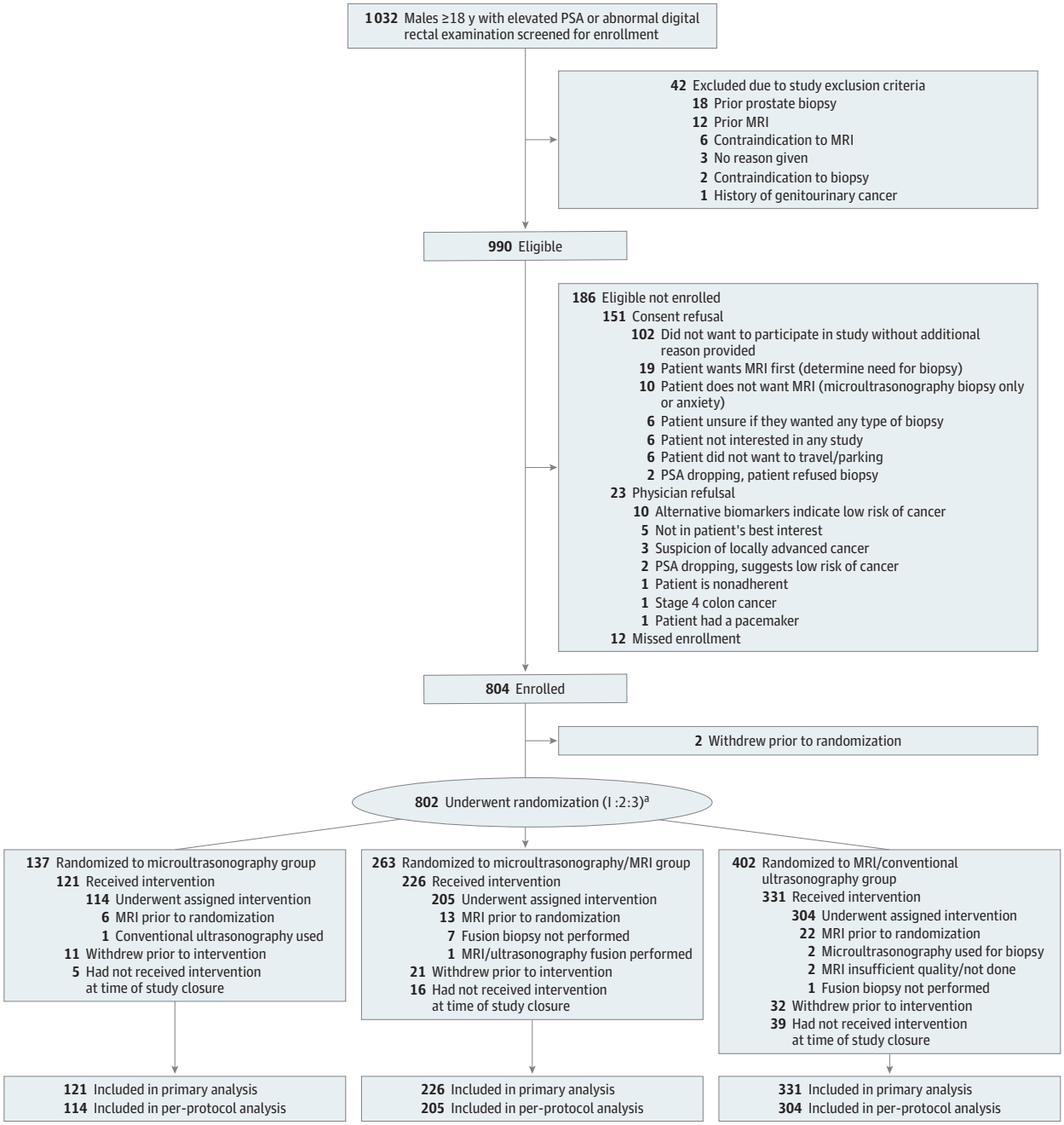
An expert panel was convened specifically to design this trial using an approach based on the RAND procedure. The justification of the noninferiority margin is based on review of 11 studies reporting on the benefit of multiparametric MRI-directed biopsy over systematic biopsy.[20] The differences between the multiparametric MRI-directed biopsy and systematic biopsy were tabulated and found to range from 5% to 18%. The panel selected 10% noninferiority and a 1-sided α of .025 as a reasonable threshold that would demonstrate clinically similar outcomes. We calculated that randomization of 1082 participants would be needed for 90% power at a clinically significant prostate cancer rate of 43% in the intention-to-treat population. This was increased to 1200 to account for dropout and simplify randomization ratios. A 43% clinically significant prostate cancer detection rate was anticipated based on the mean of published rates of detection of Gleason Grade Group 2 or higher cancer by MRI/ultrasonography fusion biopsy in previously published trials such as Precision (38%), PROMIS (37%), PAIREDCAP (61%), and PRECISE (35%).[1,2,22,23] A prespecified interim analysis was planned at 50% enrollment, which would stop the study early for success if proven with $P < .0026$ (equivalent to 99.48% CI). This was calculated using O'Brien-Fleming bounds and lowers the maximum P value at final analysis from .025 to .024. The interim analysis was successful (n = 617; 44% clinically significant prostate cancer in the microultrasonography-guided group vs 42% clinically significant prostate cancer in MRI/conventional ultrasonography-guided group (99.48% CI, −9.94 to 12.3; $P = .0025$) and thus study enrollment was concluded. A total of 802 patients were randomized due to continued recruitment during collection of data and statistical testing of the interim analysis. Both primary and secondary outcomes were prespecified in the statistical analysis plan for this study. All other results are presented ad hoc and are exploratory.

