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SPECIAL FEATURE: REVIEW ARTICLE

Recent development of diagnostics and therapeutics ultrasound for urological disease

Current status and future outlook of ultrasound treatment for prostate cancer

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Abstract

Radical prostatectomy and radiation therapy are the standard treatment options for localized prostate cancer (PC). However, radical prostatectomy may cause the deterioration of urinary and sexual function, and radiation-induced hemorrhagic cystitis and severe rectal bleeding are risk factors for fatal conditions in patients after radiation therapy. With the recent development of magnetic resonance imaging (MRI) for the localization of clinically significant PC (csPC) and treatment modalities, "focal therapy", which cures csPC while preserving anatomical structures related to urinary and sexual functions, has become a minimally invasive treatment for localized PC. Based on the clinical results of transrectal high-intensity focused ultrasound (HIFU) for localized PC in the whole gland and focal therapy, HIFU is considered an attractive treatment option for focal therapy. Recently, the short-term clinical results of transurethral high-intensity directional ultrasound (HIDU) have been reported. With the resolution of some issues, HIDU may be commonly used for PC treatment similar to HIFU. Because HIFU and HIDU have limitations regarding the treatment of patients with large prostate calcifications and large prostate volumes, the proper use of these modalities will enable the treatment of any target area in the prostate. To establish a standard treatment strategy for localized PC, pair-matched and historically controlled studies are required to verify the oncological and functional outcomes of ultrasound treatment for patients with localized PC.

Keywords Prostate cancer · High-intensity focused ultrasound · High-intensity directional ultrasound · Oncological outcomes · Functional outcomes

Introduction

The standard management for localized prostate cancer (PC) is active surveillance (AS) and radical treatment. AS is the preferred disease management strategy for patients with low-risk (Gleason score ≤ 6) and intermediate-risk (low-volume Gleason 3 + 4 = 7) localized PC [1]. In contrast, radical treatments, such as radical prostatectomy or radiation therapy, are recommended for patients with unfavorable intermediate- or high-risk prostate cancer with an estimated life expectancy of > 10 years [2]. However, the deterioration of urinary [3] and sexual function [4] is considered the main issue after radical prostatectomy. Radiation-induced hemorrhagic cystitis [5] and severe rectal bleeding [6] are risk factors for fatalities after radiation therapy.

Recently, ultrasound treatments including transrectal high-intensity focused ultrasound (HIFU) [7] and high-intensity directional ultrasound (HIDU) [8] have become modalities for minimally invasive "focal therapy" to treat clinically significant PC (csPC) and preserve the anatomical structures related to urinary and sexual function. HIFU is considered an attractive treatment option for localized PC, based on its long- and medium-term clinical results. HIFU is frequently used because it is appropriate for prostate cancer

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treatment based on three-dimensional millimeter-accurate planning in real-time transrectal ultrasound (TRUS) [9, 10] and magnetic resonance imaging (MRI) [11, 12], allowing for a distinct margin between the treated area and the adjacent untreated tissue without puncturing the prostate [13]. As no special construction work is required for installation, TRUS-guided HIFU is widely used as an ultrasound treatment device for localized PC, especially for focal therapy [7]. In HIDU, a continuous sweeping directional ultrasound beam is delivered from the prostatic urethra based on real-time MRI for planning, thermometry, and cooling of the urethra and rectum [8]. Recently, the short-term clinical results of HIDU have been reported.

This review summarizes the current status and future outlook of ultrasound therapies for localized PC.

