High Intensity Focused Ultrasound Hemigland Ablation for Prostate Cancer: Initial Outcomes of a United States Series

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Purpose: We report outcomes of hemigland high intensity focused ultrasound ablation as primary treatment for localized prostate cancer in the United States.

Materials and Methods: A total of 100 consecutive men underwent hemigland high intensity focused ultrasound (December 2015 to December 2019). Primary end point was treatment failure, defined as Grade Group 2 or greater on followup prostate biopsy, radical treatment, systemic therapy, metastases or prostate cancer specific mortality. IIEF (International Index of Erectile Function), I-PSS (International Prostate Symptom Score) and 90-day complications were reported.

Results: At study entry patients had very low (8%), low (20%), intermediate favorable (50%), intermediate unfavorable (17%) and high (5%) risk prostate cancer. Median followup was 20 months. The 2-year survival free from treatment failure, Grade Group 2 or greater recurrence, repeat focal high intensity focused ultrasound and radical treatment was 73%, 76%, 90% and 91%, respectively. Bilateral prostate cancer at diagnosis was the sole predictor for Grade Group 2 or greater recurrence ($p=0.03$). Of men who underwent posttreatment biopsy (58), 10 had in-field and 8 out-of-field Grade Group 2 or greater positive biopsy. Continence (zero pad) was maintained in 100% of patients. Median IIEF-5 and I-PSS scores before vs after hemigland high intensity focused ultrasound were 22 vs 21 ($p=0.99$) and 9 vs 6 ($p=0.005$), respectively. Minor and major complications occurred in 13% and 0% of patients. No patient had rectal fistula or died.

Conclusions: Short-term results of focal high intensity focused ultrasound indicate safety, excellent potency and continence preservation, and adequate short-term prostate cancer control. Radical treatment was avoided in 91% of men at 2 years. Men with bilateral prostate cancer at diagnosis have increased risk for Grade Group 2 or greater recurrence. To our knowledge, this is the initial and largest United States series of focal high intensity focused ultrasound as primary treatment for prostate cancer.

Key Words: high intensity focused ultrasound ablation, prostatic neoplasms

Abbreviations and Acronyms

BF = biochemical failure
CSPCa = clinically significant prostate cancer
DRE = digital rectal examination
FDA = U.S. Food and Drug Administration
FU-PBx = followup biopsy
GG = Grade Group
h-HIFU = hemigland HIFU
HIFU = high intensity focused ultrasound
IIEF = International Index of Erectile Function
I-PSS = International Prostate Symptom Score
mpMRI = multiparametric MRI
MRI = magnetic resonance imaging
PCa = prostate cancer
PGA = partial gland ablation
PI-RADS® = Prostate Imaging Reporting and Data System
PSA = prostate specific antigen
RT = radical treatment
TURP = transurethral resection of the prostate

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High intensity focused ultrasound has been applied as an alternative treatment option for localized prostate cancer.[1–4] Some of the largest series of whole gland HIFU ablation for PCa showed long-term oncologic outcomes comparable to standard radical treatments (prostatectomy and radiation), yet with moderate potency and good continence preservation, and high rates of urethral and bladder outlet obstruction.[2,4,5]

Partial gland ablation for PCa emerged as an organ sparing concept with the benefits of low morbidity and maintained quality of life (potency and continence) using minimally or noninvasive techniques and technologies. Whole or partial gland HIFU ablation for PCa has been performed in several countries for longer than 20 years.[2,3,5] In November 2015 the U.S. Food and Drug Administration cleared HIFU for prostatic tissue ablation.[4] Since then, HIFU has been applied for PCa ablation. However, reports of HIFU PGA performed in the U.S. are sparse. To our knowledge, we report the initial and largest U.S. series of HIFU PGA as primary treatment for PCa.

MATERIAL AND METHODS

Study Population

We retrospectively reviewed data from 174 consecutive patients undergoing HIFU ablation for PCa from December 2015 to December 2019. The inclusion criteria were hemigland HIFU as primary treatment for PCa; biopsy proven unilateral PCa or selected men with bilateral PCa, where the contralateral lobe had nondominant, low volume, GG 1 PCa; and localized PCa (patients with clinical T3 on DRE were not offered partial gland ablation). Patients undergoing three-quarters, subtotal, whole gland or salvage HIFU were excluded. h-HIFU was performed by one of 3 surgeons (ALA, SPe, ISG) at 2 facilities in the U.S. De-identified data were retrospectively merged after institutional review board approval (IRB No. HS-17-00749). h-HIFU was defined as hemigland ablation of the prostate lobe harboring the dominant biopsy proven PCa (only 1 patient had anterior hemigland ablation for bilateral anterior dominant lesion).