Results

Patient Characteristics

From December 2021 to September 2024, a total of 804 patients were enrolled and 802 were randomized at 20 centers: 137 patients randomized to the microultrasonography group, 402 randomized to the MRI/conventional ultrasonography group, and 263 patients to the microultrasonography/MRI group (**Figure 1**). Overall, the 3 groups were balanced with respect to baseline characteristics (**Table 1**; eTable 3 in Supplement). A total of 121 patients (88%) in the microultrasonography group, 331 (82%) in the MRI/conventional ultrasonography group, and 226 (86%) microultrasonography/MRI group underwent prostate biopsy (Figure 1). No significant differences in PSA level, digital rectal examination findings, or other risk-related parameters were found between the groups (Table 1).

Figure 1. Flow of Participants in the OPTIMUM Trial



[a]Randomization was performed using an online tool built into the electronic data capture system. No stratification or other adjustments were performed.

Outcomes

The primary outcome, detection of clinically significant prostate cancer by microultrasonography-guided biopsy vs MRI/conventional ultrasonography-guided biopsy, occurred in 160 patients who underwent microultrasonography (46%; 57 of 121 from the microultrasonography group and 103 of 226 from the blinded portion of the microultrasonography/MRI group) and in 141 patients (43%) who underwent MRI/conventional ultrasonography-guided biopsy (difference, 3.52% [95% CI, −3.95% to 10.92%]; noninferiority $P < .001$) (**Figure 2**). The outcome was similar in the per-protocol analysis, with clinically significant prostate cancer detected in 147 patients (46%) who underwent microultrasonography and 131 (43%) who underwent MRI/conventional ultrasonography (difference, 2.96% [95% CI, −4.84% to 10.72%]; noninferiority $P < .001$). Comparing only the microultrasonography group vs the MRI/conventional ultrasonography group yielded similar results (difference, 4.5% [95% CI, −5.8% to 14.8%]; noninferiority $P = .003$).

