Partial gland ablation with high intensity focal ultrasound impact on genito-urinary function and quality of life: our initial experience

Ioana Fugaru, MD,[1] David Bouhadana, MD,[1] Gautier Marcq, MD,[2,3] Joseph Moryousef, MD,[4] Alexis Rompré-Brodeur, MD,[1] Andrew Meng, MD,[4] Oleg Loutochin,[1] George Loutochin,[1] Maurice Anidjar, MD,[1] Frank Bladou, MD,[5] Rafael Sanchez-Salas, MD[1]

[1]Division of Urology, Department of Surgery, McGill University, Montreal, Quebec, Canada
[2]Department of Urology, Claude Huriez Hospital, CHU Lille, Lille, France
[3]Université de Lille, CNRS Inserm, CHU Lille, Institut Pasteur de Lille, Lille, France
[4]Faculty of Medicine, McGill University, Montreal, Quebec, Canada
[5]Department of Urology, Pellegrin University Hospital, Bordeaux, France

FUGARU I, BOUHADANA D, MARCQ G, MORYOUSEF J, ROMPRE-BRODEUR A, MENG A, LOUTOCHIN O, LOUTOCHIN G, ANIDJAR M, BLADOU F, SANCHEZ-SALAS R. Partial gland ablation with high intensity focal ultrasound impact on genito-urinary function and quality of life: our initial experience. *Can J Urol* 2024;31(1):11784-11792.

Introduction: *Partial gland ablation (PGA) using high intensity focal ultrasound (HIFU) is an alternative to active surveillance for low to intermediate risk localized prostate cancer. This pilot study assessed quality of life (QoL) outcomes during the implementation of PGA-HIFU at our institution.*

Materials and methods: *We prospectively enrolled 25 men with a diagnosis of localized low/intermediate risk prostate cancer who elected to undergo PGA-HIFU in a pilot study at our institution between 2013 and 2016. Patients underwent pre-treatment mpMRI and transrectal ultrasound-guided biopsies. The primary endpoints were impact on patient-reported functional outcomes (erectile, urinary function, QoL) assessed at 1, 3, 6- and 12-months.*

Results: *The median age was 64 years old (IQR 59.5-67). Baseline median International Index of Erectile Function-15 score was 50, which decreased to 18 at 1 month ($p < 0.0005$), returned to baseline by 3 months and thereafter. International Prostate Symptom Score median at baseline was 8, which worsened to 12 at 1 month ($p = 0.0088$), and subsequently improved to baseline thereafter. On the UCLA-Expanded Prostate Cancer Index Composite urinary function, there was a decrease in median score from 92.7 at baseline to 76.0 at 1 month ($p < 0.0001$), which improved to or above baseline afterwards. QoL remained similar to baseline at each follow up period as assessed by EQ-5D and the Functional Cancer Therapy-Prostate score.*

Conclusions: *In this initial cohort of PGA-HIFU men at our institution, patients demonstrated a slight, but transient, deterioration in urinary and erectile function at 1 month prior to normalization. All QoL metrics showed no impact upon 1 year of follow up post-treatment.*

Key Words: high intensity focal ultrasound, prostate cancer, quality of life

Accepted for publication December 2023

Address correspondence to Dr. Rafael Sanchez-Salas, McGill University Health Centre Glen Site, 1001 Decarie Boulevard, Montreal, QC H4A 3J1 Canada

Introduction

Partial gland ablation (PGA) using high intensity focal ultrasound (HIFU) therapy has emerged as a less invasive treatment option for patients with localized

prostate cancer. While active surveillance (AS) for low-risk prostate cancer is a non-invasive option, it is known that up to 30% of patients will ultimately require radical therapy.[1] Radical treatments for localized disease include radical prostatectomy and radiation therapy. These treatments are often associated with worsening urinary, bowel and erectile outcomes, and their respective impacts on quality of life (QoL).[2] PGA-HIFU appears as a suitable alternative to offer acceptable oncologic outcomes with minimal impact on functional outcomes.[3]

