



# MRI-guided focused ultrasound focal therapy for patients with intermediate-risk prostate cancer: a phase 2b, multicentre study

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## Summary

**Background** Men with grade group 2 or 3 prostate cancer are often considered ineligible for active surveillance; some patients with grade group 2 prostate cancer who are managed with active surveillance will have early disease progression requiring radical therapy. This study aimed to investigate whether MRI-guided focused ultrasound focal therapy can safely reduce treatment burden for patients with localised grade group 2 or 3 intermediate-risk prostate cancer.

**Methods** In this single-arm, multicentre, phase 2b study conducted at eight health-care centres in the USA, we recruited men aged 50 years and older with unilateral, MRI-visible, primary, intermediate-risk, previously untreated prostate adenocarcinoma (prostate-specific antigen  $\leq 20$  ng/mL, grade group 2 or 3; tumour classification  $\leq T2$ ) confirmed on combined biopsy (combining MRI-targeted and systematic biopsies). MRI-guided focused ultrasound energy, sequentially titrated to temperatures sufficient for tissue ablation (about 60–70°C), was delivered to the index lesion and a planned margin of 5 mm or more of normal tissue, using real-time magnetic resonance thermometry for intraoperative monitoring. Co-primary outcomes were oncological outcomes (absence of grade group 2 and higher cancer in the treated area at 6-month and 24-month combined biopsy; when 24-month biopsy data were not available and grade group 2 or higher cancer had occurred in the treated area at 6 months, the 6-month biopsy results were included in the final analysis) and safety (adverse events up to 24 months) in all patients enrolled in the study. This study is registered with ClinicalTrials.gov, NCT01657942, and is no longer recruiting.

**Findings** Between May 4, 2017, and Dec 21, 2018, we assessed 194 patients for eligibility and treated 101 patients with MRI-guided focused ultrasound. Median age was 63 years (IQR 58–67) and median concentration of prostate-specific antigen was 5.7 ng/mL (IQR 4.2–7.5). Most cancers were grade group 2 (79 [78%] of 101). At 24 months, 78 (88% [95% CI 79–94]) of 89 men had no evidence of grade group 2 or higher prostate cancer in the treated area. No grade 4 or grade 5 treatment-related adverse events were reported, and only one grade 3 adverse event (urinary tract infection) was reported. There were no treatment-related deaths.

**Interpretation** 24-month biopsy outcomes show that MRI-guided focused ultrasound focal therapy is safe and effectively treats grade group 2 or 3 prostate cancer. These results support focal therapy for select patients and its use in comparative trials to determine if a tissue-preserving approach is effective in delaying or eliminating the need for radical whole-gland treatment in the long term.

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## Introduction

Although prostate cancer is the most common malignancy in men, the course of the disease varies drastically. In men with low-risk prostate cancer, predominantly grade group 1 disease, closely monitoring the cancer using an active surveillance strategy is recommended.<sup>1</sup> Conversely, therapeutic strategies for men with intermediate-risk (ie, grade group 2 or 3) prostate cancer are directed at the whole gland, despite substantial variation in cancer volume, location, and other risk factors within this category.<sup>2</sup> Notably, radical prostatectomy or radiotherapy with or without systemic therapy is associated with substantial erectile dysfunction

in more than half of treated patients, and up to 10% of men experience long-term stress urinary incontinence.<sup>2</sup>

In contrast to whole-gland approaches, focal therapy involves selective treatment of visible and biopsy-confirmed areas of malignancy within the prostate, with preservation of normal prostate tissues outside of the treatment margins and surrounding structures. The strategy is to reduce the risk of metastases and preserve quality of life by treating only the index tumour—that is, the highest-grade tumour with the highest risk of metastasis.<sup>3</sup> The emergence of multiparametric MRI and the introduction of ultrasound–magnetic resonance fusion devices to perform MRI-targeted prostate biopsies

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### Research in context

#### Evidence before this study

We searched PubMed, with no language or date restrictions, on March 23, 2022, for all previously published observational studies or clinical trials, using the terms (“prostate cancer”) AND [“focal” OR “partial gland ablation”] AND [“therapy” OR “treatment”]. Studies typically reported single-centre retrospective data or observational registries. Overall, studies were highly heterogeneous in design and findings, including in terms of cancer risk eligibility, follow-up duration, and outcome assessment. Most prospective trials were single-centre, had small sample sizes, and did not mandate post-treatment biopsy to assess efficacy. Furthermore, most prospective studies included men with low-risk cancer for whom contemporary guidelines recommend active surveillance. Notably, the TACT study enrolled men with intermediate-risk prostate cancer treated with whole-gland ablation, using an MRI-guided transurethral ultrasound device capable of focal therapy.

#### Added value of this study

To our knowledge, this is the first phase 2 study evaluating outcomes of imaging-guided focal therapy to treat intermediate-risk prostate cancer. Our study provides longitudinal self-reported quality-of-life data across multiple domains, including sexual and erectile function, urinary

continence, and bothersome symptoms to better inform clinicians and patients. We provide complete post-treatment prostate biopsy results for all patients to enable more accurate estimates of the durability of focal therapy than 6-month biopsy results allow. In addition, we evaluate the outcomes of an imaging-guided treatment (MRI-guided focused ultrasound) that incorporates real-time magnetic resonance thermometry to continually monitor treatment effect, which is absent from other technologies used to treat prostate cancer. Our study met the prespecified criteria to establish effectiveness on the basis of the proportion of negative biopsy outcomes at 24 months, and shows that MRI-guided focused ultrasound focal therapy for patients with intermediate-risk prostate cancer is safe, and that quality-of-life outcomes compare favourably with those from studies of whole-gland treatments, such as radical prostatectomy or radiotherapy.