Table 1. Baseline Participant Characteristics

	No. (%)		
	Microultrasonography (n = 121)	Microultrasonography/MRI (n = 226)	MRI/conventional ultrasonography (n = 331)
Age, median (IQR), y	65 (60-71)	64.5 (59-69)	66 (59-71)
Family history of prostate cancer	113 (93)	211 (93)	317 (96)
No	84 (74)	156 (74)	239 (75)
Yes	29 (26)	55 (26)	78 (25)
Ethnicity (self-reported)	120 (99)	217 (96)	321 (97)
Asian	3 (2)	9 (4)	13 (4)
Black	3 (2)	8 (4)	16 (5)
Hispanic	9 (7)	20 (9)	15 (5)
White	105 (87)	180 (80)	277 (84)
DRE findings	89 (74)	180 (80)	277 (84)
Nonsuspicious	64 (72)	132 (73)	196 (71)
Suspicious	25 (28)	48 (27)	81 (29)
PSA, median (IQR), ng/mL	7.2 (5.5-11.0)	7.0 (5.2-9.4)	6.7 (5.1-9.5)
PRI-MUS[a]	119 (98)	222 (98)	
1	4 (3)	5 (2)	
2	20 (17)	42 (19)	
3	21 (18)	38 (17)	
4	43 (36)	68 (31)	
5	24 (20)	57 (26)	
Anterior	7 (6)	12 (5)	
PI-RADS[b]		206 (91)	307 (93)
1		3 (1)	6 (2)
2		65 (32)	105 (34)
3		17 (8)	42 (14)
4		67 (33)	84 (27)
5		54 (26)	70 (23)
Biopsy samples, median (IQR)	15 (2)	15 (4)	14 (4)
Transperineal cases, %	56 (46)	97 (43)	132 (40)

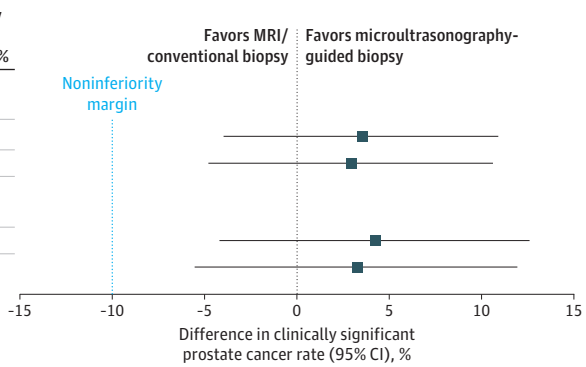
Abbreviations: DRE, digital rectal examination; PSA, prostate-specific antigen.

[a] Prostate risk identification using microultrasound (PRI-MUS), a validated risk scale for interpreting microultrasonography images of the prostate from 1 (low risk of clinically significant prostate cancer) to 5 (high risk of clinically significant prostate cancer).[7]

[b] Prostate Imaging Reporting and Data System (PI-RADS), a validated risk scale for interpreting multiparametric magnetic resonance imaging (MRI) of the prostate from 1 (low risk of clinically significant prostate cancer) to 5 (high risk of clinically significant prostate cancer).[24]

Figure 2. Primary and Per-Protocol Analyses of the Primary and Secondary Outcomes for the Detection of Clinically Significant Prostate Cancer

Outcome	Difference in clinically significant prostate cancer rate (95% CI), %
Primary outcome (microultrasonography vs MRI/conventional ultrasonography)	
Primary analysis	3.52 (-3.95 to 10.92)
Per-protocol analysis	2.96 (-4.84 to 10.72)
Secondary outcome (microultrasonography/MRI vs MRI/conventional ultrasonography)	
Primary analysis	4.29 (-4.06 to 12.63)
Per-protocol analysis	3.24 (-5.49 to 12.00)



The secondary outcome, detection of clinically significant prostate cancer by combined microultrasonography/MRI-guided biopsy vs MRI/conventional ultrasonography-guided biopsy, occurred in 106 patients (47%) who underwent microultrasonography/MRI-guided biopsy and in 141 (43%) who underwent MRI/conventional ultrasonography-guided biopsy (difference, 4.29% [95% CI, −4.06% to 12.63%]; noninferiority $P < .001$) (Figure 2). The outcome was similar in the per-protocol analysis with clinically significant prostate cancer detected in 95 (46%) patients who underwent microultrasonography/MRI-guided biopsy and 131 (43%) who underwent MRI/conventional ultrasonography-guided biopsy