PGA was first applied in a demographic of patients with localized low-risk prostate cancer (T1-2N0M0, Gleason score 6) who were unsuitable candidates for radical treatment and for patients who elected against radical management.[4,5] The possible indications of PGA have since been extended to include low-risk and intermediate-risk prostate cancer.[6,7] Currently, the American Urological Association (AUA) recommends that low-risk prostate cancer be preferentially managed with AS and that focal therapies may be offered in select cases of intermediate-risk prostate cancer.[8] The current limitation for focal therapy is the lack of high-quality data pertaining to long term oncological outcomes.[8] PGA has the benefit of a favorable safety profile as compared to the alternative radical interventions. The most common side effects associated with PGA are voiding dysfunction, bladder outlet obstruction and erectile dysfunction; however, the frequency of these complications are unclear as the literature is composed of small cohort studies with limited follow up duration.[9-11]

We initiated a pilot study during the implementation period of PGA-HIFU at our center in order to assess QoL outcomes and cancer-specific outcomes associated with this therapy. The primary objective of this study was to analyze the patient–reported functional outcomes (erectile, urinary and QoL impact) of PGA-HIFU therapy on patients with localized, low-to-intermediate risk prostate cancer using standardized questionnaires up to 12 months after therapy. The secondary objective of this study was to assess presence of clinically-significant prostate cancer at systemic control biopsies and the rates of salvage therapy and metastasis.

Materials and methods

Institutional review board approval was obtained before recruiting patients prospectively (IRB #12030). Men with histologically proven localized prostate cancer, low to favorable-intermediate risk (PSA ≤ 10 ng/mL, Gleason score ≤ 7(3+4), T1c to T2b) were recruited for this study. The patients were offered all potential options, including AS, robotic-assisted radical prostatectomy (RARP) and external beam radiation therapy (EBRT) and were informed of the lack of long term data about the use of PGA-HIFU. A total of 25 consenting patients were recruited from September 2013 to July 2016. The patients had a prospective follow up as part of the study at 1, 3, 6 and 12 months after treatment.

Inclusion and exclusion criteria

Patients diagnosed with prostate cancer aged ≥ 50 years, with clinical stage T1c, T2a and T2b and PSA level ≤ 10 ng/mL were screened for inclusion. Patients had pre-biopsy multiparametric MRI (mpMRI). Prostate cancer diagnosis was based on TRUS biopsies, which included random (12) and, often, targeted biopsies (2-4 target lesions). Patients with a Gleason score ≤ 7 were considered for recruitment. The patients considered for this study were Gleason Grade Group (GGG) 1 or 2, with one exception made for a GGG3 patient due to very low burden of disease. All biopsies were read by an experienced genito-urinary pathologist. Patients also had flow studies prior to therapy and were included if they had a flow of > 12 mL/sec with a minimal void of 125 mL and a residual volume < 100 mL. Moreover, only patients with normal anal and rectal anatomy and with an American Society of Anesthesiologists physical status of 1 or 2 were recruited. All patients with metastasis to lymph nodes, bones or organs detected by MRI, CT scan and bone scan were excluded. Patients with tumors visible on MRI and identified to be located < 5 mm from the midline or < 6 mm from the apex were excluded. Patients with active urogenital infection, previous pelvic radiotherapy, bladder cancer, bladder neck/urethral stenosis or with a catheter located <1 cm from the target area were also excluded. Patients with rectal fistula or a history of inflammatory bowel disease were not enrolled.

Screening visit

At the screening visit, informed consent was obtained, and patients were selected based on the inclusion and exclusion criteria enumerated above. Medical history, physical exam with digital rectal examination were recorded. A flow study measuring post-void residual volume (PVR) was obtained. All patients had a mpMRI obtained at least after 2 months from any previous biopsy. If a previous biopsy had been obtained at another center, the biopsy was either re-read at our center by an experienced genito-urinary pathologist or repeated.

PGA-HIFU treatment

The morning of treatment, the patients received a sodium-phosphate enema. To avoid movement, the procedure was performed under general anesthesia. TED stockings were used for peri-procedural thromboprophylaxis. Patients received 500 mg of IV Ciprofloxacin as antibiotic prophylaxis and had the insertion of a urethral catheter prior to the treatment. Ultrasound images were acquired with the HIFU probe. The probes were covered with a latex protector and primed with degassed water, and then lubricated with degassed lubricant gel. Gel was also placed in the rectum, and the probe was introduced into the rectum. Prostate views were acquired and if deemed satisfactory, the operator proceeded with the treatment plan in the ipsilateral side of the gland where the significant lesion(s) had been identified by mpMRI and biopsy. The first 10 cases were performed using Ablatherm (EDAP TMS, Vaulx-en-Velin, France) and the following 15 cases were performed using the FocalOne device (EDAP TMS, Vaulx-en-Velin, France).