#### Implications of all the available evidence

Our results and the existing literature support MRI-guided focused ultrasound focal therapy in select patients and pursuit of a comparative phase 3 trial to ascertain whether a tissue-preserving approach that maintains quality of life can delay or eliminate the need for radical whole-gland treatment in the long term for patients with intermediate-risk prostate cancer.

have raised the possibility of an organ-sparing focal therapy approach.<sup>4</sup>

Novel technologies capable of focal ablation use both thermal and non-thermal energy sources. Among these treatments, high-intensity focused ultrasound has been shown to be safe and to successfully thermally ablate malignant prostate tissue in early-phase clinical trials and retrospective case series.<sup>3,5–8</sup> However, most trials of high-intensity focused ultrasound to date have occurred in single centres, included predominantly patients with low-risk prostate cancer, and were performed under ultrasound guidance, which means that treatment areas could not be directly monitored in real time. More recently, the TACT study of MRI-guided transurethral ultrasound whole-gland ablation, which enrolled men with both low-risk and intermediate-risk prostate cancer, reported that 65% of patients had no evidence of cancer at 1 year.<sup>9</sup> The MRI-guided focused ultrasound system for the prostate used in our study combines a transrectal ultrasound device for energy delivery with MRI of the pelvis to visualise the targeted tumour, monitor the therapy with magnetic resonance thermometry for real-time thermal feedback and control, and evaluate the ablated tissue immediately after treatment.<sup>10</sup> In this Article, we describe the results of a multicentre, phase 2b, clinical trial of MRI-guided focused ultrasound for the focal treatment of intermediate-risk prostate cancer.

## Methods

### Study design and participants

In this single-arm, multicentre, phase 2b study, men aged 50 years and older with unilateral, organ-confined, intermediate-risk prostate adenocarcinoma (prostate-specific antigen  $\leq 20$  ng/mL; grade group 2 or 3; tumour classification  $\leq T2$ ) visible on MRI and confirmed on combined MRI-targeted and systematic biopsy,<sup>11</sup> and with no previous treatment for prostate cancer were recruited from eight health-care centres in the USA (appendix p 3). The following exclusion criteria were applied across all sites: younger than 50 years of age; findings suspicious for extracapsular extension on MRI; calcifications detected by pre-therapy CT scan measuring 2 mm or more and within 5 mm of the rectal wall, or measuring 5 mm or more and located between the target and the sonication array; anterior margin of an index lesion 40 mm or more from the rectal wall or beyond the focal length of the transducer as measured on MRI; or hip arthroplasty-induced image distortion (a full list of exclusion criteria can be found in the protocol [appendix]). No upper age limit or minimum life expectancy requirement was imposed. Only grade group 2 or 3 cancer foci were treated; concomitant grade group 1 prostate cancer elsewhere in the gland were not treated and kept under observation. Independent institutional approval of the study was obtained by each participating research site, and all patients gave written informed consent. This

See Online for appendix

study was done according to the Declaration of Helsinki and good practice guidelines.

### Procedures

The protocol required either transperineal or transrectal MRI-targeted biopsy at baseline, 6 months, and 24 months; however, the same technique used to assess eligibility was required for the post-treatment biopsies (at 6 months and 24 months). Systematic transperineal biopsy was based on a saturation-biopsy template using a 5 mm grid. Systematic transrectal biopsy comprised 14 cores, including two cores directed to the anterior prostate gland (appendix p 1).<sup>11</sup> Targeted sampling included at least two cores directed at the MRI-visible index lesion. Pre-treatment and post-treatment biopsies were used to detect prostate cancer, assign a Gleason grade, and provide tumor quantification based on morphological features and immunohistochemistry. All biopsy results were reviewed by dedicated genitourinary pathologists. Pathology was also reviewed centrally at a core pathology laboratory, and a single pathologist at the Memorial Sloan Kettering Cancer Center was designated to confirm Gleason grading if a discrepancy was found between the treatment site and the core laboratory.