Table 2. Comparison of Cancer Detection Between Groups

Tumor characteristic	No. (%)				Combined microultrasonography vs MRI/conventional ultrasonography[a]		Microultrasonography/MRI vs MRI/conventional ultrasonography[b]	
	Microultra-sonography (n = 121)	Microultra-sonography/MRI (n = 226)	Combined microultra-sonography (n = 347)[c]	MRI/conventional ultrasonography (n = 331)	Absolute difference (95% CI), %	Noninferiority *P* value	Absolute difference (95% CI), %	Noninferiority *P* value
Benign	50 (41)	81 (36)	134 (39)	139 (42)	−3 (−11 to 4)		−6 (−14 to 2)	
Grade Group ≥2	57 (47)	106 (47)	160 (46)	141 (43)	4 (−4 to 11)	<.001	4 (−4 to 13)	<.001
Grade Group ≥3	30 (25)	54 (24)	81 (23)	88 (27)	−3 (−10 to 3)	.02	−3 (−10 to 5)	.02
Gleason Grade group								
1	14 (20)	39 (27)	53 (25)	51 (27)	−2 (−10 to 6)		0 (−9 to 10)	
2	27 (38)	52 (36)	79 (37)	53 (28)	9 (−0 to 18)		8 (−2 to 18)	
3	13 (18)	24 (17)	34 (16)	39 (20)	−5 (−12 to 3)		−4 (−12 to 5)	
4	11 (15)	18 (12)	29 (13)	33 (17)	−4 (−11 to 3)		−5 (−12 to 3)	
5	6 (8)	12 (8)	18 (8)	16 (8)	0 (−5 to 5)		0 (−6 to 6)	

[a] Primary outcome.

[b] Secondary outcome.

[c] Combining the microultrasonography group with the samples taken in the microultrasonography/MRI group prior to unblinding of the MRI. Using only the microultrasonography group vs MRI/conventional ultrasonography group yielded similar results (absolute difference, 4.5% [95% CI, −5.8% to 14.8%]; noninferiority *P* = .003).

Table 3. Comparison of Cancer Detection by Targeted Samples

Diagnosis based on targeted samples	No. (%)			Microultrasonography vs MRI/conventional ultrasonography		Microultrasonography/MRI vs MRI/conventional ultrasonography	
	Microultra-sonography (n = 121)	Microultra-sonography/MRI (n = 226)	MRI/conventional ultrasonography (n = 331)	Absolute difference (95% CI), %	Noninferiority *P* value	Absolute difference (95% CI), %	Noninferiority *P* value
Grade Group ≥2	46 (38)	91 (40)	113 (34)	4 (−6 to 14)	.002	6 (−2 to 14)	<.001
Grade Group ≥3	25 (21)	49 (22)	66 (20)	1 (−7 to 9)	.004	2 (−5 to 9)	<.001

(difference, 3.24% [95% CI, −5.49% to 12.00%]; noninferiority *P* = .001).

There was no significant difference in the detection of Grade Group 1 cancer between the groups: 14 of 121 (11.6%) in the microultrasonography group, 51 of 331 (15.4%) in the MRI/conventional ultrasonography group, and 39 of 226 (17.3%) in the microultrasonography/MRI group; 1-way analysis of variance [ANOVA] *P* = .37; **Table 2**). The number of biopsy samples was slightly higher in the microultrasonography/MRI group (likely due to the additional targeting modality) compared with the other groups (mean, 15.6 samples; 1-way ANOVA *P* = .007); however, there was no significant difference between the MRI group and the microultrasonography group (mean, 14.7 vs 15.0 samples; 1-way ANOVA *P* = .39). Overall negative predictive value for clinically significant prostate cancer for PRI-MUS less than 3 was 83.1% and for Prostate Imaging Reporting and Data System (PI-RADS) less than 3 was 89.4% (difference, −6.29% [95% CI, −17.2% to 2.65%]; superiority *P* = .91). Less than 10% of biopsies showed only Gleason Grade Group 1 prostate cancer with PRI-MUS 5 or PI-RADS 5 scores.