The principles and devices of the ultrasound treatment

HIFU produces ultrasound waves generated by a spherical transducer, delivering ultrasonic energy to pinpoint foci millimeters in diameter [14]. The thermal and mechanical effects of HIFU destroy the target prostate tissue (Fig. 1) [14]. The anti-cancer effect of HIFU was evaluated using rats with subcutaneously implanted PC cell lines [15, 16]. In a study of a canine prostate model for clinical application, coagulative necrotic change was found in the focally ablated area with distinct margins after 1-s exposure to an acoustic intensity of 1000 W/cm^2 [17]. Minimal changes in tissues surrounding the ablated area with HIFU have also been reported [18]. Madersbacher et al. reported their experiences of focal ablation with HIFU in ten patients just before radical prostatectomy: the temperature of the entire focal ablation area ranged from 70 to 98.6 °C during the ablation as measured with a transperitoneal thermocouple, and the targeted area of the prostate was accurately ablated [13]. Beerlage et al. also confirmed pathological focal ablation and necrosis in the ablated area using a resected specimen of the prostate immediately after hemi-ablation with HIFU [19]. In commercial HIFU devices for PC, treatment planning can be performed based on high-resolution TRUS images. Treatment planning is determined based on three cross-sections of the axial, sagittal, and coronal images of the prostate (Fig. 2a). The "popcorn" phenomenon formed by the cavitation of treated tissue may act as an indicator of the arrival of sufficient energy for treatment (Fig. 2b) [20]. Therefore, the energy can be adjusted using real-time TRUS images to determine the appearance of the phenomenon [21]. Safety measures have been incorporated into HIFU devices, such as rectal cooling systems, automatic rectal wall position monitoring, and reflectivity index systems. The endorectal probe for HIFU is covered with a condom, inserted into the rectum, and filled with cooling water or fluid. Cooling water or liquid circulates in the probe and cools the rectum wall, which keeps the temperature of the rectum wall below 22 °C during treatment [22]. An automatic rectal wall position-monitoring system monitors the distance of the probe from the rectal wall to prevent off-target treatment. The reflectivity index system alerts the operator to changes in the rectal wall on TRUS images during the treatment [22].

Recently, MRI-guided ultrasound has been reported for the treatment of localized PC. MRI-guided ultrasound treatment allows thermal feedback and real-time power adjustment to optimize tissue ablation temperatures [23]. In MRI-guided HIFU, the endorectal probe is covered with a probe cover and filled with degassed water at 14 °C for rectal cooling and protection [23]. Fast spin-echo T2-weighted images in three planes and diffusion-weighted imaging are acquired for treatment planning [23]. MRI-visible lesions

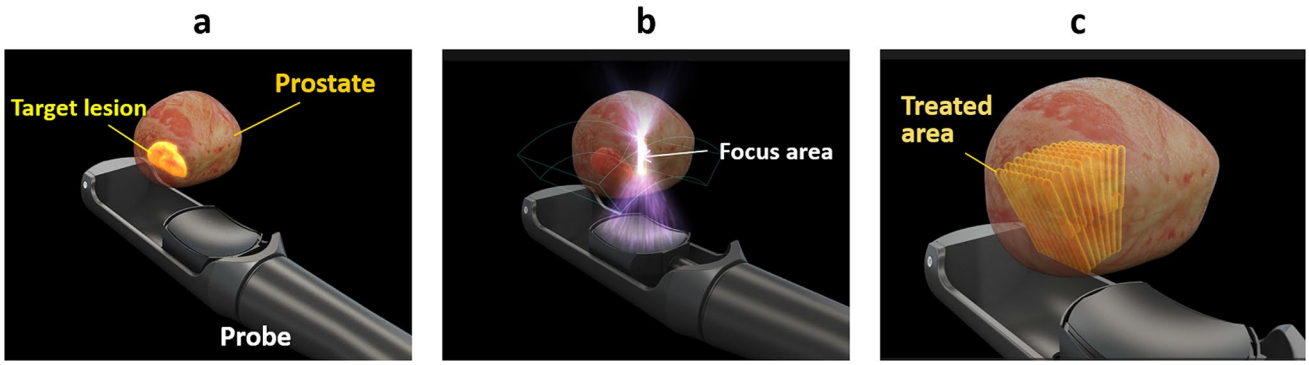

Fig. 1 Computer graphic images of a commercial device for high-intensity focused ultrasound, Sonablate® 500. **a** For high-intensity focused ultrasound (HIFU) treatment, the probe is inserted into the rectum, and the treatment range is planned on transrectal ultrasound images using the probe. **b** HIFU produces ultrasound waves generated by a spherical transducer, delivering ultrasonic energy to pinpoint foci millimeters in diameter. **c** The thermal and mechanical effects of HIFU destroy targeted prostate tissue. The focal areas move in an overlapping fashion, treating the entire planned area

