

REVIEW ARTICLE

# Technical development in high-intensity focused ultrasound for localized prostate cancer: Intraoperative compression of the prostate

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## Abstract

High-intensity focused ultrasound (HIFU) has emerged as a widely adopted, minimally invasive treatment for localized prostate cancer (PC). Although originally applied for whole-gland treatment, recent advancements in imaging and technology have facilitated the adoption of HIFU as a focal therapy modality, targeting clinically significant prostate cancer (CSPC) while preserving surrounding functional structures. Recently, transrectal prostate compression during HIFU has been developed to improve treatment precision by reducing intraoperative prostatic swelling and minimizing target displacement. This method improves the ultrasound propagation path, enhances cavitation, and mitigates the heat-sink effect by reducing blood flow within the prostate. Clinical outcomes using HIFU with compression in 240 patients demonstrated high biochemical and pathological disease-free survival rates across low-, intermediate-, and high-risk groups (93.7%/92.2%, 88.5%/91.6%, and 84.8%/86.6%, respectively), with radical treatment-free survival >94% in all groups. Complication rates were low, with no cases of recto-urethral fistula reported. The rate of CSPC detection in follow-up biopsies was significantly lower than in previous studies, suggesting improved local control. These findings support the efficacy and safety of focal HIFU therapy with intraoperative compression as a promising treatment for localized PC.

## KEYWORDS

clinical outcomes, high-intensity focused ultrasound, prostate cancer, technical development

## 1 | INTRODUCTION

High-intensity focused ultrasound (HIFU) has been applied as a minimally invasive treatment modality for prostate cancer (PC)<sup>[1]</sup>. Initially used for whole-gland therapy, HIFU has recently been implemented as a focal therapy approach that targets clinically significant cancer while preserving normal tissues. Advances in HIFU technology have led to improved therapeutic outcomes<sup>[2]</sup>, and further enhancements have been achieved through refinements in treatment techniques<sup>[3,4]</sup>. Here,

we present an overview of HIFU treatment outcomes, focusing on the underlying principles, technical innovations, and their contribution to clinical efficacy.

## 2 | PRINCIPLES AND DEVICES OF HIFU FOR PC

HIFU generates ultrasound waves through a spherical transducer, which focuses ultrasonic energy on a focus area, which are precise focal points of mm in diameter<sup>[5]</sup>.

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The thermal and mechanical effects of HIFU destroy the target prostate tissue<sup>[5]</sup>. Madersbacher et al. studied focal ablation using HIFU in 10 patients before radical prostatectomy. They measured the temperature in the treated area with a trans-peritoneal thermocouple and found a range of 70–98.6°C during ablation. The results confirmed that the targeted prostate area was accurately treated<sup>[1]</sup>. Additionally, by examining prostate specimens removed immediately after hemi-ablation, Beerlage et al. verified that HIFU successfully caused focal ablation and necrosis<sup>[6]</sup>. PC treatment planning using commercial HIFU devices is based on high-resolution transrectal ultrasound (TRUS) imaging. To accurately define the treatment area, three-dimensional (3D) cancer localization data from pre-operative MRI-TRUS fusion image-guided biopsies were combined with 3D ultrasound images from the HIFU device. Treatment was planned using axial, sagittal, and coronal views of the prostate (Figure 1A). During treatment, the “popcorn” phenomenon, caused by tissue cavitation, indicates that the targeted area has received sufficient energy for effective ablation (Figure 1B)<sup>[7]</sup>. This energy delivery can be adjusted based on real-time TRUS images to evaluate the appearance of the phenomena<sup>[8]</sup> and monitor tissue change in the Sonablate® device (Figure 1C). However, currently, there are no established objective indicators to evaluate the so-called “popcorn” phenomenon. Future studies are warranted to develop standardized criteria for its assessment. The endorectal probe used in HIFU is sheathed for protection, placed into the rectum, and cooled with circulating water or fluid. This cooling system continuously circulates liquid to keep the rectal wall temperature <22°C, thereby preventing heat damage during treatment<sup>[9]</sup>.

