Prostate International 12 (2024) 104–109

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Research Article

Propensity score matched analysis of functional outcome in five thousand cases of robot-assisted radical prostatectomy versus high-intensity focused ultrasound

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ARTICLE INFO

Article history:
Received 7 March 2024
Received in revised form
18 March 2024
Accepted 25 March 2024
Available online 27 March 2024

Keywords:
High-intensity focused ultrasound ablation
Prostatic neoplasms
Robotic surgical procedures

ABSTRACT

Background: To evaluate functional outcome after robot-assisted radical prostatectomy (RARP) and high-intensity focused ultrasound (HIFU) ablation for prostate cancer.

Methods: We retrospectively reviewed 4,983 RARP and 230 HIFU procedures performed at a single tertiary center. A 1:4 ratio propensity score matching (PSM) was performed to achieve baseline equivalence in age, body mass index (BMI), comorbidities, clinical stage, prostate specific antigen (PSA), prostate volume, biopsy grade, and number of positive cores. Functional outcomes based on International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF-5) scores, and incontinence rates were evaluated at 6, 12, and 24 months.

Results: total of 193 HIFU cases matched to 760 cases of RARP, were included. No differences were observed in perioperative IPSS at all follow-up periods. Despite comparative erectile function at baseline, HIFU showed significantly better erectile function preservation compared to RARP, with mean IIEF-5 scores of 9.5 versus 4.8, 9.5 versus 5.8, and 8.4 versus 6.7 at 6, 12, and 24 months, respectively (all $P < 0.001$). Pad-free rates at 6 and 12 months were comparable, with over 96% achieving continence at 12 months in both groups, although the rate of $\leq$1 pad/day at last follow-up was slightly better in HIFU (98.9% vs. 96.7%, $P = 0.049$). Subgroup analysis on partial (PGA) and whole gland ablation (WGA) showed no differences in IIEF-5 and incontinence but increased voiding difficulty in WGA versus PGA after 12 months of therapy ($P < 0.05$). Preoperative IIEF-5 $\geq$17 and HIFU were significant predictors of early erectile function recovery at 6 months (HR 4.4 and 5.0; all $P < 0.001$). No differences were observed in treatment-free survival between PGA, WGA, and RARP.

Conclusion: HIFU shows better performance in early recovery and preservation of erectile function after treatment for prostate cancer without increasing the risk of treatment failure. Patients with moderate to severe erectile dysfunction (IIEF-5 <17) prior to surgery should be warned of poor recovery after treatment.

1. Introduction

Prostate cancer (PCa) is a solid organ tumor that ranks second in incidence among tumors occurring in men worldwide, with rapid growth in Asian populations including, Korea and Australia.[1–3] As diagnostic tools for early detection are widely adopted, the diagnosis rate has gradually increased, especially with PSA screening and improved imaging modalities.[4–6] Various treatment options depend on preoperative risk and clinical needs, but currently, radical prostatectomy (RP), especially robot-assisted radical prostatectomy (RARP), remains the mainstay for localized PCa. However, as diagnostic techniques such as multi-parametric MRI and fusion biopsy become more accurate, focal therapy in non-metastatic PCa is increasingly considered, based on the oncological principle that the index lesion drives oncological progression and outcome.[7]

A widely adopted and well-established technique, high-intensity focused ultrasound (HIFU) uses thermal energy generated

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https://doi.org/10.1016/j.prnil.2024.03.004

through high-intensity ultrasound to induce necrosis of prostatic tissue.[8] Thus, HIFU can be considered a treatment option for low- to intermediate-risk PCa limited to the unilateral lobes, especially for patients seeking less-invasive treatment with fewer side-effects such as incontinence and erectile dysfunction, almost unanimously observed in patients undergoing RP. Through appropriate patient selection, such as localized PCa, small to medium-sized prostates, and low-grade group tumors, HIFU serves to fill the gap between active surveillance and radical treatment.[9,10]

However, because of its relatively recent introduction, data on postoperative prognosis after HIFU are limited compared to RARP and radiotherapy. Oncological results for HIFU have been analyzed and compared to other radical treatments to some extent, showing favorable prognosis, especially in low-intermediate disease.[11,12] However, relatively few studies have assessed the effects on functional outcome, which is one of the clear advantages focal therapy holds against radical treatment. Meanwhile, due to the evolution of robotic technology, many operators are trying to preserve erectile function with RARP, utilizing the nerve-saving technique in various ways.[13] Therefore, comparative analysis of functional outcomes and complication rate is required between the two types of operations, and in this study, we assessed the real-world contemporary comparisons of functional outcomes between RARP and HIFU performed at a high-volume institution.