Outcomes

To assess functional outcomes, at the initial visit and at 1, 3, 6 and 12 months after treatment, patients completed self-administered validated questionnaires including:

- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function – 15 (IIEF-15)
- Expanded Prostate Cancer Index Composite (EPIC) urinary function
- Expanded Prostate Cancer Index Composite (EPIC) bowel function
- EQ-5D and Visual analogue scale (VAS) of EQ-5D
- Functional Assessment Cancer Therapy-Prostate (FACT-P)

Patients were also scheduled to undergo uroflow/PVR and PSA measurement at each follow up visit.

To assess oncological outcomes, enrolled patients underwent a systematic control mpMRI at 6 months post-treatment and TRUS mpMRI-fusion biopsies (Koelis SAS, Grenoble, France and Princeton, NJ, USA) with bilateral random biopsies and targeted biopsies of treated zone. Data concerning oncological outcomes was collected retrospectively.

Statistical analysis

Data was collected prospectively and analyzed retrospectively. Median values and interquartile ranges were used to report quantitative variables. Percentages and absolute numbers were for categorical variables. Data was analyzed using Prism 9.0. To assess for differences at follow up visits (1, 3, 6 and 12 months) with the baseline visit, we used the Wilcoxon rank test for questionnaire outcomes. For comparison of continuous variables, Student t-test was used. For comparison of binary outcomes, Chi-square or Fisher's test were used. Statistical significance was set at $p < 0.05$.

Results

Demographic data

A total of 25 consecutive and consenting patients were prospectively enrolled in this study. Baseline characteristics are presented in Table 1. Median age was 64 years old (IQR 60-67) and median PSA was 6.3 ng/mL (IQR 4.8-9.3). The initial pre-treatment biopsies demonstrated 18 (72%) patients with GGG 2 disease, 5 (20%) with GGG1 disease and 2 (8%) with GGG3 disease. Pre-treatment biopsy was repeated in 8 (32%) of patients and, at the last pre-treatment biopsy the GGG distribution was as follows: 20 patients (80%) GGG2, 4 patients (16%) GGG1 and 1 patient (4%) GGG3. The GGG3 patient only had 1 positive core out of 15, with only 5% of the core involved, and thus was still included.

Pre-treatment median mpMRI volume was 36.0 mL (IQR 24.5-59.8), intra-operative volume was measured at 39.4 mL (IQR2 4.8-48.6) and post-treatment median mpMRI volume was estimated at 28.5 mL (IQR 24.5-43.7). The median volume treated was 11.4 mL (IQR 9.5-14.2). On pre-treatment mpMRI, 13 patients (52%) had 1 target lesion, 8 (32%) had 2 target lesions and 1 patient had 3 target lesions. Three pre-treatment mpMRI studies were excluded from current analysis: two of these were performed at outside institutions with different protocols and non-standardized reporting, and 1 did not identify an initial target lesion (lesion subsequently identified after being re-read at our institution by an experienced radiologist). A total of 20 patients (80%) had PIRADS 4 or 5 lesions identified on the pre-treatment mpMRI.

A median of 14 biopsies were sampled, of which, 2 were positive pre-treatment. The median anesthesia time was 140 min (IQR 125-170) and the median procedure time was 64 min (IQR 51.5-73.0). Median follow up was 72 months following treatment, however, data was only collected prospectively for the first 12 months after treatment.

Functional outcomes

The primary outcomes examined patient-reported erectile and urinary function and QoL outcomes at baseline, 1, 3, 6 and 12 months post-treatment. By 12 months, participation significantly decreased to 15-16 participants responding to the questionnaires at the final follow up visit.