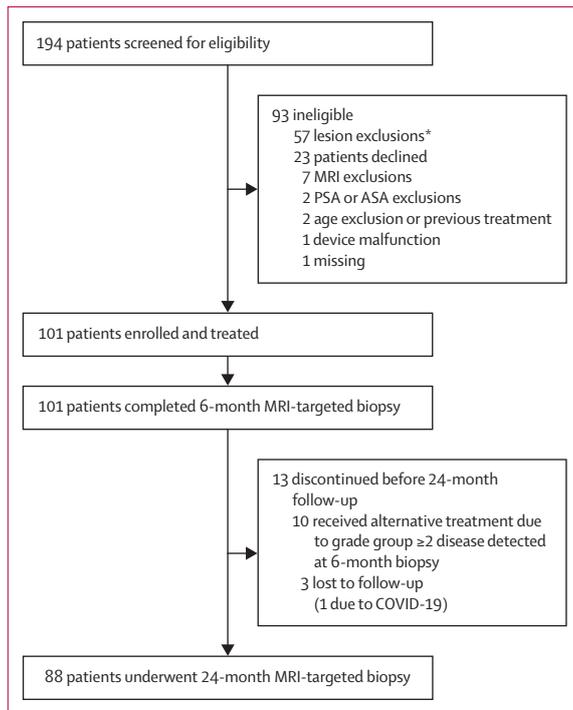
For the MRI-guided focused ultrasound procedure, patients underwent general anaesthesia and were positioned in the lithotomy position on the magnetic resonance table, and the transducer was placed in the rectum. Multiplanar MRI (axial, sagittal, and coronal T2-weighted, fast spin-echo, 3 Tesla; repetition time: 4 s; echo time: 129 ms; echo train length: 15; flip angle: 111 degrees; field of view: 20 cm; slice thickness: 3 mm; slice spacing: 0 mm; matrix: 416x256; bandwidth: 35 kHz; number of averages: 3) was then obtained and used for planning. The phased-array transducer (ExAblate; Insightec; Miami, FL, USA) configuration enabled the system to direct ultrasound energy to the desired location within the prostate on the basis of real-time thermometry MRI images acquired during sonication. Acoustic energy was sequentially titrated to temperatures sufficient for tissue ablation (about 60–70°C) guided by real-time MRI-based temperature feedback (axial echo planar imaging; three slices; repetition time: 150 ms; echo time: 11.2 ms; echo train length: 12; flip angle: 35 degrees; field of view: 28 cm; slice thickness: 3–6 mm; slice spacing: 1 mm; matrix: 144x144; bandwidth: 281 kHz; number of averages: 2; number of phases: 5) of the treated region. Between each sonication, updated anatomical MRI (axial and sagittal T2-weighted fast spin-echo, 3 Tesla; repetition time: 5459 ms; echo time: 116 ms; echo train length: 21; flip angle: 111 degrees; field of view: 28 cm; slice thickness: 3 mm; slice spacing: 0 mm; matrix: 384x256; bandwidth: 31 kHz; number of averages: 1) was acquired to allow for intraoperative modification of the treatment plan to account for treatment-induced changes in the gland volume. Sonications swept across the region of treatment

slice-by-slice through the prostate gland, with sonication repeated on each axial slice until the user-specific tumour and treatment margin were covered by thermal dose. This MRI-guided focused ultrasound acoustic energy was delivered to the MRI-visible lesion (grade group 2 or 3), including a planned margin of at least 5 mm of surrounding, healthy-looking tissue. The MRI-visible lesion was defined as having a Prostate Imaging Reporting and Data System score of 3 and above. Details of the ExAblate MRI-guided focused ultrasound device and treatment protocol are described in the appendix (pp 1–2).

All patients underwent combined MRI-targeted and systematic prostate biopsy 6 months and 24 months after the procedure; these biopsies also included at least two cores aimed at the ablated area. Patients who met criteria for failure (grade group  $\geq 2$  on the 6-month or 24-month biopsy) and underwent radical prostatectomy or radiotherapy exited the study but were included in the final analysis. When biopsy results were not available at 24 months and grade group 2 or higher cancer had been found in the treated area at 6 months, 24-month results were assumed to be grade group 2 or higher. Standard multiparametric MRI was used before the biopsy at 6 and 24 months after treatment. Safety of the MRI-guided focused ultrasound therapy was assessed with standard adverse event reporting at each follow-up visit (at 1 week, and at 1, 3, 6, 9, 12, 18, and 24 months). Adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Urinary function was measured with the International Prostate Symptom Score and the International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form (ICIQ–UI SF).<sup>12,13</sup> Erectile function was measured with the 15-item International Index of Erectile Function (IIEF); this questionnaire also measured intercourse and overall satisfaction.<sup>14</sup> Health-related quality of life was evaluated using the Functional Assessment of Cancer Therapy–Prostate.<sup>15</sup> These measures were all taken at baseline and 3, 6, 9, 12, 18, and 24 months after. We also measured prostate-specific antigen concentrations in the serum of patients at baseline and 6, 12, and 24 months.

We collected data on the use of medications or devices to support sexual function as recommended by the International Consortium for Health Outcomes Measurement; post-treatment erectile dysfunction was defined using the CTCAE version 4.03. Grade 0 erectile dysfunction was defined as an IIEF score of 24 or higher, or a 4-point or less decrease from baseline with no change in medication status. Grade 1 erectile dysfunction was defined as an IIEF score of 11 or higher (moderate erectile dysfunction) without initiating medications or devices to support sexual function. Grade 2 erectile dysfunction was defined as moderate erectile dysfunction supported by medication initiated after treatment.



**Figure 1: Study flow diagram**

\*Lesion exclusions were due to a Gleason score of more than 3, the lesion not being visible or a PI-RADS score of less than 3, calcifications as described in the protocol, the lesion being more than 4 cm from the rectal wall or a tumour size of more than 50% of the prostate gland volume, or lesion contact with capsule or extracapsular extension. ASA=American Society of Anesthesiologists. PI-RADS=Prostate Imaging-Reporting and Data System. PSA=prostate-specific antigen.

Grade 3 erectile dysfunction was defined as an IIEF score of less than 11, independent of whether medication was initiated after treatment.

**Outcomes**

Co-primary outcomes were oncological outcomes and safety. Oncological efficacy was defined as absence of cancer that was grade group 2 or higher in the treated area on prostate biopsy 6 months and 24 months after treatment. Safety was measured by standard adverse event reporting 24 months after treatment. We also report biopsy results for the whole prostate gland. The secondary endpoints were genitourinary functional outcomes (urinary and erectile function) and overall quality of life.