Patient Selection for h-HIFU

Patients were selected for h-HIFU after being diagnosed with localized PCa by imaging fusion software based (Koelis® or UroNav®) 12-core systematic plus targeted biopsy of suspicious areas on mpMRI. Patients with unfavorable-intermediate or high risk PCa underwent metastatic workup as recommended by current guidelines.[6] TURP was proposed prior to h-HIFU for prostate downsizing, as per surgeon discretion, usually for prostate volume greater than 50 cc.[7]

h-HIFU Treatment

With the patient under general anesthesia, h-HIFU was performed transrectally, according to the standards recommended by the manufacturer. The Sonablate® 500 or Ablatherm® device was used according to prostate size and machine availability. After recovering from anesthesia, the patients were discharged home with indwelling urethral 16Fr Foley catheter or suprapubic 14Fr Foley catheter. Antibiotics were prescribed for 7 days. On postoperative day 7 the catheter was removed with a trial of void.

h-HIFU Followup

Followup was scheduled 3-monthly in the first year and 6-monthly thereafter assessing symptoms, questionnaires and serum prostate specific antigen. DRE was performed at 3 months, at time of followup biopsy (6 to 12 months) and annually thereafter. mpMRI was recommended at 6 to 12 months and annually thereafter. Followup biopsies were performed with similar technique and rigor as diagnosis biopsies (systematic and image targeted biopsy of suspicious areas). FU-PBx was strongly recommended for all patients at 6 to 12 months per protocol, or at any time, for a cause, if clinically indicated, for biochemical failure, rising PSA, or suspicious for PCa recurrence on DRE or mpMRI.

h-HIFU Outcomes Measurements and Study End Points

Definitions were 1) biochemical failure—PSA nadir + 2 ng/ml (Phoenix criteria),[8–12] 2) clinically significant PCa—GG 2 or greater on followup biopsies,[8,13,14] 3) repeat focal HIFU—HIFU PGA re-treatment on followup,[8,14,15]

Table 1. *Baseline characteristics*

Median age (IQR)	65	(59—70)
Median ng/ml PSA (IQR)	5.9	(4.5—7.2)
Median cc prostate vol (IQR)	34	(27—46)
Median ng/ml/cc PSA density (IQR)	0.16	(0.11—0.22)
MRI findings:*		
Median No. suspicious lesion (IQR)	1	(1—2)
No. highest PI-RADS score (%):		
1—2	30	(32)
3	12	(13)
4	37	(39)
5	15	(16)
No. PI-RADS 3 or greater (%)	64	(71)
No. clinical stage (%):		
T1c	85	(85)
T2a	12	(12)
T2b	1	(1)
T2c	2	(2)
No. ISUP Grade Group (%):		
1	29	(29)
2	55	(55)
3	11	(11)
4	5	(5)
5	0	(0)
Entry biopsy:		
Median No. cores taken (IQR)	12	(12—13)
Median pos cores (any Ca) (IQR)	3	(1—5)
Median max Ca core % (IQR)	40	(20—70)
No. bilat Ca on biopsy (%)	24	(24)
No. NCCN risk group (%):		
Very low	8	(8)
Low	20	(20)
Intermediate favorable	50	(50)
Intermediate unfavorable	17	(17)
High	5	(5)
Very high	0	(0)

* In 94.

Table 2. *Followup biopsy outcomes after hemigland HIFU ablation according to prostate cancer Grade Group at baseline*

		Followup Biopsy Outcomes			
		% Neg Biopsy*		% Neg Biopsy for CSPCa	
	No.	1-Yr	2-Yr	1-Yr	2-Yr
Any GG at baseline:					
All pts	89	82	58	94	76
Pts with followup biopsy†	58	73	42	91	66
GG 1 at baseline:					
GG 1	26	83	59	95	84
GG 1 with followup biopsy†	19	78	46	94	79
GG 2 or greater at baseline:					
GG 2 or greater	63	81	58	93	72
GG 2 or greater with followup biopsy†	39	71	39	89	59

Only patients with followup greater than 6 months included in this table.
* Considering any GG (1-5) cancer on followup prostate biopsy.
† Considering only the patients who underwent followup prostate biopsy.