TABLE 1. **Basic demographic features**

Age, median (IQR)	64 (60-67)
BMI, median (IQR)	27.9 (25.5-31.0)
Weight, median (IQR), self-reported, kg	86 (73-96)
PSA, median (IQR), ng/mL	6.3 (4.8-9.3)
Pre-treatment biopsy features	
Number of cores, median	14
Number of positive cores, median	2
Location of positive cores	
Left	9
Right	13
Bilateral	3
Maximum % of disease in positive core on last biopsy, median (IQR)	30% (12.5-52.5%)
PSA density, median (IQR), ng/ml^2	0.18 (0.11-0.26)
GGG1 on initial biopsy, n (%)	5 (20%)
GGG2 on initial biopsy, n (%)	18 (72%)
GGG3 on initial biopsy, n (%)	2 (8%)
GGG1 on last biopsy, n (%)	4 (16%)
GGG2 on last biopsy, n (%)	20 (80%)
GGG3 on last biopsy, n (%)	1 (4%)
Patients who underwent a 2nd biopsy, n (%)	8 (32%)
Prostate volume	
Pre-treatment mpMRI volume, median (IQR), mL	36.0 (24.5-59.8)
Intra-operative volume, median (IQR), mL	39.4 (24.8-48.6)
Post-treatment mpMRI volume, median (IQR), mL	28.5 (24.5-43.7)
Pre-operative mpMRI	
Number of target lesions	
1	13
2	8
3	1
Highest PI-RADS score	
PI-RADS 3	2
PI-RADS 4	9
PI-RADS 5	11
Treatment characteristics	
Procedure time, median (IQR), min	64 (51.5-73.0)
Anesthesia time, median (IQR), min	140 (125-170)
Volume treated, median (IQR), mL	11.4 (9.5-14.2)
% Volume treated from total	33.3% (21.1-40.1%)

IQR = interquartile range; BMI = body mass index
PSA = prostate-specific antigen
GGG = Gleason grade group
mpMRI = multiparametric magnetic resonance imaging
PI-RADS = prostate imaging reporting and data system

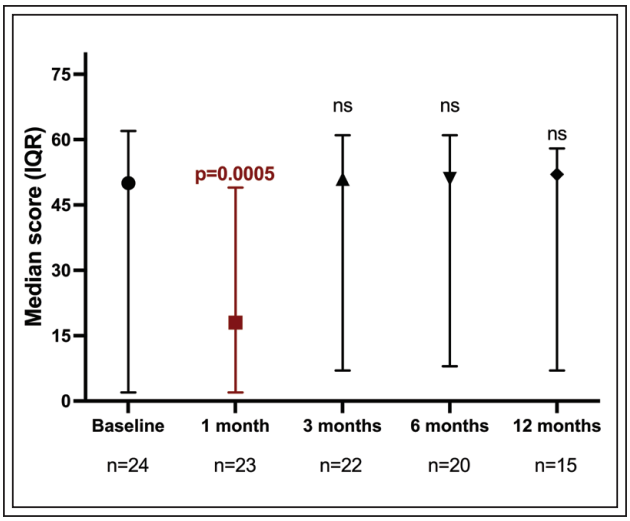

Figure 1. Erectile function measured using the International Index of Erectile Function – 15 questionnaire.
IQR = interquartile range; IIEF = International Index of Erectile Function; ns = not significant

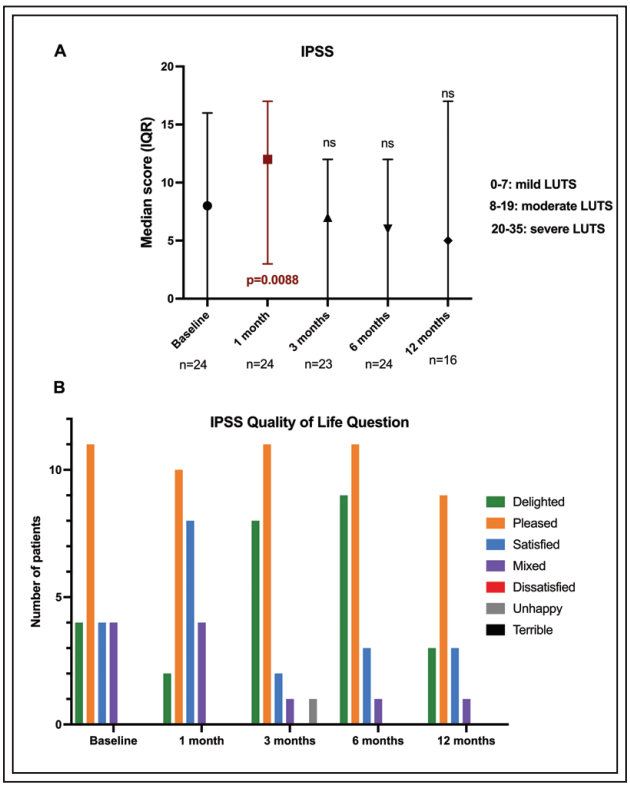

Figure 2. Evaluation of lower urinary tract symptoms using the International Prostate Symptom Score.
IPSS = International Prostate Symptom Score
IQR = interquartile range; ns = not significant