**Statistical analysis**

The original sample size required 40 patients, on the basis of a one-stage phase 2 design with null and alternative proportions of 60% and 80% of patients free of grade group 2 or higher cancer in the treated area at 24 months, and a decision rule of 30 responders at 6 months. After institutional review board approval at multiple institutions, the US Food and Drug Administration’s 510K study guidance mandated expanding the sample size to

	Patients (n=101)
Age, years	63 (58–67)
Prostate-specific antigen, ng/mL	5.7 (4.2–7.5)
Race	
White	87 (86%)
Black	7 (7%)
Other	7 (7%)
Clinical classification ≤T1c	84 (83%)
Grade group	
2	79 (78%)
3	22 (22%)
Baseline patient-reported functional outcomes	
Functional erection: IIEF-15≥24	58/99 (59%)
Urinary continence: ICIQ<10	98/100 (98%)
Treatment parameters	
Duration, min	110 (79–141)
Number of sonications	15 (12–18)

Data are median (IQR) or n (%). IIEF=International Index of Erectile Function. ICIQ=International Consultation on Incontinence Questionnaire.

**Table 1: Baseline patient and treatment characteristics**

100 patients to adequately estimate the adverse event profile with clinically meaningful precision, including the incidence of infrequent device-related or procedure-related complications. Therefore, the protocol was amended, adding a range of 100–103 participants to allow any patients in the screening process and who met eligibility requirements to be treated, even if we were approaching our treatment limit. We report descriptive statistics for biopsy outcomes with 95% exact binomial CIs. The null and alternative proportions of 60% and 80% free of grade group 2 or higher cancer in the treated area at 24 months were maintained. Efficacy, safety, and quality of life were assessed in all patients enrolled in the study.

To assess changes in genitourinary functional outcomes, quality of life, and prostate-specific antigen concentrations, we used generalised estimating equations regression to estimate the mean change from baseline scores along with 95% CIs. We specified these models using exchangeable correlation structure. We described changes in erectile function after treatment by stringently defining functional erections as having an IIEF-15 score of 24 or higher.<sup>16</sup> Similarly, we report longitudinal generalised estimating equations probability estimates for urinary continence, defined as an ICIQ-UI SF score of less than 10.

Statistical analyses were done on R version 4.0.4 with the geepack (v1.3.1), tidyverse (v1.3.1), and gtsummary (v1.5.2) packages.<sup>17–20</sup> This study is registered with ClinicalTrials.gov, NCT01657942.

**Role of the funding source**

The funders of the study had no role in study design, data analysis, data interpretation, or writing of the report. Insightec played a limited role in the centralised collection and monitoring of data from the sites.

	Targeted area only		Whole prostate gland	
	6 months (n=101)	24 months (n=89)*	6 months (n=101)	24 months (n=98)†
<b>Oncological efficacy</b>				
No evidence of grade group $\geq 2$	96 (95%)	78 (88%)	77 (76%)	59 (60%)
<b>Biopsy outcome</b>				
No evidence of cancer	92 (91%)	71 (80%)	41 (41%)	39 (40%)
Grade group 1	4 (4%)	7 (8%)	36 (36%)	20 (20%)
Grade group 2	4 (4%)	6 (7%)	18 (18%)	24 (24%)
Grade group 3	1 (1%)	2 (2%)	3 (3%)	9 (9%)
Grade group 4	0	1 (1%)	2 (2%)	3 (3%)
Grade group 5	0	2 (2%)	1 (1%)	3 (3%)

Data are as n (%). \*There was one patient with a grade group 2 or higher result in the treatment region at 6 months and missing data at 24 months; this patient was assumed to be grade group 2 or higher at 24 months. †There were nine participants with grade group 2 or higher results outside of the treated area at 6 months and missing data at 24 months; these participants were assumed to be grade group 2 or higher at 24 months.

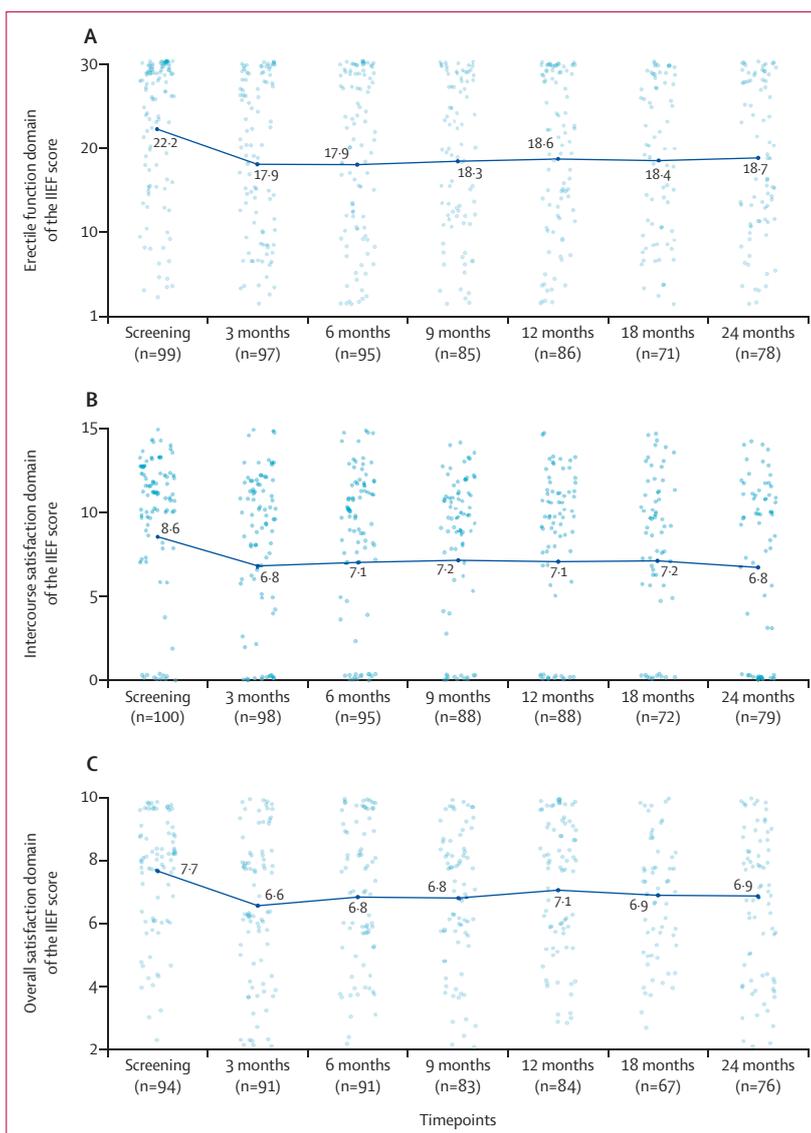
**Table 2: Detection of prostate cancer from the combined MRI-targeted and systematic biopsy at 6 and at 24 months**