4) radical treatment—any radical/whole gland treatment, including ablation, radiation or surgery[7,8,14,15] and 5) treatment failure—CSPCa on FU-PBx, any whole gland treatment (RT criteria), initiation of systemic therapy, metastases or PCa specific mortality. PCa is graded according to ISUP (International Society of Urological Pathology) standards.[13]

Functional outcomes were evaluated using the best score on validated questionnaires within 2 years after h-HIFU.[8,16] Continence was strictly defined as the use of no pads.[7,8,14–16] Potency and urinary symptoms were evaluated by IIEF-5 and I-PSS, respectively.[8,16–19] Perioperative complications were evaluated within 90 days after h-HIFU according to Clavien-Dindo classification.[16,20]

Oncologic outcomes are reported according to NCCN® (National Comprehensive Cancer Network®) PCa risk groups.[6] Followup biopsy outcomes were evaluated according to PCa GG at baseline and FU-PBx status.[8] Performance of mpMRI on followup after h-HIFU was analyzed. The primary end point was failure-free survival. Secondary end points were survival free from BF, CSPCa, repeat focal HIFU and RT. Predictors for primary and secondary end points were assessed. End points were evaluated using data of patients with followup longer than 6 months who had at least 2 PSA measurements and were eligible for followup mpMRI and biopsy.

Sensitivity Analysis

The 2 sensitivity analyses performed were 1) comparing patients eligible for but not undergoing FU-PBx vs those with benign or GG 1 on FU-PBx vs those with CSPCa on FU-PBx, and 2) comparing patient demographics and outcomes from 1 center (USC) that used available HIFU machines by a single surgeon (ALA) (supplementary Appendix and tables 1, *A-C*, https://www.jurology.com).

Statistical Analysis

Statistical analysis was performed using JMP®14. Wilcoxon rank sum and chi-square or Fisher's exact test were used for continuous and categorical variables, respectively. Kaplan-Meier methods were used to estimate the probabilities of survival. Univariate Cox regression analysis was performed to assess predictors for BF, CSPCa recurrence, RT and failure. Wilcoxon signed rank test was performed for functional outcomes and statistical significance was set at $p < 0.05$.

RESULTS

A total of 100 men underwent h-HIFU and met the study inclusion criteria (supplementary figure, https://www.jurology.com). Demographics and preoperative data are summarized in table 1. Median preoperative age, PSA density and prostate volume were 65 years, 0.16 ng/ml/cc and 34 cc, respectively. Ninety-four patients had mpMRI at baseline and PI-RADS® 3 or greater was found in 64 (68%) of them. At study entry patients had very low (8%), low (20%), intermediate favorable (50%), intermediate unfavorable (17%) and high (5%) risk PCa.

Median followup was 18 months, with 89 patients having followup greater than 6 months and, therefore, eligible for followup mpMRI and FU-PBx. Detailed FU-PBx outcomes are presented in tables 2 and 3. A total of 58 (65%) patients underwent FU-PBx. Of these, CSPCa was found in 18, with 8 in-field and 10 out-of-field. A sensitivity analysis was performed including the 31 patients eligible for but not undergoing FU-PBx. These patients had fewer positive cores (3 vs 5, $p=0.04$) at diagnosis and shorter followup (18 vs 25 months, $p=0.03$) compared to patients with CSPCa on FU-PBx. There was no statistically significant difference for all parameters analyzed for those patients with no FU-PBx vs benign or GG 1 on FU-PBx (supplementary table 2, https://www.jurology.com).

The 2-year survival rates are detailed in table 4. The 2-year failure-free survival was 73%. Median times to PSA nadir, PSA at nadir and percent PSA reduction at nadir were 3 months, 1.3 ng/ml and 75%, respectively. Bilateral PCa at entry was the sole significant predictor ($p=0.03$) for CSPCa on FU-PBx. There were no predictors for failure (supplementary table 3, https://www.jurology.com). One patient with GG 4 PCa had 1 metastatic lymph node

Table 3. *Followup biopsy outcomes after hemigland HIFU*

No. with followup biopsy (%)*	58 (65)
Median No. cores taken (IQR)	12 (8-16)
No. benign biopsy	26
No. Ca on biopsy:	32
No. GG 1:	14†
In-field	2
Out-of-field	13
No. GG 2 or greater:	18
In-field	8
Out-of-field	10

* Out of 89 patients with followup greater than 6 months who were eligible for followup biopsy.
† One patient had bilateral GG 1 prostate cancer.