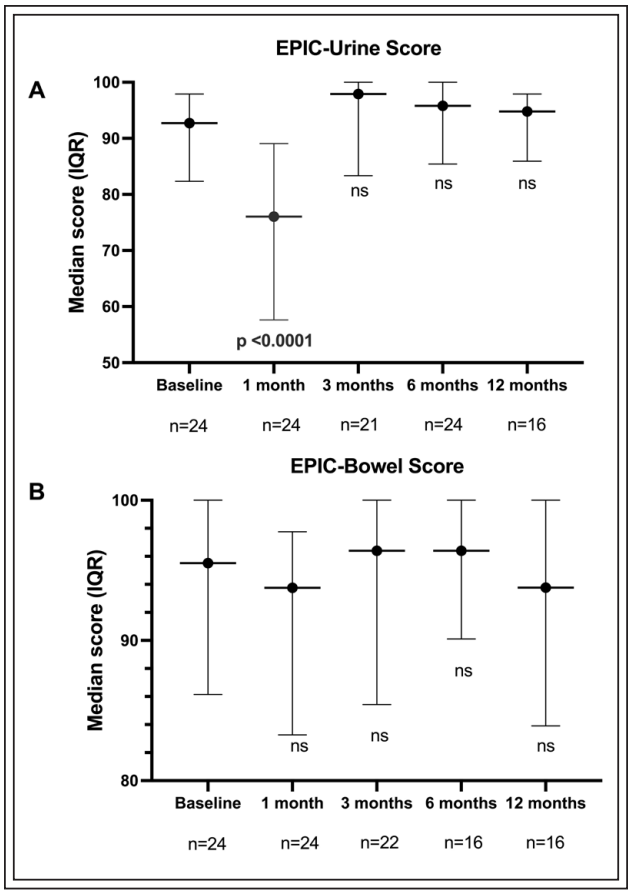

Figure 3. Evaluation of urinary and bowel function using the Expanded Prostate Cancer Index.
EPIC = Expanded Prostate Cancer Index Composite
IQR = interquartile range; ns = not significant

The baseline erectile function as assessed by the IIEF-15 questionnaire indicated a median score of 50 (IQR 18-62), Figure 1. Erectile function significantly decreased to 18 (IQR 11-49) points at 1-month following treatment ($p < 0.001$). At 3, 6 and 12 months after PGA-HIFU, the median IIEF-15 scores returned to similar baseline values of 51 (IQR 18-61), 51 (IQR 21-61) and 52 (IQR 43-58), respectively.

Lower urinary tract symptoms (LUTS) were evaluated using the IPSS, Figure 2a, with a baseline score of 8 (IQR 3-16) points, corresponding to moderate severity LUTS. At 1-month post-treatment, the median score increased to 12 (IQR 5-17) points ($p < 0.05$) and remained within the moderate severity LUTS group. Interestingly, at 3, 6 and 12 months, the median IPSS scores decreased compared to the baseline score (7 [IQR 5-12], 6 [IQR 2-12], and 5 [3-16], respectively), which corresponded to a mild LUTS severity category; however, this difference was