## Results

From May 4, 2017, to Dec 21, 2018, 194 men were assessed for eligibility; 93 did not pass screening and 101 were enrolled on the study and treated with MRI-guided focused ultrasound (figure 1). Overall, 53 (52%) of 101 patients had treatment in the apex, 81 (80%) had treatment in the mid-gland, 44 (44%) had treatment in the base, and 26 (26%) had treatment directed anteriorly in the transition zone. The median age was 63 years (IQR 58–67), and median concentration of prostate-specific antigen was 5.7 ng/mL (4.2–7.5). The median treatment duration was 110 min (IQR 79–141), including the time after induction of anaesthesia and the patient being positioned before the initial MRI scan until the final sonication before the patient was extubated (table 1).

Overall, 96 (95% [95% CI 89–98]) of 101 patients had no evidence of grade group 2 or higher prostate cancer on 6-month MRI-targeted and systematic biopsy in the treated area of the prostate gland, and 78 (88% [79–94]) of 89 patients had no evidence of grade group 2 or higher cancer in the treated area on 24-month biopsy (table 2). Our findings met the original prespecified criteria for effectiveness: the lower bound of the 95% CI was greater than 60% for the proportion of biopsies negative for grade group 2 or higher cancer at 24 months and the observed rate exceeded 80%. Among the 11 men with grade group 2 or higher cancer detected in the treatment area at 24 months, three had grade group 4 or higher cancer.

There was no evidence of grade group 2 or higher cancer anywhere in the prostate gland in 77 of 101 men (76% [95% CI [67–84)]) at 6-month combined MRI-targeted and systematic biopsy or in 59 of 98 men (60%



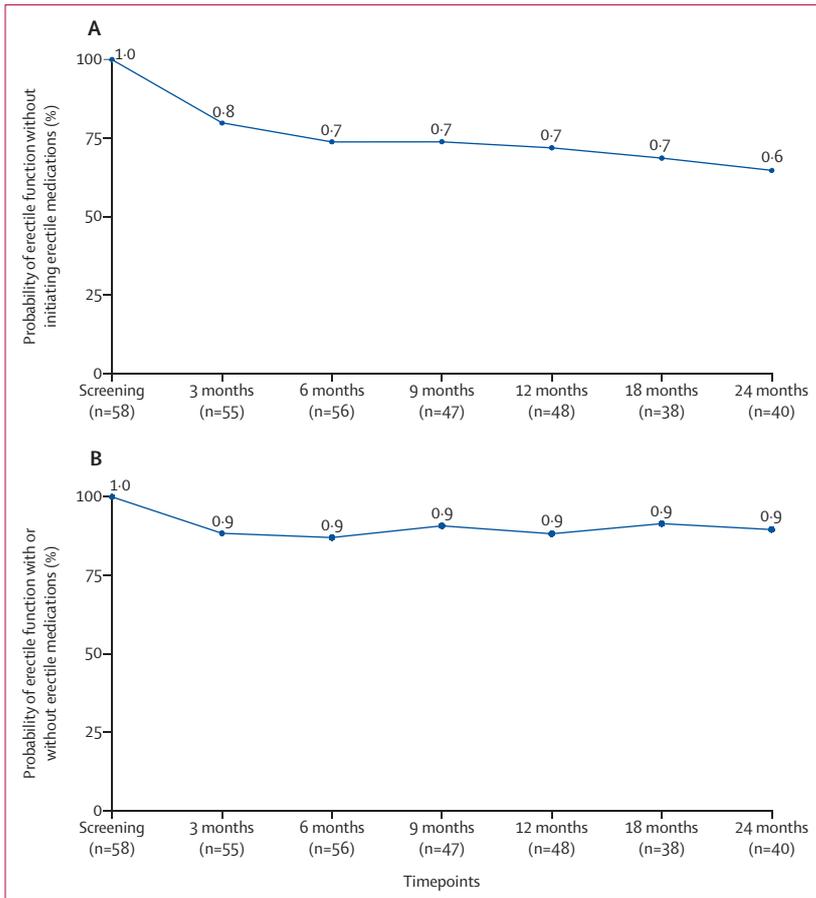
**Figure 2: Baseline and longitudinal mean IIEF-15 scores**

(A) Erectile function. (B) Intercourse satisfaction. (C) Overall satisfaction. Jitter has been added to mitigate point overlap. Blue dots and solid line denote means. At each timepoint, values are given for the mean. IIEF=International Index of Erectile Function.