Table 4. *Oncologic outcomes after hemigland HIFU according to prostate cancer risk group*

	Overall	PCa Risk Group by NCCN		
		Very Low + Low	Intermediate Favorable	Intermediate Unfavorable + High
No. pts (%)*	89	25 (28)	44 (50)	20 (22)
Median mos followup (IQR)	20 (13—29)	22 (15—32)	23 (15—29)	16 (13—19)
Median PSA nadir (IQR)	1.3 (0.7—2.6)	1.5 (0.7—2.9)	1.2 (0.8—2.4)	1.1 (0.6—2.2)
Median time to PSA nadir (IQR)	3 (3—6)	4 (3—6)	3 (3—6)	3 (3—5)
Median % PSA decreased (IQR)†	75 (52—89)	72 (50—89)	75 (55—85)	83 (63—92)
%2-Yr free survival:				
Biochemical failure - Phoenix criteria	92	92	100	71
Clinically significant PCa‡	76	84	75	63
Repeat focal HIFU	90	85	90	100
Radical treatment§	91	92	91	88
Failure‖	73	75	75	63
Systemic therapy	100	100	100	100

* Patients with followup greater than 6 months who had at least 2 PSA measurements and were eligible for followup mpMRI and biopsy.
† Percent of PSA decreased at nadir = (PSA at entry − PSA nadir) / (PSA at entry x 100).
‡ On followup biopsy.
§ Radical treatment defined as any whole gland treatment.
‖ Failure was defined as Grade Group 2 or greater PCa on followup biopsy, any whole gland treatment, initiation of systemic therapy, metastases or prostate cancer specific mortality.

(N1) at time of salvage radical prostatectomy. No patient received systemic therapy or died.

Followup mpMRI was performed in 61 (69%) eligible patients (table 5). There were no suspicious lesions in 43 men. For detection of CSPCa on FU-PBx, the mpMRI sensitivity was 44%, specificity 71%, negative predictive value 74%, positive predictive value 41% and accuracy 63%.

Minor 90-day complications occurred in 13 (13%) patients. There were no major complications and no rectal fistula occurred (table 6). TURP was performed in 11 (11%) patients prior to h-HIFU. For the 47 patients with baseline and post-h-HIFU available questionnaires, median (IQR) IIEF-5 and I-PSS scores were 22 (18—25) vs 21 (16—24) (p=0.99) and 9 (3—15) vs 6 (3—11) (p=0.005), respectively (see figure). There was no new onset urinary incontinence.

DISCUSSION

HIFU was cleared for prostatic tissue ablation by the FDA in December 2015.[4] Although PGA for PCa using HIFU has been applied nationwide, there is no report from the U.S. on the current clinical practice and outcomes of focal HIFU as primary treatment for selected men with PCa.[1–4] Indeed, Jones et al reported the safety and efficacy of salvage whole gland HIFU in 100 men with radiorecurrent PCa.[21] As first adopters in the U.S. of HIFU as an alternative treatment for localized PCa, we started offering and performing h-HIFU in December 2015. Therefore, this study reports the initial outcomes of the first series of focal h-HIFU ablation as primary treatment for localized PCa from the U.S.

There is no widely accepted definition for PGA failure.[22] We used a broadly composed definition for failure, including the most relevant oncologic outcomes of ablation or selection failure (in-field or out-of-field CSPCa on FU-PBx), conversion to radical or systemic treatment, occurrence of metastasis or cancer specific mortality.[7,8,15] We report a 2-year failure-free survival of 73%. A recent European study using similar definitions reported a 2-year failure-free survival of 76% for focal HIFU in 190 men with low-intermediate risk PCa.[7]

One goal of PGA is to avoid or delay radical treatment and its inherent quality of life deterioration.[18,23] We report 2-year RT-free survival of 91%. Bass et al reported that at a median followup of 24.3 months, whole gland treatment was avoided in 81% of 150 patients undergoing HIFU PGA.[18] One desirable characteristic of ablation therapies, including HIFU, is its repeatability. We reported a 2-year repeat focal HIFU-free survival of 90%. Recently a study on a large multi-institutional prospective registry of patients undergoing focal HIFU reported a 3-year freedom from repeat HIFU of 84%.[15]

There is no consensus for a biochemical failure definition after focal therapy. However, post-treatment PSA monitoring is important. We used Phoenix criteria for BF as previously reported.[8–12] Additionally, we report 75% of PSA reduction from baseline to post-h-HIFU. PSA decrease 70% or greater

Table 5. *Followup mpMRI outcomes*

No. pts (%)*	61	(69)
Median cc prostate vol (IQR)	20 (15—28)	
No. Likert score (%):		
2 or Less	43	(70)
3	11	(18)
4	5	(8)
5	2	(3)
No. with suspicious lesion (Likert score 3 or greater) (%)	18	(30)

* 61 out of 89 patients with followup greater than 6 months.