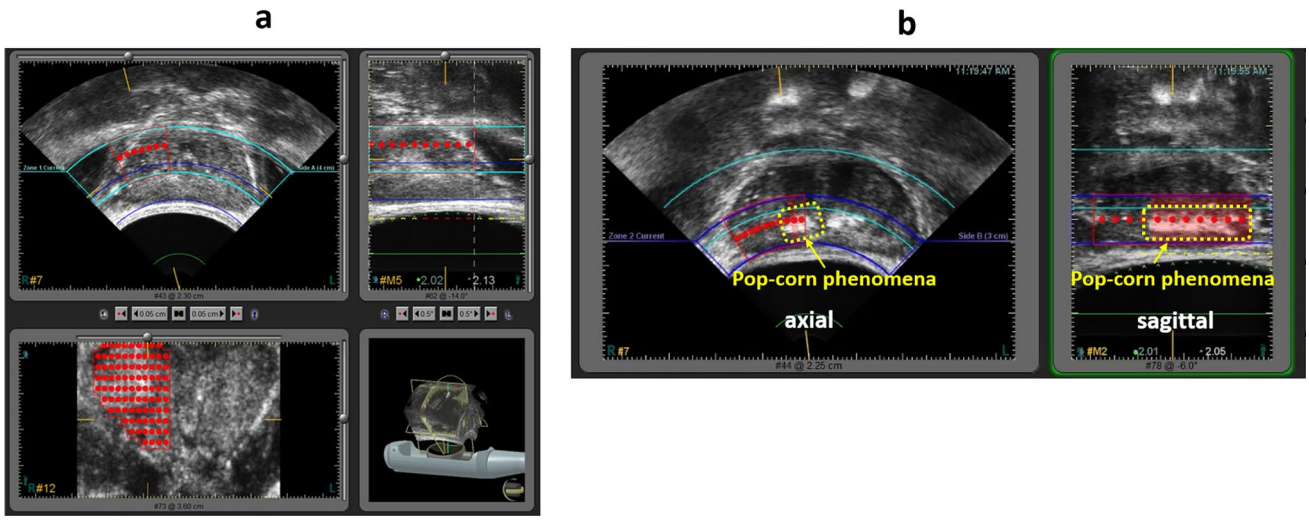

Fig. 2 The roles of transrectal ultrasound using an HIFU probe in treatment range planning and the evaluation of treatment effect. **a** The treatment range can be planned on three-dimensional transrectal ultrasound (TRUS) using axial, sagittal, and coronal images of the prostate. The red spot indicates the treatment planned area. **b** The "popcorn" phenomenon formed by the cavitation of treated tissue may act as an indicator of sufficient energy for treatment on TRUS images. Based on the real-time TRUS images for the appearance of the phenomenon, ablation energy can be controlled

with a 5-mm margin and anterior rectal wall are planned for treatment on T2-weighted images [23]. Macrosonication of multiple spots is applied to the target area. The target area and the rectum are monitored using real-time MR thermography. Treatment is considered to be successful when the temperature in the target area reaches more than 65 °C [23]. HIDU for PC was designed as an MRI-guided transurethral ultrasound ablation for monitoring intraprostatic temperature via MRI thermometry (Fig. 3) [24]. In a canine model, accurate spatial heating patterns were observed in the target area within the prostate [24]. In the study, the acoustic power was adjusted to achieve a temperature of 55 °C along the outer boundary of the target region based on the spatial temperature, which was measured every 5 s using MR thermometry, and pathological thermal damage was confirmed in the ablated area on H&E-stained tissue sections [24]. Chopra et al. reported their experience of HIDU for the human prostate just before radical prostatectomy in eight patients with localized PC [25]. In their experience, a temperature uncertainty of less than 2 °C and a spatial targeting accuracy of -1.0 ± 2.6 mm were observed [25]. The mean temperature measured along the boundary of thermal coagulation was 52.3 ± 2.1 °C, and the mean treatment rate was 0.5 mL/min [25].