### 3 | CLINICAL RESULTS OF WHOLE-GLAND THERAPY USING HIFU

Long- and medium-term clinical outcomes of HIFU for localized PC have been previously reported. Crouzet et al. studied transrectal HIFU with a median follow-up period of 6.4 (0.2–13.9) years. Among the patients, 60% ( $n = 596$ ) underwent HIFU once, 38% ( $n = 383$ ) twice, and 2% ( $n = 23$ ) thrice. Additionally, 392 patients were treated with neoadjuvant hormone therapy (NHT) before HIFU<sup>[10]</sup>. Biochemical recurrence (Phoenix ASR-RO definition<sup>[11]</sup>) was observed in 205 (21.2%) patients<sup>[10]</sup>. The biochemical recurrence-free survival (BFSR) rates at 5 years and 8 years were 86% and 76% in the low-risk group, 78% and 63% in the intermediate-risk group, and 68% and 57% in the high-risk group, respectively<sup>[10]</sup>. Among patients treated with neoadjuvant hormone therapy (NHT) and those who were not, the 8-year BFSRs were 70% and 66% ( $p = 0.992$ )<sup>[10]</sup>. The overall survival and cancer-specific survival at 10 years were 80% and 97%, respectively<sup>[10]</sup>. With respect to adverse events, grade 1 urinary incontinence was observed in 18.7% of patients, grade 2/3 incontinence in 5.0%, acute urinary retention in 7.6%, urethral stricture in 9.0%, and rectourethral fistula in 0.4%<sup>[10]</sup>.

### 4 | CLINICAL RESULTS OF FOCAL THERAPY USING HIFU

Advances in multiparametric magnetic resonance imaging (mpMRI) have greatly improved the precision of prostate cancer (PC) diagnosis. mpMRI offers both structural and functional assessments of the

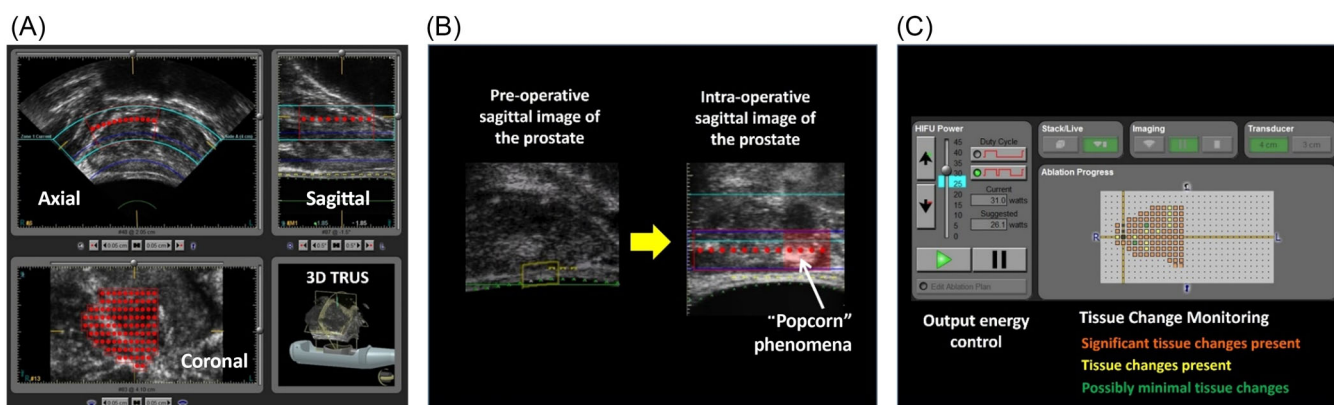


**FIGURE 1** Treatment planning and real-time monitoring in HIFU for PC. (A) Cross-sectional treatment planning. High-intensity focused ultrasound treatment planning is based on axial, sagittal, and coronal views of the prostate. These imaging perspectives help precisely identify the target area and guide the accurate delivery of ultrasound energy to the intended region. (B) “Popcorn” phenomenon. During HIFU treatment, hyperechoic areas often appear on B-mode ultrasound within the treated area; this is known as the “popcorn” phenomenon. It results from tissue cavitation caused by the focused energy and serves as a visual indicator that effective ablation is present. (C) Real-time energy adjustment and tissue change monitoring. The Sonablate® system enables continuous monitoring using real-time transrectal ultrasound imaging. This allows clinicians to adjust energy delivery based on visual cues, such as the cavitation effect, and observe ongoing tissue changes to ensure precise and effective treatment.