Table 6. *90-day complications after hemigland HIFU ablation for prostate cancer*

Clavien Grade	No. (%)	Complication	Management (No.)
I	1 (1)	Neuropraxia	Physical therapy
	7 (7)	Urinary retention/insufficient voiding	Clean intermittent catheterization (2) Prolonged Foley catheterization (3) Prolonged suprapubic tube (1) Urethral dilation (1)
II	5 (5)	Urinary tract infection	Antibiotics
III-V	0	-	-

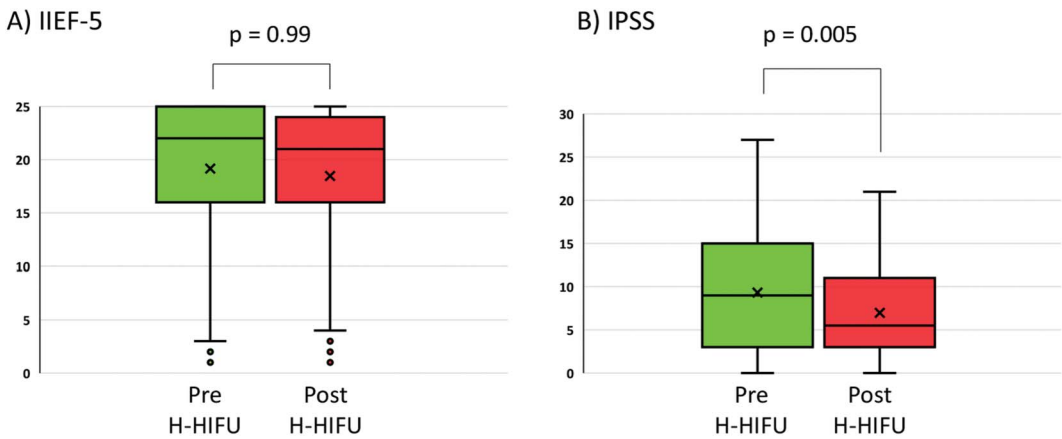
There were no rectal fistulas.

from baseline to post-focal therapy is indicative of proper ablation of the index cancer.[8,10–12]

Patients with unilateral localized intermediate risk PCa would be the optimal candidates for PGA. However, PGA has also been applied to carefully selected men with low and high risk PCa.[8,14,15,18,23–27] A recent trial randomized 404 men to active surveillance vs PGA for low risk PCa and showed that those undergoing PGA had less PCa progression, more negative FU-PBx rate and less conversion to radical treatment, yet with similar continence and potency as those on active surveillance.[23,25] Recent studies exploring the oncologic efficacy of PGA for high risk PCa reported 5-year failure-free survival of 84% after focal HIFU and 78% after hemigland cryoablation.[8,15] The caveat is that higher PSA, GG 3 or greater and clinical T3 stage at baseline were independent predictors for failure.[8,15] There are no data to indicate that GG 4 PCa would inherently be more resistant to ablative therapies than GG 1 PCa. However, high risk PCa carries enhanced risk of lymph node micrometastases that may not be reliably detected by current imaging modalities. To address this issue, a risk adapted approach with concurrent minimally invasive lymphadenectomy can be considered.[24]

MRI was performed before h-HIFU. However a few patients (6) with noncompliant pacemakers or claustrophobia did not undergo mpMRI and were selected by systematic biopsy only. Similarly, 19% of 150 men undergoing HIFU PGA and the majority of 160 men undergoing hemigland cryoablation in other series did not have mpMRI at baseline.[12,18] Nevertheless, the oncologic outcomes among series that used or did not use mpMRI for patients selection appear to be similar.[1–3,7,8,14,15,18] Although mpMRI is the preferred imaging modality for followup after PGA, our data showed low sensitivity (44%) of mpMRI for detection of CSPCa recurrence after h-HIFU.[28] Similarly, Mortezavi et al found mpMRI to have a sensitivity of only 14% for detection of CSPCa after HIFU PGA as measured against extensive histological sampling (transperineal template saturation PBx).[29] These results emphasize the importance of mandatory FU-PBx after PGA.