HIFU and HIDU have similar limitations in patients with large calcifications because large calcifications prevent ultrasound penetration. For patients who have large calcifications, HIFU and HIDU are not able to treat PC located in the

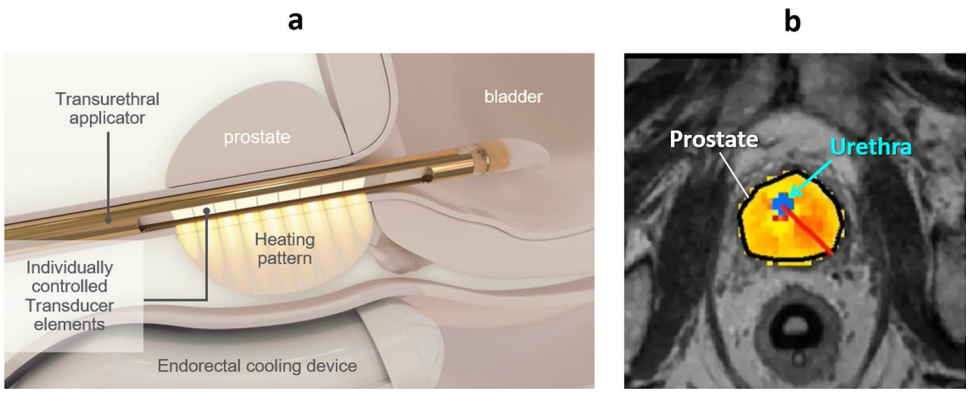

Fig. 3 Schema of transurethral high-intensity directional ultrasound for localized prostate cancer, TULSA-PRO®. **a** For transurethral high-intensity directional ultrasound (HIDU) treatment for localized prostate cancer, the transurethral applicator, which includes an individually controlled transducer, is inserted. **b** During treatment, the HIDU transducer is rolled to treat the planned prostate area based on the thermometry on magnetic resonance imaging

transition and peripheral zones without transurethral resection of the prostate (TUR-P), which has been shown to have no negative impact on the clinical outcome of patients with PC [26], to remove the calcification. Another limitation is related to the penetration depth of ultrasound. Because the penetration depth of HIFU is limited, the anterior portion of a large prostate cannot be completely treated and requires size reduction with TUR-P or hormonal therapy before treatment. Similarly, the energy reaching the limbus of the large prostate is decreased in HIDU.

Clinical results of whole-gland therapy with HIFU and HIDU

Long- and medium-term clinical results have been reported for HIFU in patients with localized PC. Crouzet et al. reported the clinical results of transrectal HIFU for patients with PC (median age, 71 years old; median PSA value, 7.7 ng/mL; number of patients per D'Amico risk group, low = 375, intermediate = 452, high = 174, undefined = 19) with a median follow-up of 6.4 years (0.2–13.9). Of these patients, 596 (60%), 383 (38%), and 23 (2%) received HIFU once, twice, and three times, respectively. Of these, 392 patients received neoadjuvant hormone therapy (NHT) [9]. Biochemical recurrence (Phoenix ASRRO definition [27]) was observed in 205 patients (21.2%) [9]. The 5- and 8-year biochemical-free survival rates (BFSRs) for low-, intermediate-, and high-risk patients were 86%, 78%, and 68%, and 76%, 63%, and 57%, respectively [9]. The 8-year BFSRs in patients with and without NHT were 70% and 66%, respectively ($P = 0.992$) [9], while the 10-year overall survival rate and disease-specific survival rates were 80% and 97%, respectively [9]. Shoji et al. reported the clinical results of single HIFU treatment with a median follow-up of 5 years (9–144 months) in patients with localized PC. The BFSRs of patients who underwent HIFU for localized PC in the total population and low- ($n = 102$), intermediate- ($n = 240$), and high-risk groups ($n = 86$) according to the D'Amico risk groups were 68.4%, 80.4%, 65.6%, and 61.6%, respectively. In multivariate logistic regression analyses performed to predict the biochemical failure of treatment, NHT was a significant factor that reduced the risk of biochemical failure after treatment in the high-risk group (odds ratio [OR] 0.225, $P = 0.015$). In their treatment procedure, the compression method [28] was implemented in selected patients to prevent intraprocedural prostatic swelling [29] due to interstitial edema [30]. Compression methods are recommended for patients with a prostate volume < 25 cc because they are prone to intraprocedural prostatic swelling [10]. For intraoperative compression of the prostate, a balloon was expanded by adding 80–280 mL of degassed water, and the distance from the rectal surface to the ultrasound transducer was set parallel to 20–30 mm, depending on the prostate volume [10]. During treatment, the degassed water was manually adjusted to the starting position by a physician [10]. In multivariate logistic regression analyses performed to predict the biochemical failure of treatment, the compression method was a significant factor that reduced the risk of biochemical failure after treatment in the low- (OR 0.178, $P = 0.030$), intermediate- (OR 0.291, $P < 0.0001$), and high-risk (OR 0.316, $P = 0.049$) groups [10].