prostate<sup>[12]</sup>, and is widely regarded as a valuable tool for identifying clinically significant prostate cancer (CSPC)<sup>[13]</sup>. CSPC is generally defined as a tumor volume exceeding 0.5 cm<sup>3</sup> or pathological stage  $\geq$ T3 in whole-mount sections<sup>[14]</sup>, and represents the key disease entity requiring treatment to prevent cancer progression<sup>[8,15]</sup>. It has been reported that MRI-TRUS fusion biopsy, when combined with systematic biopsy, detects 90%–95% of index lesions, which correspond to the largest or highest-grade tumors in patients with CSPC<sup>[16,17]</sup>. Moreover, the use of mpMRI facilitates individualized strategies such as focal therapy, aimed at eradicating CSPC while preserving the prostate structures essential for urinary continence and sexual function<sup>[18,19]</sup>. Focal therapy is indicated for patients with localized PC, including those with Gleason score 3 + 3 and an MRI-visible lesion, and those with Gleason score  $\geq$ 3 + 4; cases with Gleason score 4 + 4 should be considered cautiously, considering tumor size and patient age. It is not indicated for cases with Gleason score  $\geq$ 4 + 5, or if extracapsular extension or seminal vesicle invasion is suspected<sup>[4,19]</sup>. Patient selection plays a critical role in the success of focal therapy, and this consideration has been addressed in the revised manuscript. During the last decade, numerous investigations have documented the clinical results of focal therapy with high-intensity focused ultrasound (HIFU) for patients with localized prostate cancer. The oncological efficacy of this approach has generally been evaluated by rates of biochemical recurrence, the presence of residual cancer on follow-up biopsy, and failure-free survival (FFS), which is defined as avoiding the need for local salvage surgery or radiotherapy, systemic therapy, metastatic progression, or prostate cancer-specific death<sup>[20]</sup>. Although the Phoenix ASTRO definition<sup>[11]</sup> is most frequently employed to define biochemical recurrence after focal therapy, there is still a recognized demand for novel biomarkers<sup>[21,22]</sup>. At present, repeat biopsy is usually conducted to assess recurrence after focal therapy, often triggered by an increase in PSA. Nevertheless, studies have reported the potential predictive roles of PSA nadir<sup>[23]</sup>, PSA density, the percentage decline in PSA<sup>[24]</sup>, and MRI findings<sup>[8,24]</sup> in estimating the likelihood of cancer detection on subsequent biopsy.

Over the past decade, prospective clinical investigations of focal therapy using high-intensity focused ultrasound (HIFU) have been conducted, each including at least 20 patients with a minimum follow-up of 12 months (Table 1)<sup>[4,8,20,25–34]</sup>. With technological refinements in HIFU related to treatment planning, therapeutic performance, and safety<sup>[35]</sup>, ultrasound-guided HIFU has become the most extensively adopted modality in clinical trials for localized prostate cancer<sup>[18]</sup>. Reported outcomes of follow-up biopsies after HIFU demonstrated clinically significant prostate cancer (CSPC) detection rates ranging from 8.9% to 33% within the first 12 months<sup>[8,25,26,28,29,34]</sup>, 6.4% at 5 years<sup>[31]</sup>, and

46% at 8 years<sup>[31]</sup>. In a large-scale, multicenter prospective trial with intermediate follow-up, failure-free survival (FFS) rates were 96%, 88%, and 84% for low-, intermediate-, and high-risk groups, respectively, at 5 years<sup>[20]</sup>, and 88%, 68%, and 65% at 7 years<sup>[33]</sup>. Nevertheless, further studies remain necessary to establish the long-term oncological effectiveness of focal therapy for localized prostate cancer. In terms of urinary function, continence was maintained in 80%–100% of patients following treatment<sup>[4,8,20,25–30,36]</sup>. Transient urinary dysfunction after treatment was associated with prostatic swelling<sup>[37]</sup>. Multivariate analysis identified a lower baseline maximum flow rate and treatment of the anterior transition zone as significant risk factors<sup>[38]</sup>. Erectile dysfunction occurs in 14%–30% of patients<sup>[8,25,27–30]</sup>. Previously, lower baseline IIEF-5 and EPIC sexual domain scores and treatment near the neurovascular bundle were significant risk factors for severe erectile dysfunction at 12 months post-treatment<sup>[39]</sup>.