[50–70]) at 24-month combined biopsy (table 2; appendix p 4). At the 6-month biopsy, 19 of 101 men (19% [12–28]) had newly detected grade group 2 or higher cancer outside of the treatment area only.

Serum prostate-specific antigen measurements decreased after treatment and stabilised at 6 months before rising slightly at 24 months (appendix p 5). The mean decrease in prostate-specific antigen after treatment was  $-3.0$  ng/mL (95% CI  $-3.6$  to  $-2.4$ ) at 6 months and  $-2.6$  ng/mL ( $-3.3$  to  $-2.0$ ) at 24 months.

IIEF-15 erectile function scores were slightly worse at 24 months than at baseline (mean score difference  $-3.5$  [95% CI  $-5.4$  to  $-1.6$ ]), as were mean intercourse satisfaction ( $-1.8$  [ $-2.9$  to  $-0.8$ ]) and overall satisfaction scores



**Figure 3: Probability of functional erections over time**  
 (A) Patients reporting functional erections (IIEF score  $\geq 24$  or  $\leq 4$ -point decrease) or moderate erectile function (IIEF score  $\geq 11$ ) without a change in medication status. (B) Patients reporting functional erections (IIEF score  $\geq 24$  or  $\leq 4$ -point decrease) or moderate erectile function (IIEF score  $\geq 11$ ) whether or not medication was initiated. Patients who did not report an IIEF score of 24 or higher ( $n=43$ ) at baseline are excluded. Blue dots and solid line denote mean. IIEF=International Index of Erectile Function.

( $-0.8$  [ $-1.3$  to  $-0.3$ ; figure 2). On the basis of a commonly used alternative definition of adequate erections (IIEF question 2 score  $\geq 2$ ), 69 (76%) of 91 patients who met that definition at baseline responded to a 24-month follow-up survey and 58 (84%) of 69 reported achieving erections adequate for intercourse.

The probability of functional erections decreased slightly over the follow-up period. Of 58 men who reported functional erections at baseline (IIEF score  $\geq 24$ ), 40 (69%) responded at the 24-month follow-up, of whom 18 (45% [95% CI 29–62]) reported grade 0 erectile dysfunction, seven (18% [7–33]) reported grade 1 erectile dysfunction (no change in erectile medications), 11 (28% [15–44]) reported grade 2 erectile dysfunction (initiation of erectile medications; figure 3), and four (10% [3–24]) reported grade 3 erectile dysfunction (IIEF score  $< 11$  regardless of medication). The mean IIEF score difference between baseline and 24 months among participants with an IIEF score less than 24 at baseline was  $-0.16$  (95% CI  $-3.2$  to  $2.8$ ; appendix p 6).

Lower urinary tract symptoms, assessed by International Prostate Symptom Score, were similar at baseline ( $n=99$ ) and at 24 months ( $n=79$ ; mean score difference 1.1 [95% CI 0.33 to 1.8]), as were mean International Prostate Symptom Score quality of life scores (0.07 [ $-0.12$  to 0.27]). Overall, most patients reported moderate or mild lower urinary tract symptoms at baseline and throughout the study period (appendix p 7). Although 18 (18%) of 101 patients reported grade 2 or lower incontinence, no patient reported stress urinary incontinence requiring pad use throughout the study period. The reported probability of excellent urinary continence, defined as an ICIQ-UI SF score of less than 10, was 100% (79 of 79) 24 months after treatment for those who reported continence by this definition at baseline (appendix p 8). Functional Assessment of Cancer Therapy–Prostate overall scores were similar at 24 months ( $n=80$ ; mean change  $-2.6$  [ $-5.6$  to 0.4]) compared with baseline ( $n=97$ ).

No serious treatment-related adverse events were observed during the study period. Only one grade 3 adverse event (urinary tract infection) related to the device or procedure was reported, and it resolved within 3 days. Common adverse events that were grade 2 or lower were haematuria, reported in 24 (24%) of 101 patients and urinary retention, in 15 (15%) of 101 patients. Urinary retention was observed immediately after treatment and resolved within 7 days. One patient experienced a urethral stricture after 90 days that resolved after a single dilation (table 3). There were no deaths.

## Discussion

The results of this study show that MRI-guided focused ultrasound focal therapy targeting an MRI-visible index lesion using real-time magnetic resonance thermometry has a low rate of genitourinary adverse events and can be used to treat grade 2 and 3 index lesions with a high degree of success. These data support the efficacy of MRI-guided focused ultrasound focal therapy for targeting prostate cancer tissue in adequately selected patients with intermediate-risk prostate cancer seeking to avoid radical whole-gland treatment. No serious adverse events associated with MRI-guided focused ultrasound treatment were reported, showing the safety of the procedure as a minimally invasive approach to selectively treat cancer within the prostate gland and preserve adjacent structures crucial for urinary and bowel continence and erectile function.