Regarding adverse events associated with HIFU, grade 1 transient urinary incontinence occurred in 3.7% [10] and 18.7% [9] of patients, grade 2/3 urinary incontinence occurred in 5.0% [9], acute urinary retention occurred in 7.6%, urethral stricture occurred in 9.0% [9] and 19.8% [10], rectourethral fistula occurred in 0.4% [9] and 0.46% [10], and erectile dysfunction (ED) occurred in 42.3% [10]. There were no significant differences in adverse events between patients treated with compression and those treated conventionally.

The 3-year outcomes of a prospective multicenter phase I study of near-whole-gland therapy in HIDU have been reported [31]. In the 30 patients in the series, the PSA level decreased by 95% to a median (interquartile range) nadir of 0.33 (0.1–0.4) ng/mL [31]. Follow-up biopsies revealed csPC in 34% of the patients and cancer in 59%. By year 3, seven patients had undergone salvage treatment [31] and there were no new severe adverse events [31].

Clinical results of focal therapy with HIFU and HIDU

The development of multiparametric MRI has contributed to the accurate diagnosis of PC. MpMRI, which combines anatomical and functional evaluations of the prostate [32], is considered a useful modality for the detection of csPC [33]. CsPC is defined as prostate cancers > 0.5 cm^3 or tumor category ≥ T3 in whole-mount specimens [34] and is regarded as a target to be managed to control the progression of PC [21, 35]. In previous reports, MRI-TRUS fusion image-guided biopsy, a representative technique of MRI-based targeted biopsy, and systematic biopsy achieved a high detection rate of index lesions, which were the largest or highest Gleason scores of csPC in each patient, from 90 to 95% [36, 37]. The development of mpMRI contributes to tailor-made treatment such as "focal therapy" that cures csPC while preserving the anatomical structures related to urinary and sexual function [38, 39]. The representative modalities of focal therapy are HIFU, cryotherapy, and brachytherapy, which have been reported previously; however, there have been no studies comparing these treatment modalities in focal therapy for localized PC. The treatment modality for each patient should be selected based on the location of PC and

the patient's background. During the last 8 years, the clinical results of focal therapy with HIFU for localized PC have been reported. Oncological outcomes have been evaluated based on biochemical recurrence, pathological PC detection at follow-up biopsy, and failure-free survival (FFS), which is defined as the avoidance of local salvage therapy with surgery or radiotherapy, systemic therapy, metastases, or PC-specific death [40]. As benign prostatic tissue remains, such as in benign prostatic hyperplasia and chronic inflammation, the nadir value of the serum PSA level and changes in the numerical values after treatment would be different in each case. Although the Phoenix ASTRO definition [26] has been used to evaluate biochemical recurrence after focal therapy, novel biomarkers are required [41, 42]. At present, follow-up biopsy is generally performed, depending on PSA elevation, to evaluate PC recurrence after focal therapy. However, the predictive values of the PSA nadir value [43], PSA density, and MRI findings [21] at the time of a negative predictive value for the detection of PC on follow-up biopsy have been reported. Therefore, routine follow-up biopsy has been excluded from the design of focal therapy clinical studies, considering the burden to the patient.