## 5 | TECHNICAL DEVELOPMENT OF HIFU FOR PC: INTRAOPERATIVE COMPRESSION OF THE PROSTATE

In terms of oncological outcomes following focal HIFU, 77% of patients who underwent lesion-targeted therapy showed no evidence of recurrence on prostate biopsy at 6 months<sup>[40]</sup>. The rate was inferior to that observed in patients who underwent hemi-ablation (89.5%)<sup>[41]</sup> in studies conducted at the same institution. The differences in oncological outcomes were thought to be attributable to intraoperative prostatic swelling and intraprostatic point shift, as most swelling (median 13%) and displacement (transition zone: median 3.7 mm; peripheral zone: median 5.5 mm) occurred within the first 25 minutes of whole-gland therapy, likely resulting from diffuse coagulative necrosis and stromal edema<sup>[15,42]</sup>. Intraoperative localization of small target regions during focal therapy with HIFU is technically demanding. Therefore, it is essential to establish a strategy that allows accurate lesion-directed ablation using HIFU. Previous research has shown that the pre-operatively estimated circle area ratio, derived from the prostatic pressure coefficient, was significantly correlated with both the percentage increase in prostate volume ( $r=0.607$ ,  $p<0.001$ ) and the degree of intraprostatic displacement ( $r=0.433$ ,  $p=0.01$ ) during treatment. It has also been reported that increased intraprostatic pressure can suppress prostate enlargement by reducing the effects of tissue stress produced by the thermal and mechanical action of HIFU energy<sup>[37]</sup>. Based on this evidence, we postulated that elevated intraoperative prostatic pressure might decrease swelling and positional shifts. As a simple technique to enhance intraprostatic pressure, transrectal compression with the HIFU probe has been proposed.

TABLE 1 Prospective clinical studies of focal therapy with transrectal ultrasound-guided high-intensity focused ultrasound that included at least 20 patients with follow-up of at least 12 months

| Author (year)                        | Design                    | Diagnosis                                                        | Patients' number | Age                 | TNM classification (n)                                                                | PSA value, ng/mL (range) | Gleason score   | Risk stratification (low, intermediate, high) (n) |  |  | Treatment range                               | Oncological outcomes                                                                               | Functional outcomes                                                        | Median follow-up (month) |
|--------------------------------------|---------------------------|------------------------------------------------------------------|------------------|---------------------|---------------------------------------------------------------------------------------|--------------------------|-----------------|---------------------------------------------------|--|--|-----------------------------------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------|
|                                      |                           |                                                                  |                  |                     |                                                                                       |                          |                 |                                                   |  |  |                                               |                                                                                                    |                                                                            |                          |
| Ahmed (2015) <sup>[25]</sup>         | Individual cohort study   | MpMRI, biopsy (template mapping or biopsy or TRUS-guided biopsy) | 56               | 63.9 (range, 51–76) | T1c: 16, T2a: 9, T2b: 18, T2c: 11, T3a: 2                                             | 7.4 (5.6–9.5)            | 3 + 3 to 4 + 4  | 7, 47, 2                                          |  |  | Hemi-ablation, focal ablation                 | CSPC detection at follow-up biopsy: 19.2%                                                          | Pad-free continence: 92.3%, leak-free, pad-free continence: 92.0%, ED: 23% | 12                       |
| Feijoo (2016) <sup>[26]</sup>        | Individual cohort study   | MpMRI, TRUS-guided biopsy (at least 20 cores)                    | 71               | 70.2 (SD = 6.8)     | NA                                                                                    | 6.1 (1.6–15.5)           | 3 + 3, 3 + 4    | NA                                                |  |  | Hemi-ablation                                 | PC detection at follow-up biopsy: 15%                                                              | Leak-free, pad-free continence: 100%                                       | 12                       |
| van Velthoven (2016) <sup>[27]</sup> | Individual cohort study   | MpMRI, TRUS-guided biopsy                                        | 50               | 74 (IQR: 70–77)     | T1c: 16, T2: 34                                                                       | 6.3 (3.9–8.3)            | 3 + 3 to 4 + 3  | 24, 26, 0                                         |  |  | Hemi-ablation                                 | 5-year actuarial Phoenix recurrence-free survival in low- and intermediate-risk groups: 75%, 36%   | Pad-free continence: 95%, ED: 20%                                          | 35                       |
| Rischmann (2017) <sup>[28]</sup>     | Multicenter, cohort study | MpMRI, random biopsy (at least 12 cores) and target biopsy       | 111              | 64.9 (IQR: 61–69)   | T1: 77, T2: 33, unknown 1                                                             | 5.6 (IQR: 4.7–7.6)       | 3 + 3 to 4 + 3  | NA                                                |  |  | Hemi-ablation                                 | CSPC detection at follow-up biopsy at 6–12 months after the treatment: 33%                         | Pad-free continence: 97%, ED: 22%                                          | 30.4                     |
| Guillaumier (2018) <sup>[29]</sup>   | Multicenter, cohort study | MpMRI, biopsy (template mapping or biopsy or TRUS-guided biopsy) | 625              | 65 (IQR: 61–71)     | T1: 65, T2a: 82, T2b: 73, T2c: 93, missing T2 subclassification: 184, T3a: 75, T3b: 7 | 7.2 (IQR: 5.2–10.0)      | 3 + 3 to ≥4 + 4 | 78, 316, 189 (missing data: 16)                   |  |  | Wide and normal hemi-ablation, focal ablation | Failure-free survival in low-, intermediate-, high-risk groups, total (5 years) 96%, 88%, 84%, 88% | Leak-free, pad-free continence: 80%                                        | 56                       |