2. Materials and methods

2.1. Patient demographics and propensity score matching

Patients who underwent HIFU or RARP at a single tertiary institution were retrospectively enrolled, with the final inclusion of 230 HIFU and 4,983 RARP cases performed from October 2007 to March 2022 after the institutional review board approval (B-2208-773-110). Clinico-pathologic variables were obtained in a prospectively managed prostatectomy database, and further survival and functional outcomes were assessed from a review of medical records. The choice of treatment modality was up to the individual surgeon's discretion, as well as thorough the consultation of treatment outcome and possible adverse effects after surgery. While RARP was considered for all stages of surgically resectable disease, HIFU was primarily offered to low-intermediate-risk patients highly motivated for focal tumor control rather than active surveillance or radical therapy. However, higher-risk patients with identified index lesions at preoperative imaging were also considered for HIFU if located in either hemigland.

After exclusion of patients with preoperative androgen deprivation therapy or missing clinical variables, including Gleason grade group (GG), core counts, or PSA, patients were matched in a 1:4 ratio for age, body mass index (BMI), presence of diabetes mellitus (DM) or hypertension (HTN), clinical stage, prostate volume (PV), GG, and positive biopsy cores. Further pre- and post-surgical functional outcomes for voiding symptoms and erectile function were assessed based on International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF-5), respectively, at the preoperative stage and at postoperative 6-, 12-, and 24-months. Continence after surgery was assessed based on the pad used at each timeline, with a percentage of complete continence (0 pad/day) and social continence (up to 1 pad/day) evaluated.

Propensity score matching (PSM) was performed via nearest neighbor matching with a 0.2 caliper width at a 1:4 ratio to adjust for discrepancies in sample size. Minimized mean standard difference (<0.05) was assured after PSM, as shown in Table 1. Comparative analysis of continuous and categorical variables was performed with the student t-test and Pearson chi-square tests, respectively. All statistics were performed using SPSS (version 26; SPSS Inc., Chicago, IL, USA) and R software (version 3.6.3), with a two-sided $P < 0.05$ considered significant.

2.2. Surgical procedure for high-intensity focused ultrasound

For HIFU, Focal One (Edaps TMS, France) was utilized in conjunction with transurethral resection of the prostate performed in a supine lithotomy prior to both partial and whole gland ablation (PGA, WGA), with the exception of patients with previous endoscopic resection. The patient's position was then modified to right lateral decubitus, and the probe was inserted at the rectum. After fusion of MRI imaging with real-time ultrasound, ablation of prostatic tissue was performed over a course of 10-15 minutes. The probe consists of a central transducer providing real-time imaging and a peripheral therapeutic transducer used for producing focalized ultrasound for ablation. Via electromechanical vibration waves

Table 1
Baseline clinical characteristics before and after 1:4 propensity score matching

Variables	Before PSM				After PSM			
Covariates	HIFU ($n = 194$)	RARP ($n = 4671$)	*P*	Standardized difference	HIFU ($n = 193$)	RARP ($n = 760$)	*P*	Standardized difference
Age (years)	67.2 ± 7.0	66.3 ± 7.1	0.090	0.130	67.2 ± 7.0	67.2 ± 6.7	0.986	−0.011
BMI (kg/m^2)	25.2 ± 2.5	24.6 ± 2.7	0.003	0.235	25.2 ± 2.5	25.1 ± 2.7	0.672	0.014
DM	42 (21.6)	849 (18.2)	0.220	0.084	42 (21.8)	161 (21.2)	0.861	0.016
HTN	100 (51.5)	2212 (47.4)	0.252	0.084	99 (51.3)	387 (50.9)	0.926	−0.002
Clinical stage			0.687	0.030			0.770	−0.037
T1	83 (42.8)	2067 (44.3)			83 (43.0)	318 (41.8)		
T2	107 (55.2)	2082 (44.6)			106 (54.9)	386 (50.8)		
T3	4 (2.1)	522 (11.2)			4 (2.1)	56 (7.4)		
≥T2	111 (42.8)	2604 (55.7)			110 (57.0)	442 (58.2)		
PSA (ng/ml)	7.1 ± 4.6	12.5 ± 19.6	<0.001	−1.167	7.1 ± 4.6	7.3 ± 4.6	0.684	−0.020
Prostate volume (ml)	34.9 ± 15.0	36.2 ± 14.4	0.207		35.0 ± 15.0	35.2 ± 13.3	0.876	
ISUP grade			<0.001	−0.425			0.404	0.009
≤2	140 (72.2)	2817 (60.3)			139 (72.0)	563 (74.1)		
3	41 (21.1)	901 (19.3)			41 (21.2)	133 (17.5)		
≥4	13 (6.7)	953 (20.4)			13 (6.7)	64 (8.4)		
Number of positive biopsy cores	3.0 ± 2.0	4.0 ± 2.9	<0.001	−0.533	3.0 ± 2.0	3.1 ± 2.3	0.413	−0.054