Prospective clinical studies on focal therapy with HIFU and HIDU in the last 5 years that included atleast 20 patients who were followed-up for atleast 12 months have been reported (Tables 1, 2) [8, 12, 21, 23, 40, 44–53]. With the development of HIFU technology in treatment planning, therapeutic technologies, and safety [7], ultrasound-guided HIFU has become one of the most frequently used techniques in recent clinical studies on focal therapy for patients with localized PC [38]. Five-year actuarial biochemical recurrence-free survival rates in the low- and high-risk groups were 75% and 36%, respectively [46]. In terms of follow-up biopsy results of HIFU, the rates of csPC detection were 6.8% at 5 months [23], 8.9–33% within 12 months [21, 44, 47, 48, 51, 53], 12% at 24 months [12], 36.4% at 5 years [50], and 46% at 8 years [50] after treatment. In a large multicenter prospective study with medium-term follow-up, the FFS rates in the low-, intermediate-, and high-risk groups were 96%, 88%, and 84% in the 5-year follow-up [40] and 88%, 68%, and 65% in the 7-year follow-up [52], respectively. Further studies are required to evaluate the oncological role of focal therapy in localized PC. In previous studies, 11–20% of patients who were assessed as having selection failure or recurrence received re-treatment with HIFU after focal therapy with HIFU [40, 49]. Regarding urinary function, continence is preserved in 80–100% of patients after treatment [12, 21, 23, 40, 44–49]. According to longitudinal analysis of urinary function during the 12 months after treatment, the International Prostate Symptom Score (IPSS) ($P<0.0001$), IPSS quality of life (QOL) ($P=0.001$), overactive bladder symptom score (OABSS) ($P<0.0001$), EPIC urinary domain ($P<0.0001$), and maximum urinary flow rate ($P<0.0001$) significantly deteriorated at 1 month after treatment but improved to preoperative levels at 3 or 6 months [21]. The transient deterioration of urinary function was thought to be due to transient prostatic swelling that occurred immediately after treatment [29]. According to analysis of the risk of transient deterioration of urinary function, a lower maximum pretreatment flow rate (OR 1.083, $P=0.023$) and treatment of the anterior portion of the TZ (OR 3.386, $P=0.029$) were significant risk factors for deterioration, with ≥ 32% of the preoperative status of maximum flow rates in the multivariate logistic regression analysis [54]. ED occurred in 14–30% of patients [12, 21, 23, 44, 46–49]. In a longitudinal analysis of the International Index of Erectile Function-5 (IIEF-5), which is used to evaluate ED, IIEF-5 was significantly impaired in the initial 3 months after treatment compared to pretreatment values, but it improved to baseline at 6 months after focal therapy [21]. In a recent study, lower pre-procedural IIEF-5 score (OR 0.812, $P=0.005$), lower pre-procedural score of the sexual domain of the Expanded Prostate Cancer Index Composite (OR 0.960, $P=0.038$), and treatment of the edge of the peripheral zone (PZ) in proximity to the neurovascular bundle [treated vs. untreated, OR 8.048, $P=0.028$] were significant risk factors for severe ED 12 months after treatment in multivariable logistic regression analysis [55]. These results will contribute to the informed consent of patients at risk for severe ED after treatment. The clinical results of focal therapy with HIDU have been reported as a urethra-sparing treatment after 12 months follow-up in a multicenter study [8]. After treatment of patients with low- and intermediate-risk PC, the csPC detection rate was 21% at follow-up biopsy. Regarding functional outcomes, the rates of urinary incontinence and ED were less than 1% and 25%, respectively [8].

Future outlook of ultrasound treatment for prostate cancer

Ultrasound therapy, particularly focal therapy, is a minimally invasive treatment for localized PC. Owing to the characteristics of ultrasound, the proper use of HIFU and HIDU would cover focal therapy for targets located at any site within the prostate. Verification of the oncological and functional outcomes of HIDU in further large-scale studies involving patients with localized PC is expected. In terms of the specific limitations of HIDU, the cost of the disposable HIDU device is high, and it needs to be compatible with specific MRI equipment. By resolving these issues, HIDU can be easily introduced for the treatment of PC, similar to HIFU.