(Continues)

TABLE 1 (Continued)

| Author (year)                   | Design                    | Diagnosis                                                     | Patients' number | Age               | TNM classification (n)           | PSA value, ng/mL (range) | Gleason score  | Risk stratification (low, intermediate, high) (n) | Treatment range               | Oncological outcomes                                                                                                              | Functional outcomes                          | Median follow-up (month) |
|---------------------------------|---------------------------|---------------------------------------------------------------|------------------|-------------------|----------------------------------|--------------------------|----------------|---------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------|
| Ganzer (2018) <sup>[29]</sup>   | Multicenter, cohort study | TRUS-guided (12 cores) systematic biopsy                      | 49               | 63.4 (SD: 8.3)    | NA                               | 6.2 (SD: 2.1)            | 3 + 3, 3 + 4   | NA                                                | Hemi-ablation                 | CSPC detection at follow-up biopsy on treated side: 8.2%, rates of CSPC detection at follow-up biopsy on contralateral side: 2.0% | Leak-free, pad-free continence: 100% ED: 30% | 12                       |
| Johnston (2019) <sup>[30]</sup> | Individual cohort study   | MpMRI, prostate biopsy                                        | 107              | 66 (range: 47–81) | T1: 9, T2: 90, T3: 8             | 7.7 (1.2–26.2)           | 3 + 3 to 4 + 4 | 13 (low), 94 (intermediate and high)              | Hemi-ablation, focal ablation | PC detection at follow-up biopsy: 73%                                                                                             | Leak-free, pad-free continence: 99% ED: 14%  | 30                       |
| Stabile (2019) <sup>[31]</sup>  | Multicenter, cohort study | MpMRI, Biopsy (template mapping biopsy or TRUS-guided biopsy) | 1032             | 65 (range: 60–70) | T1: 78, T2: 802, T3: 123         | 7 (IQR: 4.9–9.7)         | 3 + 3 to 4 + 4 | NA                                                | Hemi-ablation, focal ablation | CSPC detection at follow-up biopsy: 36.4% (at 5 years), 46% (at 8 years)                                                          | NA                                           | 36                       |
| Shoji (2020) <sup>[8]</sup>     | Individual cohort study   | MpMRI-fusion image-guided biopsy                              | 90               | 70 (range: 39–85) | T2a: 71, T2b: 15, T2c: 4         | 7.26 (2.48–19.95)        | 3 + 3 to 4 + 4 | 31, 44, 15                                        | Hemi-ablation, focal ablation | CSPC detection at follow-up biopsy: 8.9% (at 6 months after the treatment)                                                        | Leak-free, pad-free continence: 100% ED: 14% | 21                       |
| Abreu (2020) <sup>[32]</sup>    | Individual cohort         | MpMRI-TRUS fusion image-guided biopsy                         | 100              | 65 (IQR: 59–70)   | T1c: 85, T2a: 12, T2b: 1, T2c: 2 | 5.9 (IQR: 4.5–7.2)       | 3 + 3 to 4 + 4 | 28, 67, 5                                         | Hemi-ablation                 | CSPC detection at follow-up biopsy: 31%                                                                                           | NA                                           | 20                       |