Targeted biopsy–only detection rates (ie, ignoring systematic samples) were 38% (46/121) in the microultrasonography group and 34% (113/331) in the MRI/conventional ultrasonography group (difference, 3.88% [95% CI, −6.12% to 13.89%]; noninferiority *P* = .003) (**Table 3**). Targeted-only detection rate in the microultrasonography/MRI group was 40% (91/226) (difference vs MRI/conventional ultrasonography group, 6.12% [95% CI, −1.89% to 14.16%]; noninferiority *P* < .001). Systematic biopsy–only detection rates (ie, not including targeted samples) were 31% in the microultrasonography group, 33% in the MRI/conventional ultrasonography group, and 28% in the microultrasonography/MRI group. Systematic biopsy alone was inferior to combined targeted and systematic biopsy across all groups (difference, −13.7% [95% CI, −18.8% to 8.56%]; noninferiority *P* = .92).

When both imaging test results were negative (34/226 [15.0%] cases), clinically significant prostate cancer was detected in 8.8% of these patients compared with 73.6% of patients in whom both imaging test results were positive, which occurred in 121 of 226 patients (53.5%). Seven cases of clinically significant prostate cancer were identified by MRI when microultrasonography was negative, and 7 cases were identified by microultrasonography when MRI was negative.

Ten adverse events were reported (1.5%), with no significant differences in rates of adverse events between the groups. All adverse events were anticipated and minor; the 2 most common were postbiopsy infection (n = 3) and urinary retention (n = 4) (eTable 4 in Supplement 1).

Discussion

In this international, multicenter, randomized clinical trial, microultrasonography-guided biopsy was shown to be noninferior to MRI/conventional ultrasonography fusion-guided biopsy for the detection of clinically significant prostate cancer in biopsy-naive men. Furthermore, combined microultrasonography/MRI fusion-guided biopsy was also noninferior to MRI/conventional ultrasonography fusion-guided biopsy. These findings are consistent with previous work on microultrasonography in the form of prospective, blinded, cohort studies, all of which concluded that microultrasonography-guided biopsy was noninferior or equivalent to MRI fusion-guided biopsy.[10,11,16,19]

These findings have significant clinical implications. For patients and physicians, microultrasonography is a novel method of imaging and biopsy with potential greater accessibility for patients considering prostate biopsy, particularly for patients with contraindications to MRI. From a resource perspective, the requirement for 2 procedures (prebiopsy MRI, usually with gadolinium, and biopsy) becomes a single encounter using microultrasonography with no contrast requirement, thereby reducing wait times, cost, contrast-related morbidity, and patient anxiety. For regions with limited MRI access, microultrasonography represents an imaging and biopsy technique that omits the accessibility and resource limitations of MRI capabilities. This has particular importance given the predicted increase in prostate cancer incidence and limited MRI capacity worldwide.[25]

The findings of this multicenter international study should be generalizable to the broader urological community, but some caveats are warranted. As with MRI, physician training is required for microultrasonography. All physicians participating in the study had achieved at least "Advanced" level certification through the formal training program provided by Exact Imaging (including completion of at least 50 cases), and 12 were at "Expert" level (including at least 90 completed cases). This was implemented to avoid learning curve effects, which have been previously described.[26] The requirement for physician training is similar to learning curve and expertise requirements in studies of MRI/conventional ultrasonography fusion biopsy and MRI interpretation.[27] Care was taken to ensure all participating centers had sufficient expertise in both of these areas (eTables 5 and 6 in Supplement 1). The success of this strategy was reflected in both the low percentage of patients with PI-RADS 3 "equivocal" scores (12%) and high clinically significant prostate cancer detection rate in PI-RADS 4 (60%) and PI-RADS 5 (88%) (eFigure 2 in Supplement 1). Furthermore, as a new technology, capital investment will be required to offer this new biopsy technique. Also, the medicolegal burden of both the imaging interpretation and biopsy performance rests on the operating physician, rather than being spread across several physicians as in an MRI/ultrasonography fusion biopsy (in which a radiologist and a urologist are involved in interpretation and biopsy, respectively).