As a standard treatment strategy for localized PC, focal therapy should prove superior to conventional treatments in

Table 1 Prospective clinical studies of focal therapy with transrectal ultrasound-guided high-intensity focused ultrasound that included atleast 20 patients with follow-up of atleast 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 (months)
Ahmed (2015)	Individual cohort study	MpMRI, biopsy (template mapping 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 (2015)	Individual cohort study	MpMRI, TRUS-guided biopsy (atleast 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)	Individual cohort study	MpMRI, TRUS-guided biopsy	50	74 (IQR 70–77)	T1c 16, T2 34	6.3 (range 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)	Multicenter, cohort study	MpMRI, random biopsy (atleast 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)	Multicenter, cohort study	MpMRI, Biopsy (template mapping 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

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 (months)
Ganzer (2018)	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)	Individual cohort study	MpMRI, prostate biopsy	107	66 (range 47–81)	T1 9, T2 90, T3 8	7.7 (range 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)	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)	Individual cohort study	MpMRI-TRUS fusion image-guided biopsy	90	70 (range 39–85)	T2a 71, T2b 15, T2c 4	7.26 (range 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)	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 (months)
Reddy (2022)	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 (8.0)	6.9 (range 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)	Individual cohort	MpMRI-TRUS fusion image-guided biopsy	50	68 (range 48–80)	T1c 50	6.5 (range 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

MpMRI multi-parametric magnetic resonance imaging, *TRUS* transrectal ultrasound, *NA* not available, *IQR* interquartile range, *ED* erectile dysfunction

Table 2 Prospective clinical studies of focal therapy with magnetic resonance imaging-guided ultrasound treatment that included atleast 20 patients with follow-up of atleast 12 months

Author (year)	Design	Treatment modality	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 (months)
Ghai (2021)	Individual cohort study	HIFU	MRI-TRUS fusion image-guided biopsy	44	67 (IQR 62–70)	NA	6.4 (IQR 4.3–9.6)	3 + 4, 4 + 3	NA	Focal ablation	CsPC detection at follow-up biopsy: 6.8% at 5 months	Urinary incontinence 0%, ED: 4%	24
Ehdaie (2022)	Multicenter, cohort study	HIFU	MRI-targeted and systematic biopsy	101	63 (IQR 58–67)	≤T1c 84	5.7 (IQR 4.2–7.5)	3 + 4, 4 + 3	NA	Focal ablation	CsPC detection at follow-up biopsy: 12%	Urinary incontinence: 18% (CTCAE grade 1, 2), ED: 20% (CTCAE grade 1, 2)	24
Klotz (2021)	Multicenter, cohort study	HIDU	MpMRI, prostate biopsy	115	65.0 (range 46–79)	T1c 89, T2a 20, T2b 1, T2, unspecified substage	6.3 (range 4.6–7.9)	3 + 3 to 4 + 3	38, 77, 0	Urethra-sparing ablation	CsPC detection at follow-up biopsy in the patients: 21%	Urinary incontinence less than 1%, ED: 25%	12

MRI magnetic resonance imaging, *TRUS* transrectal ultrasound, *NA* not available, *IQR* interquartile range, *HIFU* high-intensity focused ultrasound, *HIDU* high-intensity directional ultrasound, *ED* erectile dysfunction, *CTCAE* Common Terminology Criteria for Adverse Events version 4.03

selected patients with localized PC. For verification, pair-matched studies and historical controlled studies should be conducted to compare focal therapy and radical treatment as a randomized controlled trial would be challenging to design due to the differences between patients undergoing focal therapy and those receiving radical treatment. In Japan, a multicenter prospective study of focal therapy with HIFU was conducted to compare the oncological and functional outcomes of radical prostatectomy in pair-matched patients (jRCTs032220590). These clinical results contribute to evaluation of the usefulness of HIFU for the treatment of localized PC.

Conclusion

With the development of mpMRI for the localization of csPC and treatment modalities, ultrasound treatment, such as HIFU and HIDU is expected to become a minimally invasive treatment for localized PC that cures csPC while preserving urinary and erectile function. To establish a standard treatment strategy for localized PC, pair-matched and historical controlled studies with long-term follow-up are required to verify the oncological and functional outcomes of this treatment in patients with localized PC.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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