BMI, body mass index; DM, diabetes mellitus; HIFU, high-intensity focused ultrasound; HTN, hypertension; ISUP, International Society of Urological Pathology; PSA, prostate specific antigen; PSM, propensity score matching; RARP, robot assisted radical prostatectomy.

emitted from the transducer, alternating pressure and mechanical tissue displacement occur in the targeted lesion or gland, and tissue heating and subsequent necrosis ensue. The degree of surgical ablation of the focal versus whole gland HIFU was decided preoperatively based on biopsy results and the radiographic involvement of the tumor. After surgery, a Foley catheter is inserted for irrigation and prevention of post-procedural transient urinary obstruction, and the patient is discharged after an average of 2 days after surgery.

3. Results

3.1. Baseline characteristics

194 patients of HIFU group and 4,671 patients of RARP group were primarily enrolled in this study, and baseline characteristics are summarized in Table 1. A statistically significant difference in preoperative factors such as BMI ($P = 0.003$), PSA ($P < 0.001$), International Society of Urological Pathology (ISUP) grade ($P < 0.001$), and number of positive cores ($P < 0.001$) were matched at a 1:4 ratio, after which 193 of HIFU and 760 of RARP were included in the final analysis. After PSM, all cases were well matched ($P > 0.05$) and differences were minimized.

3.2. Comparison of functional outcome

Comparisons of perioperative IPSS, IIEF-5, and pad-free rates are described in Table 2. There was no difference in IPSS between HIFU and RARP at preoperative baseline and up to postoperative 24 months. ($P = 0.100$ in 6 months, $P = 0.845$ in 12 months, $P = 0.657$ in 24 months, respectively). Although preoperative erectile function was not significantly different between the two groups (IIEF-5 13.2 vs. 13.0 for HIFU vs. RARP, $P = 0.728$), erectile function was better preserved in patients undergoing HIFU beginning from postoperative month 6 (IIEF-5 9.5 after HIFU vs. 4.8 after RARP; $P < 0.001$) and was preserved up to 2 years (9.5 vs. 5.8 after 12 months, 8.4 vs. 6.7 after 24 months for HIFU and RARP, respectively; all $P < 0.001$). Evaluation of incontinence rates showed no significant difference in terms of complete pad-free achievement at 6 months and 12 months, with 93.5% and 96.8% of HIFU achieving complete continence at 6- and 12-months, respectively, compared to 91.8% and 96.7% after RARP ($P = 0.437$ and 0.962, respectively). However, the rate of social continence defined as $\leq$1 pad/day at last follow-up showed better results in HIFU patients (98.9%) compared to RARP (96.0%) ($P = 0.049$).

3.3. Subgroup analysis of partial and whole gland ablation

In subgroup analysis between PGA and WGA in HIFU, no differences were observed for erectile function and incontinence rates (Table 3; all $P > 0.05$). Absolute IIEF-5 and the rate of mild to no erectile dysfunction (ED) (IIEF-5 $\geq$17) were not different by degree of ablation. However, patients who underwent PGA were more likely to experience better voiding symptoms after 12 and 24 months (mean IPSS of 8.9 vs. 12.6 at postoperative 12 months and 8.4 vs. 14.3 at 24 months, $P = 0.040$; Table 3). Furthermore, while partial gland ablation showed gradual improvement in IPSS over