Protocol FU-PBx was strongly recommended to all patients regardless of PSA, DRE or MRI findings. Indeed, in our series the majority of men underwent per protocol FU-PBx, and not for cause only. However, as emphasized by Bass et al, "patient resistance to compliance with FU-PBx was common in the absence of rising PSA or an indication of residual disease on MRI."[18] Our sensitivity analysis showed that although there was no statistical difference, the median nadir PSA was higher in patients with CSPCa (2.4 ng/ml) vs men with negative or GG 1 (1.1 ng/ml) vs those with no biopsy (1 ng/ml). Followup biopsy rate also depends on duration of followup.[1–3,7,12,28,29] In fact, patients with no FU-PBx had shorter followup duration than those with CSPCa on FU-PBx ($p=0.03$). Our FU-PBx rate reported here is 65%. In the literature



Patient reported outcomes before and after h-HIFU ablation of prostate, showing sexual function with IIEF-5 in 47 (*A*) and urinary function with I-PSS in 46 (*B*). *Pre,* baseline. *Post,* post h-HIFU best value within 2 years. Box and whiskers plots indicate median and IQR (boxes). Circles indicate outliers.

the post-PGA biopsy rate ranges from 21% to 92% (supplementary table 4, https://www.jurology.com). We provided detailed FU-PBx outcomes including in-field and out-of-field recurrence, stratified by baseline PCa GG and by FU-PBx status, which allow full and comprehensive interpretation of our results by the readers.

Similarly to Guillaumier et al, who reported functional outcomes in 241 out of 599 (40%) men who returned validated questionnaires after HIFU PGA,[15] we reported functional outcomes in 47% of our patients. The absence of urinary incontinence and the maintenance of potency for the current cohort are noteworthy. Complications are reported according to Clavien-Dindo system.[16,18,20] We reported a 7% rate of acute urinary retention. No patient required TURP after h-HIFU. Other series reported acute urinary retention and endoscopic procedures for lower urinary tract symptoms after HIFU PGA in 13% and 9.6%, respectively.[15,18]

This study has limitations, specifically its retrospective design, short followup and relatively low number of patients. However, HIFU has only recently become available for clinical use in the U.S.[4] Nevertheless, to our knowledge, this is the first cohort from the U.S. and the followup duration and number of patients are comparable to others.[1–3,16] Followup biopsy was not performed for all men. However, this is still above the average FU-PBx rate in comparison to other retrospective studies (supplementary table 4, https://www.jurology.com). Less than 50% of the patients completed validated questionnaires. Although this might create a bias, all available questionnaires are reported and the results are in accordance with the literature.[8,15–19] We believe that these data represent the actual current clinical practice in the U.S. This study provides the initial U.S. HIFU data to PCa stakeholders, including clinicians, patients and the FDA.[4]

CONCLUSIONS

The initial results of the first and largest focal HIFU series from the U.S. are presented. Patient compliance to followup protocol is moderate. Radical treatment was avoided in 91% of men at 2 years. Focal HIFU ablation is safe and provides excellent potency and continence preservation with adequate short-term cancer control. Men with bilateral PCa at diagnosis have increased risk of clinically significant prostate cancer on followup biopsy.

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EDITORIAL COMMENT

In this retrospective study the authors should be commended for a transparent and clear report on their initial experience with partial gland ablation using high intensity focused ultrasound in 100 men with localized prostate cancer. The results mirror the encouraging results in terms of disease control and the excellent results in terms of genitourinary function preservation already reported by others (references 3 and 15 in article). After 2 years of followup 91% patients avoided radical treatment, all patients maintained full continence, there was no significant decline of erectile function and no major adverse events occurred.

A pragmatic PGA strategy was chosen, namely hemiablation. While initial enthusiasm in accurate imaging based zonal and disease stratification encouraged focal therapists to direct PGA only to the index lesion plus a margin, it is now clear to most of us that adequate oncologic margins prompt in small to mid-size glands, as in this study in which median prostate volume was 34 cc, ablation of half of the prostate. The tradeoff seems favorable in that while extended ablation ensures better control, the toxicity is similar to series reporting on focal ablation. At present, hemiablation seems to be the most reasonable and deliverable form of PGA across the board.

Since FDA clearance, this is the first U.S. series reporting on PGA using HIFU. Although this study has the inherent limitations of a retrospective analysis, the authors deserve credit for having quickly and safely adopted this technology in their program. This might serve as an example for novel centers implementing PGA.

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