TABLE 1 (Continued)

| Author (year)                   | Design                    | Diagnosis                                                     | Patients' number | Age                                                                                          | TNM classification (n)                                                                                 | PSA value, ng/mL (range)                                                                                        | Gleason score  | Risk stratification (low, intermediate, high) (n)                                             | Treatment range                       | Oncological outcomes                                                                                        | Functional outcomes                                                                             | Median follow-up (month)                                             |
|---------------------------------|---------------------------|---------------------------------------------------------------|------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Reddy (2022) <sup>[33]</sup>    | Multicenter, cohort study | MpMRI, Biopsy (template mapping biopsy or TRUS-guided biopsy) | 1379             | 66 (range: 60–71)                                                                            | T1: 95, T2a: 276, T2b: 140, T2c: 209, missing T2 subclassification: 398, T3a/b: 151, missing data: 110 | 6.9 (4.9–9.4)                                                                                                   | 3 + 3 to ≥8    | 84, 896, 386 (missing data: 13, Gleason 3 + 3 = 6, maximum cancer core length <6 mm, rT1: 20) | Quadrant, hemi-ablation, hockey-stick | Failure-free survival in low-, intermediate-, high-risk groups, total (7 years) 88%, 68%, 65%.              | NA                                                                                              | 32                                                                   |
| Westhoff (2023) <sup>[34]</sup> | Individual cohort         | MpMRI-TRUS fusion image-guided biopsy                         | 50               | 68 (range: 48–80)                                                                            | T1c: 50                                                                                                | 6.5 (1.2–9.9)                                                                                                   | 3 + 3, 3 + 4   | 35, 15, 0 (cancer of the prostate risk assessment)                                            | Focal ablation                        | CSPC detection at follow-up biopsy: 26% (at 12 months)                                                      | Urinary continence was not impaired. IIEF score changed from a median of 20 points to 13 points | 42                                                                   |
| Shoji (2024) <sup>[4]</sup>     | Individual cohort study   | MpMRI-TRUS fusion image-guided biopsy                         | 240              | Low-risk group: 67 (40–79), Intermediate risk group: 69 (39–81), High-risk group: 71 (48–85) | T2a: 159, T2b: 21, T2c: 60                                                                             | Low-risk group: 6.25 (2.48–9.35), Intermediate risk group: 6.45 (2.24–20.0), High-risk group: 6.61 (3.17–19.95) | 3 + 3 to 4 + 4 | 51, 107, 82                                                                                   | Region targeted focal ablation        | Phoenix ASTRO recurrence-free survival in low-, intermediate-, and high risk group: 92.2%, 89.7%, and 85.4% | Leak-free, pad-free continence: 100%                                                            | Low-risk group: 54, intermediate-risk group: 48, high-risk group: 48 |

Abbreviations: CSCP, clinically significant prostate cancer; ED, erectile dysfunction; IQR, interquartile range; MpMRI, multi-parametric magnetic resonance imaging; NA, not available; PC, prostate cancer; TRUS, transrectal ultrasound.