By 24 months, no patient had reported urinary incontinence requiring pad use. The probability of functional erections decreased slightly over the follow-up period. Furthermore, although the difference in mean erectile function scores was significant, the small difference should be interpreted across the range of the overall score and considered across the time range of 2 years, in which small decreases in erectile function score are expected without treatment, making this change statistically but not clinically significant. These

functional outcomes compare very favourably to patient-reported outcomes after whole-gland treatments, such as radical prostatectomy and radiotherapy, which, although effective, are associated with substantial and persistent side-effects that impact quality of life.<sup>2</sup> In an observational study including 1386 men with favourable-risk localised prostate cancer enrolled in population-based registries in the USA,<sup>2</sup> only 28% of patients who underwent nerve-sparing radical prostatectomy and 51% of patients who underwent external beam radiation therapy reported erections sufficient for intercourse 1 year after treatment; 50% reported urinary leakage requiring pad use 1 year after radical prostatectomy.

The oncological outcomes of focal therapy targeting prostate cancer using ultrasound-guided high-intensity focused ultrasound have been studied in a few single-arm trials and retrospective case reports. A single-arm study involving 42 men with low-risk and intermediate-risk prostate cancer showed no evidence of cancer after high-intensity focused ultrasound in 77%, while 92% were free of grade group 2 or higher cancer 6 months after treatment.<sup>5</sup> Another single-arm clinical trial that used high-intensity focused ultrasound to focally treat index tumours in 56 patients with low-risk and intermediate-risk prostate cancer showed that 65% of men had no evidence of cancer in the treated area.<sup>3</sup> A single-institution registry enrolling 72 patients with low-risk and intermediate-risk prostate cancer who underwent hemi-gland high-intensity focused ultrasound treatment reported that 84% of patients had no evidence of cancer in the targeted area.<sup>6</sup> A multicentre registration study of 625 men treated with high-intensity focused ultrasound, with a median follow-up of 56 months, reported that 98% of patients were free of metastasis at 5 years. This cohort described by Guillaumier and colleagues<sup>7</sup> differed from our study because it included about 30% of patients with low-risk prostate cancer and allowed retreatment with high-intensity focused ultrasound for clinically significant biopsy-detected prostate cancer within or outside of the original treatment area. In addition, unlike our study, in which every patient underwent post-treatment biopsy to assess disease recurrence, Guillaumier and colleagues relied on imaging and clinical characteristics to trigger biopsy, meaning that only 222 (36%) of 625 men in their study underwent post-treatment prostate biopsy.<sup>7</sup> Similarly, in a retrospective study of 1032 patients with prostate cancer treated with either focal or hemi-ablation, Stabile and colleagues<sup>8</sup> reported that only 424 (41%) of 1032 patients underwent post-treatment biopsy, and 208 (49%) of 424 patients had grade group 2 or higher prostate cancer after treatment.

In comparison with these previous clinical trials and observational studies, our study had a higher rate of success in treating cancer in the targeted region, which might be explained by several factors. First, the previous studies were conducted using an ultrasound-guided

	Grade 1-2 (n=101)	Grade 3 (n=101)
Anal or rectal pain	2 (2%)	..
Bladder spasm	3 (3%)	..
Bullous dermatitis	1 (1%)	..
Constipation or bloating	3 (3%)	..
Deep vein thrombosis	1 (1%)	..
Diarrhoea	1 (1%)	..
Ejaculation disorder	9 (9%)	..
Erectile dysfunction	20 (20%)	..
Fatigue	8 (8%)	..
Groin, pelvic, or suprapubic pain	3 (3%)	..
Haematospermia	13 (13%)	..
Haematuria	24 (24%)	..
Haemorrhoidal haemorrhage	1 (1%)	..
Oedema limbs	2 (2%)	..
Orchitis	1 (1%)	..
Paraesthesia	1 (1%)	..
Penile or testicular pain	13 (13%)	..
Positional pain	1 (1%)	..
Proctitis	1 (1%)	..
Prostatic cyst	1 (1%)	..
Prostatic pain	1 (1%)	..
Testicular infection	1 (1%)	..
Urethral stricture	1 (1%)	..
Urinary frequency	9 (9%)	..
Urinary hesitancy	6 (6%)	..
Urinary incontinence	18 (18%)	..
Urinary retention	15 (15%)	..
Urinary tract infection	1 (1%)	1 (1%)
Urinary tract pain	6 (6%)	..
Urinary urgency	6 (6%)	..
Vertigo	1 (1%)	..

Data are as n (%). No grade 4 or 5 events occurred in the study population.

**Table 3: Adverse events associated with the MRI-guided focused ultrasound procedure at 24 months**

device, which does not have MRI's ability to both delineate the tumour target accurately and provide precise real-time monitoring of the treatment effect by magnetic resonance thermometry. The MRI-guided focused ultrasound device is a closed-loop system that combines a transrectal phased-array transducer to guide ultrasound waves using high-resolution anatomic MRI and real-time magnetic resonance thermometry for intra-operative treatment verification. Second, as part of patient selection, the patients enrolled in our study underwent systematic biopsy and either MRI-targeted prostate biopsy or in-gantry MRI-guided prostate biopsy for selection, and treatment was imaging-guided to a region of interest on MRI confirmed to be the index cancer. Third, studies comparing 3-dimensional software-based registration of MRI and whole-mount pathology specimens after radical prostatectomy report

that MRI underestimates histologically determined tumour boundaries.<sup>21</sup> Our treatment planning included a treatment margin around the tumour of at least 5 mm and up to 10 mm—confirmed during real-time magnetic resonance treatment planning—to enhance the probability of treating the entire histological tumour volume during focal ablative therapy.