The PRI-MUS scoring system is in its first iteration, while the PI-RADS scoring system has been modified through several updated versions.[7,24] It is possible that the accuracy of targeted cores in microultrasonography-guided biopsy may change as the PRI-MUS scoring system evolves.

Results of this trial confirm previous findings that there exist tumors that are only visible on one imaging technology and not the other. It remains to be determined whether there are radiogenomic signatures that are specific for tumors when the imaging test results are not concordant and whether a microultrasonography-visible, MRI-invisible tumor portends a different prognosis then a microultrasonography-invisible, MRI-visible tumor.

Decreased detection of Gleason Grade Group 1 has been an important benefit of targeted-only biopsy.[1,28,29] In this trial, microultrasonography-guided biopsy did not increase the detection of Gleason Grade Group 1 compared with MRI fusion-guided biopsy. The caveat is that all men underwent biopsy regardless of PRI-MUS and PI-RADS scores. Similarly, the number of biopsy results showing benign tissue only did not differ between the groups. No clinically significant prostate cancer was detected in patients whose highest risk score was PRI-MUS 1 or PI-RADS 1, and Grade Group 2 or more tumors were detected in fewer than 20% of cases with PRI-MUS 2 or PI-RADS 2.

The number of targeted cores required to optimize efficiency for the detection of clinically significant cancer using microultrasonography is unclear. In this trial, 3 targeted cores were sampled per lesion. MRI studies suggest a range of 2 to 5 MRI fusion-guided cores be sampled per lesion due to registration error.[30,31] Theoretically, microultrasonography minimizes registration error encountered with MRI/conventional ultrasonography fusion devices due to the real-time visualization of the biopsy needle tracking through the abnormal-appearing (PRI-MUS 3-5) tissue. Current evidence suggests that detection rates of clinically significant cancers increases as the number of microultrasonography-guided cores (per PRI-MUS 3-5 lesion) increases to at least 3.[32]

Limitations

This study has limitations. First, the study mandated biopsy for all men in the trial. In current clinical practice, many men with PI-RADS 1 and 2 scores and a favorable PSA density avoid biopsy. Registry data suggest this is appropriate with microultrasonography as well.[17] Second, systematic biopsy in all was mandated to simplify the trial design and to provide a conservative assessment on all participants, but is at variance with current practice in some regions. If a staged screening approach with initial microUS followed by MRI when PRI-MUS was ≤3 were followed, 89/226 (39%) MRIs and 54/226 (24%) biopsies for double-negative cases would have been avoided. In turn 3 cases (1.3%) of clinically significant prostate cancer, all of which were Gleason Grade 2, would have been missed. Third, the trial design was open-label and, as such, no study team member was blinded to biopsy technique. Fourth, the MRI/ultrasonography fusion device was not standardized across sites. Investigators were permitted to use the device that they felt most confident with.

Fifth, the study was restricted to biopsy-naive men. Thus the study has not addressed the performance of microultrasonography in other clinical scenarios, including active

surveillance, men with a prior negative biopsy result, or post treatment.[9,14] Ongoing trials, such as MUSIC-Screen (in which biopsy may be avoided in the setting of negative MRI or microultrasonography imaging result; NCT06626022) and MUSIC-AS (in men with Gleason Grade Group 1 cancer undergoing confirmatory biopsy during active surveillance; NCT05558241) will help to answer these questions. Microultrasonography is a comparatively new modality that has not been studied or implemented as widely as MRI. This study was intended to draw conclusions on overall biopsy efficacy; however, there may be important differences between the technologies in implementation, potential for further advancement, and user variability that should be addressed in future work.

Conclusions

This large international, randomized clinical trial demonstrated that microultrasonography-guided biopsy is noninferior to MRI-guided fusion biopsy for the detection of clinically significant prostate cancer in biopsy-naive men. Microultrasonography represents an alternative to MRI for image-guided prostate biopsy.

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