Tansrectal compression was devised as a technical innovation to ensure adequate energy delivery to the treatment area<sup>[43]</sup>, which involves introducing an additional 80 mL–160 mL of water into the transducer balloon to apply pressure on the prostate (Figure 2A). The distance from the rectal surface to the ultrasound transducer was adjusted to approximately 20 mm–30 mm, according to prostate volume (Figure 2B)<sup>[3]</sup>. In cases with larger prostate volumes, achieving sufficient compression may be technically more challenging and may necessitate the injection of a greater volume of water into the balloon, as both the pressure and the amount of perfusate within the probe can vary depending on individual patient's anatomy. We have added this clarification to the manuscript. During treatment, a physician manually adjusted the degassed water to the starting position<sup>[3]</sup>. Compression of the prostate helps reduce intraoperative prostatic swelling<sup>[37]</sup> and decreases target displacement<sup>[43]</sup>, thereby increasing treatment accuracy. Hyperechoic changes in the B-mode of TRUS images indicate effective PC treatment with HIFU<sup>[7,44]</sup>. However, diffuse hyperechoic alterations are less commonly detected within the treated area, likely because of the cooling influence of intraprostatic blood flow and the relatively long propagation distance of HIFU. Prostatic compression decreases vascular circulation in the intraprostatic plexus, which in turn lessens the heat-sink phenomenon. Furthermore, compression reduces the acoustic

travel distance of HIFU, thereby increasing focal energy concentration and promoting cavitation<sup>[45]</sup>.

In the clinical improvement of whole-gland therapy with HIFU for PC, a study comparing treatment outcomes of HIFU with and without the compression method reported the clinical results of a single HIFU treatment with a median follow-up of 5 years (9 months–144 months) in patients with localized PC. The BFSRs for all patients combined and for those in the low- ( $n=102$ ), intermediate- ( $n=240$ ), and high-risk ( $n=86$ ) categories, as defined by the D'Amico classification, were 68.4%, 80.4%, 65.6%, and 61.6%, respectively<sup>[3]</sup>. Multivariate logistic regression analyses demonstrated that the compression method significantly reduced the risk of biochemical failure in all risk groups: low- (odds ratio [OR]: 0.178,  $p=0.030$ ), intermediate- (OR: 0.291,  $p<0.0001$ ), and high-risk (OR: 0.316,  $p=0.049$ ). There were no significant differences in complication rates between patients treated with compression and those treated using the conventional approach<sup>[3]</sup>.

Shoji et al. reported the clinical outcomes of focal therapy for PC using HIFU with compression method in 240 patients<sup>[4]</sup>. At 1 month post-treatment, DCE MRI demonstrated complete devascularization of the treated regions, with no apparent changes in the peri-target area or rectal wall<sup>[4]</sup>. In the first 100 patients, biopsy performed at 6 months confirmed the absence of clinically significant prostate cancer in the treated zones<sup>[4]</sup>. After a single focal HIFU treatment, biochemical and