Achieving successful oncological outcomes for patients treated with focal therapy is dependent not just on expertise in the technique used for treatment, but also on appropriate patient selection. At the 6-month biopsy, 19 (19%) of 101 men had newly detected grade group 2 or higher cancer outside of the treatment area only. Given the short interval between biopsies, rather than representing new sites of cancer, these men most probably harboured these additional undetected cancers before treatment. This is consistent with previous retrospective data showing that up to 20% of prostate cancer foci measuring less than 1 cm can be missed on MRI-guided targeted and systematic template biopsy.<sup>4</sup> Although the long-term clinical significance of these newly detected low-volume grade group 2 or 3 tumours is unknown, saturation systematic-template prostate biopsy combined with MRI-targeted biopsy cores might be important to minimise short-term treatment failure after focal therapy.<sup>11</sup>

Our study had three key strengths. First, we did a prospective clinical trial with oncological outcomes based on protocol-mandated imaging-guided prostate biopsy and longitudinal data collection assessing quality of life. The participation of multiple institutions, including both academic centres and a private health system, improved the generalisability of these results. Second, our study enrolled only patients with intermediate-risk prostate cancer for whom treatment was considered necessary, but for whom avoidance of radical prostatectomy or radiotherapy would reduce morbidity. Third, our results compare favourably to other prospective focal therapy trials; 88% of our patients had no clinically significant cancer (grade group 2 or higher) after treatment in the targeted area and 60% overall were observed to not have clinically significant prostate cancer detected anywhere within the prostate gland, thereby avoiding whole-gland treatment for at least 24 months after MRI-guided focused ultrasound treatment.

Important limitations of our study are that 24-month biopsy is not a sufficient surrogate endpoint for metastases or cancer-specific death. However, the aim of the study was to evaluate whether using MRI-guided focused ultrasound focal therapy can avoid whole-gland treatment based on biopsy outcomes after treatment; the detection of metastases is unlikely in an intermediate-risk prostate cancer cohort during the 2-year study period. Additionally, in the absence of a comparative group of patients with intermediate-risk prostate cancer randomised to active surveillance, we cannot estimate the long-term clinical benefit of treating these men rather than following them

on an active surveillance protocol. However, among patients with grade group 2 prostate cancer managed with active surveillance, observational studies report that about 40% have disease progression to higher-grade cancer requiring definitive treatment after a median follow-up of 3–4 years.<sup>22,23</sup> On the basis of these findings and contemporary treatment trends, most of these men would have undergone treatment with surgery or radiation if they had not been treated with MRI-guided focused ultrasound. In our study, grade group 3 or higher prostate cancer was detected in only 15% of patients 24 months after treatment.

In conclusion, MRI-guided focused ultrasound focal therapy targeting an MRI-visible index lesion using real-time magnetic resonance thermometry has a low rate of genitourinary adverse events and, on the basis of 24-month biopsy outcomes, can be used to treat grade group 2 and 3 index lesions with a high degree of success. These data support the effectiveness of MRI-guided focused ultrasound focal therapy to target prostate cancer tissue in adequately selected patients with intermediate-risk prostate cancer seeking to avoid radical whole-gland treatment.

#### Contributors

All authors contributed to study design. BE, FH, and AJV were responsible for data acquisition and collection. BE, DDS, CMT, FH, GAS, and PG did the analysis and interpretation of the data. BE, DDS, and FH accessed and verified all data. All authors participated in drafting and revising the manuscript and approved the final version before submission. All authors had full access to all data for the study, take complete responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

#### Declaration of interests

BE attends the medical advisory board of Insightec as an unpaid consultant, and has previously received consulting funds from Myriad Genetics. CMT reports consulting funds from Profound. DDS reports consulting funds from OPKO Health and Steba. ASK is on the medical advisory board of Insightec, Profound, and Janssen, and has received consulting funds from Advantagene DSMC, Bristol Myers Squibb, Merck, Bayer, and General Electric. Q-DT reports consulting funds from Astellas, Bayer, Intuitive Surgical, and Janssen. JCD is the Chief Clinical Officer for Ajax Health and Cordis Accelco and has equity interests in Cordis; is on the advisory board and has ownership or equity interests in Serpex Health and Adient Medical; and serves as the past chair of the Society of Interventional Radiology Foundation. OA has ownership or equity interests in Ezra AI. AJV is named on a patent for a statistical method to detect prostate cancer that has been commercialised by OPKO Health (from which he receives royalties and stock options) and has received consulting funds from Insightec and Steba. PTS is named on a patent for a statistical method to detect prostate cancer that has been commercialised by OPKO Health (from which he receives royalties and stock options) and chairs the medical advisory board of Insightec as an unpaid consultant. DS is the medical director and founder of Sperling Prostate Center, a private facility for prostate cancer treatment in Delray Beach, FL, USA. LAM has collaborative and research agreements with Philips Healthcare and Biobot Surgical. GAS is on the medical advisory board of miR Scientific. PG is on the medical advisory boards of Insightec and SonALASense and has ownership or equity interests in SonALASense. All other authors declare no competing interests.

#### Data sharing

All proposals for data sharing should be submitted to the corresponding author for consideration. Access to deidentified participant data that underlie the results reported in this Article will be granted if the proposal is approved (ie, found to be methodologically sound); use of the

data is intended only for the aims in the approved proposal. These data will be made available immediately after publication, with no end date. The study protocol is available to all as part of the supplemental material for this Article.

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