Table 2
Perioperative functional outcome prior to treatment and at postoperative 6, 12, 24 months

Variables		HIFU	RARP	*P*
IPSS, mean ± SD	Preoperative	11.2 ± 7.0	11.8 ± 7.2	0.326
	6 months	11.3 ± 7.7	9.8 ± 6.9	0.100
	12 months	9.7 ± 7.2	9.8 ± 6.0	0.845
	24 months	9.8 ± 7.7	9.4 ± 6.7	0.657
IIEF-5, mean ± SD	Preoperative	13.2 ± 7.3	13.0 ± 7.0	0.728
	6 months	9.5 ± 7.2	4.8 ± 5.3	<0.001
	12 months	9.5 ± 7.1	5.8 ± 5.8	<0.001
	24 months	8.4 ± 7.1	6.7 ± 6.1	<0.001
Incontinence, *n* (%)	Pad-free at 6 months	173 (93.5)	637 (91.8)	0.438
	Pad-free at 12 months	179 (96.8)	666 (96.0)	0.962
	≤1 pad/day at last f/u	183 (98.9)	671 (96.7)	0.049

HIFU, high intensity focused ultrasound; IPSS, international prostate symptom score; IIEF, international index of erectile function; RARP, robot assisted radical prostatectomy; SD, standard deviation.

Table 3
Subgroup analysis of partial versus whole gland HIFU on functional outcome

Variables		Partial gland ablation	Whole gland ablation	*P*
IPSS, mean ± SD	Preoperative	10.8 ± 6.8	12.0 ± 7.7	0.360
	6 months	10.8 ± 7.6	12.9 ± 8.2	0.182
	12 months	8.9 ± 6.8	12.6 ± 7.8	**0.032**
	24 months	8.4 ± 6.3	14.3 ± 9.9	**0.040**
IIEF-5, mean ± SD	Preoperative	13.5 ± 7.1	12.8 ± 7.5	0.600
	6 months	9.8 ± 7.1	8.8 ± 7.3	0.495
	12 months	9.8 ± 7.1	8.1 ± 7.2	0.331
	24 months	8.5 ± 7.2	8.4 ± 7.1	0.936
IIEF-5 ≥17, *n* (%)	Preoperative	53 (38.1)	13 (29.5)	0.301
	6 months	20 (19.0)	5 (16.7)	0.767
	12 months	25 (28.4)	7 (29.2)	0.942
	24 months	27 (49.1)	9 (45.0)	0.754
Incontinence, *n* (%)	Pad-free at 6 months	130 (93.5)	41 (93.2)	0.936
	Pad-free at 12 months	134 (96.4)	43 (97.7)	0.667
	≤1 pad/day at last f/u	137 (98.6)	44 (100)	0.424

HIFU, high intensity focused ultrasound; IPSS, international prostate symptom score; IIEF, international index of erectile function; SD, standard deviation.
*p-values <0.05 marked as bold

time, patients who underwent WGA showed progressively worse symptoms, increasing from preoperative IPSS scores of 12.0 to 12.9, 12.6, and 14.3 at 6, 12, and 24 months.

3.4. Predictors for preservation of functional outcome and comparison of treatment-free survival

Univariate and multivariate analyses showed preoperative IIEF-5 ≥17 and HIFU (over RARP) to be independent predictors of achieving maintained erectile recovery at 6 months (HR 4.370 and 5.002, respectively; all $P \leq 0.001$) (Table 4). Also, these factors were similarly significant predictors of IIEF-5 ≥17 at 12 month after the operation (HR 5.042 and 5.156, respectively; all $P < 0.001$). At 24 months, preoperative IIEF-5 ≥17 had OR 6.707 (3.030-14.848) and HIFU had OR 5.663 (2.735-11.726). PGA versus WGA had no significant influence on the preservation of IIEF at 6, 12, and 24 months ($P = 0.767$, 0.942, and 0.754).

Comparison of treatment-free survival by the respective methods of partial, whole gland ablation, and RARP showed no significant differences (Fig. 1).