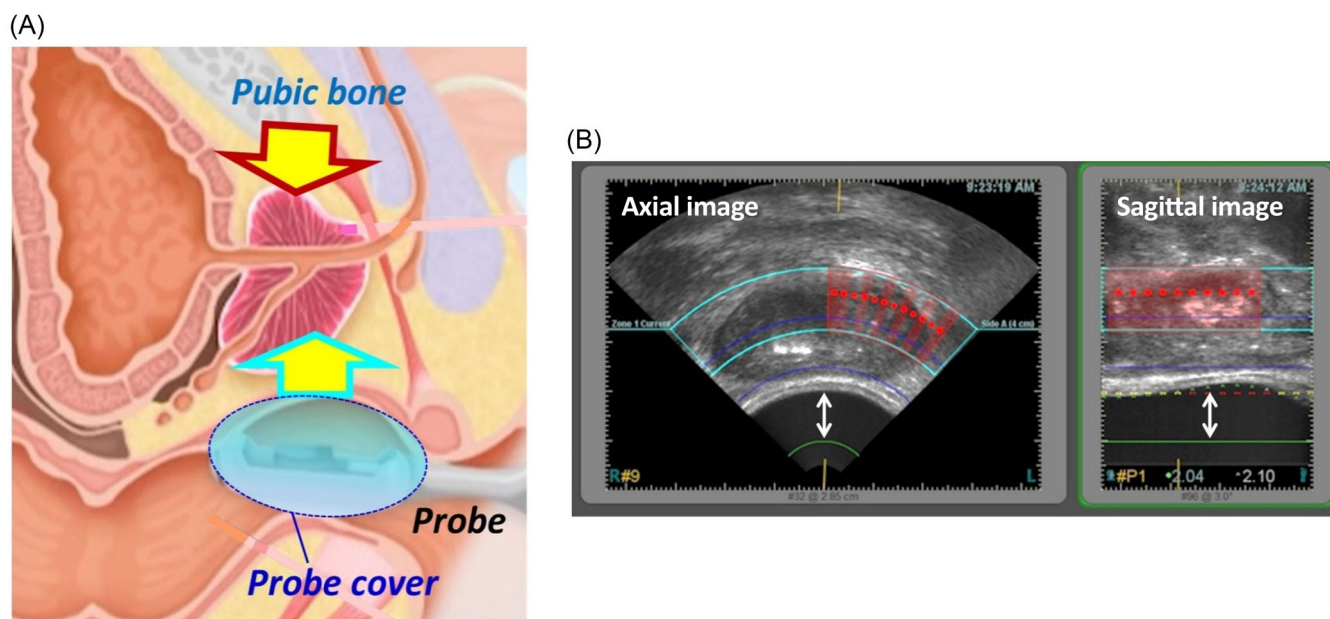


**FIGURE 2** Intra-procedural compression of the prostate during HIFU. (A) Schema of the compression method. In the compression method, the treatment probe is inserted transrectally and surrounded by a probe cover filled with circulating fluid. By increasing the fluid volume, the prostate is gently compressed between the probe and pubic bone. This approach stabilizes the prostate and brings the target area closer to the focal zone, enhancing treatment accuracy. (B) Intraoperative TRUS images during compression method. In axial and sagittal TRUS images obtained during the compression method, the distance from the transducer surface (indicated by the green line) to the rectal wall is shown to be approximately 20 mm.

pathological disease-free survival rates were 93.7% and 92.2%, 88.5% and 91.6%, and 84.8% and 86.6% in the low-, intermediate-, and high-risk groups, respectively ( $p = 0.443$  for biochemical disease-free survival,  $p = 0.445$  for pathological disease-free survival)<sup>[4]</sup>. Radical or systemic treatment-free survival rates were consistently high across all groups (96.1%, 94.4%, and 95.1%), with a median follow-up of 48 (24–84) months<sup>[4]</sup>. In complications evaluated by Common Terminology Criteria for Adverse Events v5.0, the rates of urethral stricture (grade 2), urinary tract infection (grade 2), urinary incontinence (grade 1), and recto-urethral fistula were 2.9%, 2.1%, 1.3%, and 0%, respectively<sup>[4]</sup>. Severe erectile dysfunction occurred in 24% of the patients with preoperative IIEF-5  $\geq 8$ <sup>[4]</sup>. The pathological outcomes of follow-up biopsy in this study were more favorable than those reported previously, in which CSPC detection rates within treated areas ranged from 8.2% to 40%<sup>[29,32,34]</sup> with variations in biopsy timing and methodology. The incidence and types of complications were consistent with earlier studies<sup>[20,26]</sup>, and no cases of recto-urethral fistula were observed. Collectively, these findings indicate that focal HIFU with intraoperative prostate compression can achieve adequate energy delivery for treating target CSPC, while maintaining an acceptable safety profile.

## 6 | CONCLUSION

Focal therapy performed with HIFU under intraoperative prostate compression offers a minimally invasive and effective treatment for CSPC. This technique enhances treatment precision by reducing prostatic swelling and target displacement, thereby improving energy delivery and ablation accuracy. Clinical outcomes demonstrated high biochemical and pathological disease-free survival rates across all risk groups, with low complication rates. These results suggest that HIFU with compression is a safe and promising technical development for the treatment of localized PC.

## AUTHOR CONTRIBUTIONS

Sunao Shoji conceived and designed the study, supervised the project, and critically revised the manuscript. Satoshi Kuroda, Airi Ichige, Naoko Matsumoto, Kumpei Takahashi, Tatsuya Otaki, Nobuyuki Nakajima, and Yoshiaki Kawamura were responsible for data collection. Airi Ichige and Naoko Matsumoto performed the statistical analyses. All authors contributed to data interpretation, reviewed the manuscript for important intellectual content, and approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

This article is a review and does not contain any original data. All data supporting the findings are available from the cited references.

## ETHICS STATEMENT

The authors have nothing to report.

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