4. Discussion

In our study, PSM-matched analyses of HIFU and RARP suggest that patients undergoing HIFU had significantly better functional outcome preservation in terms of voiding and erectile function

Table 4
Uni- and multi-variate regression analysis for achieving erectile function recovery at postoperative 6 and 12 months

IIEF-5 ≥17 at 6 months				
	Univariate (HR, 95% CI)	*P*	Multivariate (HR, 95% CI)	*P*
Age	0.920, 0.878−0.965	0.001	0.951, 0.901−1.003	0.065
BMI	1.015, 0.895−1.151	0.819		
DM	0.508, 0.193−1.335	0.169		
HTN	0.602, 0.312−1.163	0.131		
Clinical stage ≥ T2	1.143, 0.598−2.185	0.685		
PSA	1.044, 0.979−1.113	0.188		
Prostate volume	0.983, 0.957−1.008	0.185		
Preoperative IIEF-5 ≥17	4.889, 2.243−10.654	<0.001	4.370, 1.891-10.098	0.001
HIFU vs. RARP	4.012, 2.064−7.799	<0.001	5.002, 2.391-10.465	<0.001
IIEF-5 ≥17 at 12 months				
Age	0.932, 0.894−0.972	0.001	0.967, 0.923-1.014	0.164
BMI	0.973, 0.871−1.086	0.621		
DM	2.288, 0.942−5.555	0.068		
HTN	0.548, 0.307−0.977	0.042		
Clinical stage ≥ T2	1.232, 0.697−2.179	0.472		
PSA	1.030, 0.970−1.092	0.336		
Prostate volume	0.981, 0.957−1.005	0.115		
Preoperative IIEF-5 ≥17	4.468, 2.287−8.727	<0.001	5.042, 2.418-10.513	<0.001
HIFU vs. RALP	4.083, 2.272−7.339	<0.001	5.156, 2.657-10.007	<0.001

BMI, body mass index; DM, diabetes mellitus; HIFU, high frequency focused ultrasound; HR, hazard ratio; HTN, hypertension; IIEF, international index of erectile function; PSA, prostate specific antigen; RARP, robot assisted radical prostatectomy.
At 24 mo, preoperative IIEF-5 ≥17 had HR 6.707 (3.030−14.848) and HIFU had HR 5.663 (2.735−11.726). PGA versus WGA had no significant influence on preservation of IIEF at 6, 12, and 24 months ($P = 0.767$, 0.942, and 0.754, respectively).

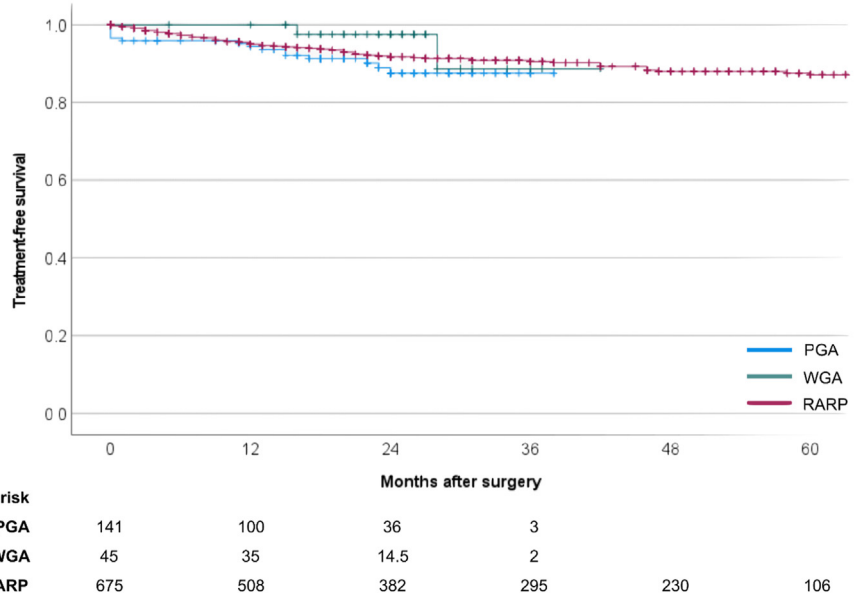

Figure 1. Treatment-free survival between PGA, WGA, and RARP. PGA, partial gland ablation; RARP, robot-assisted radical prostatectomy; WGA, whole gland ablation.

preservation compared to RARP without sacrificing treatment-free survival. While rates of complete continence were similar, rates of social continence of ≤1 pad/day were better in HIFU patients, and higher IIEF-5 scores were observed consistently at 6, 12, and 24 months at follow-up, suggesting patients who seek to preserve sexual function and avoid the risk of incontinence should be counseled for HIFU despite recent advances in robotic techniques.

HIFU is without a doubt becoming an attractive option for focal therapy in relatively low-risk localized cancer, opting for more active treatment without the associated risk of complications involved in radical curative options such as RARP or radiation therapy.[8,14] Intended to fill the gap between active surveillance and curative procedures, focal therapy has found moderate success in addressing the unmet needs for further oncological control with a good prognosis in large multicenter cohorts.[15,16] Reddy et al (2022) reported 69% overall failure-free survival at 7 yr after primary HIFU for nonmetastatic PCa and metastasis-free survival of 100%.[12] Subgroup outcomes in intermediate- to high-risk PCa were compatible, with 65–68% failure-free survival. However, reports of functional outcomes are often neglected, as long- to medium-term oncological control is primarily focused on outcome analyses.

A handful of previous studies have compared functional outcomes after HIFU compared to RARP. In a comparative matched analysis of HIFU hemi-ablation and RARP, Albisinni et al (2017) showed not only similar efficacy in controlling localized unilateral PCa but also superior functional outcomes, with patients showing better postoperative continence after HIFU.[11] About 82% of 55 patients showed no incontinence immediately after surgery, whereas 60% of 55 RARP patients required ≥0 pads during the same period ($P < 0.001$). Also, erectile function was better preserved after focal HIFU, with a higher rate of persistent erectile dysfunction after RARP ($P = 0.03$). However, only pathologic variables, including gleason scores, PSA, and clinical stage, were matched, which may be insufficient to account for other clinical factors such as age or comorbidity, which may have a stronger role in assessing functional outcome as described in the literature.[17]

He et al (2020) reported that the urinary incontinence was found in 2% of the total 7,393 HIFU cases after 3 months of WGA and an impotence rate of 21%.[18] This is in line with our results of nearly all HIFU cases socially continent after 12 months (98.6%) and only 3.2% failing to achieve complete continence. These results are better than what was reported from a Swedish prospective randomized trial, with incontinence and impotence rates of 21.3% and 70.4% after RARP, respectively.[19] However, the RARP outcome was considerably better in our study as well, with over 96% achieving complete continence. This may be due to improved nerve-sparing techniques in robotic surgery as well as the effect of matching other related variables. Better results in HIFU compared to RARP may be due to less functional deterioration in HIFU and fewer changes in the overall pelvic cavity anatomy as a result of a minimally invasive procedure and the preservation of external sphincter muscles and bladder neck.[20]

There are several limitations in our study. Due to its retrospective nature, there is a high risk of selection bias, despite our best attempts. For instance, better preoperative IIEF-5 scores identified as significant independent factors may suggest that patients with good erectile function may be more driven to choose HIFU over RARP based on the risk of sexual dysfunction. Efforts were made to reduce this bias by matching variables that affect overall erectile function, such as age, BMI, and DM, through propensity score matching. Also, a collective comparative analysis between HIFU and RARP was conducted, using the entire HIFU data conducted in a single institution without distinguishing between WGA and PGA. Although WGA and PGA subgroup analyses did not result in a significant difference, further studies should be done with an increased sample size or multicenter data collection. Also, clinical stage was stratified into only T1 and T2 or higher, which may have limited the effect of matching. Finally, while matched, the study included a relatively younger population with a mean age of 67.2 years in both groups; hence, the results may not be transferable to procedures performed in an older cohort.

Despite such limitations, our study showed further evidence to support the use of HIFU for focal therapy in patients seeking sexual function preservation and early voiding recovery. Patients with moderate to severe erectile dysfunction before surgery should be properly counseled, as these patients may not benefit from focal therapy. Further prospective trials should be performed to validate our results.

5. Conclusion

After PSM comparison to RARP, erectile function was better preserved in HIFU was performed with early continence recovery, and as preoperative IIEF-5 scores were predictive of outcome, patients with poor sexual function should be warned of poor recovery after treatment. Despite comparable treatment-free survival between surgical modalities, patients should be well informed of the compromise between oncological control after definitive treatment with RARP and a decreased risk of complications with focal therapy. Future clinical trials in localized PCa are warranted.

Conflicts of interest

None.

Acknowledgment

This study was funded by the SNUBH Research Fund (#13-2024-0014).

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