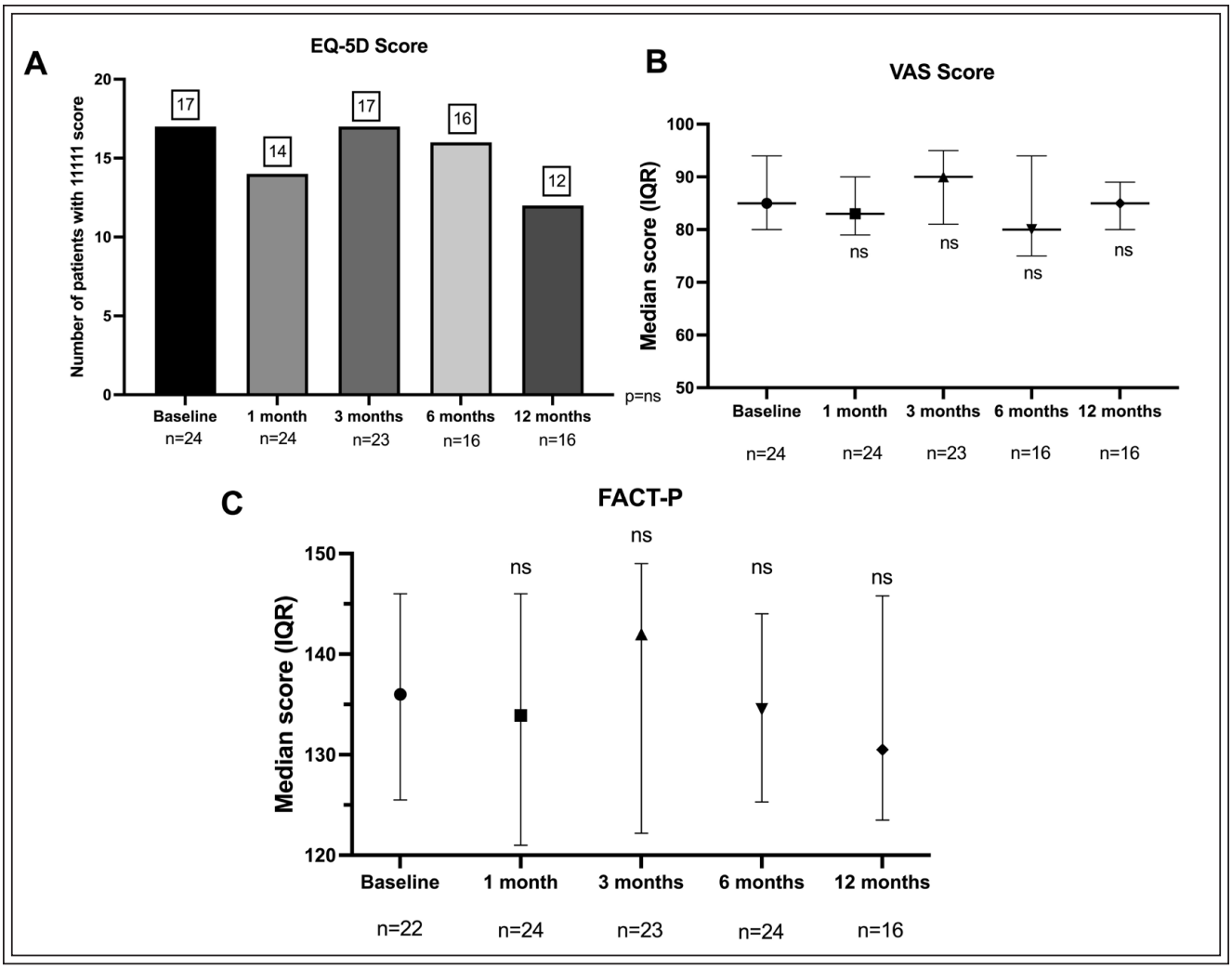

Figure 4. Evaluation of patient quality of life using validated scales.
EQ-5D = EuroQol- 5 Dimension; FACT-P = Functional Assessment Cancer Therapy-Prostate; IQR = interquartile range; ns = not significant; VAS = Visual analogue scale

not significant compared to baseline. The IPSS QoL question did not identify any significant differences between the patients who identified as "delighted" or "satisfied" with their urinary symptoms, Figure 2b. Urinary function was also assessed by the EPIC urinary function domain, Figure 3a. At baseline, the median score was 92.7 (IQR 82.3-97.9), which significantly decreased to a median score of 76.1 (IQR 57.6-89.0) at 1-month post PGA-HIFU ($p < 0.0001$). Similar to the IPSS score, patients reported better-than-baseline median scores at 3, 6, and 12 months post-treatment, however this finding was not statistically significant. There were no differences between baseline and any follow up period on the EPIC bowel function domain, Figure 3b.

The EQ-5D, VAS component of the EQ-5D and FACT-P scores were used for assessment of QoL, Figure 4. There were no significant differences in median scores at the follow up visits compared to baseline for both VAS and FACT-P. For the EQ-5D, we reported the proportion of patients who indicated an ideal score of 1/1/1/1/1. At baseline, 17/25 (68%) of patients reported a score of 1/1/1/1/1. At 3 and 6 months, there were 17 (68%) and 16 (64%) patients reporting this score. At 12 months, 75% of patients continued to report a 1/1/1/1/1 score.

Uroflowmetry was performed at each follow up visit in 8-13 of patients enrolled (varied due to patient cooperation and nursing resources at each visit). The maximum urine flow (Qmax) at baseline was 25 mL/sec,

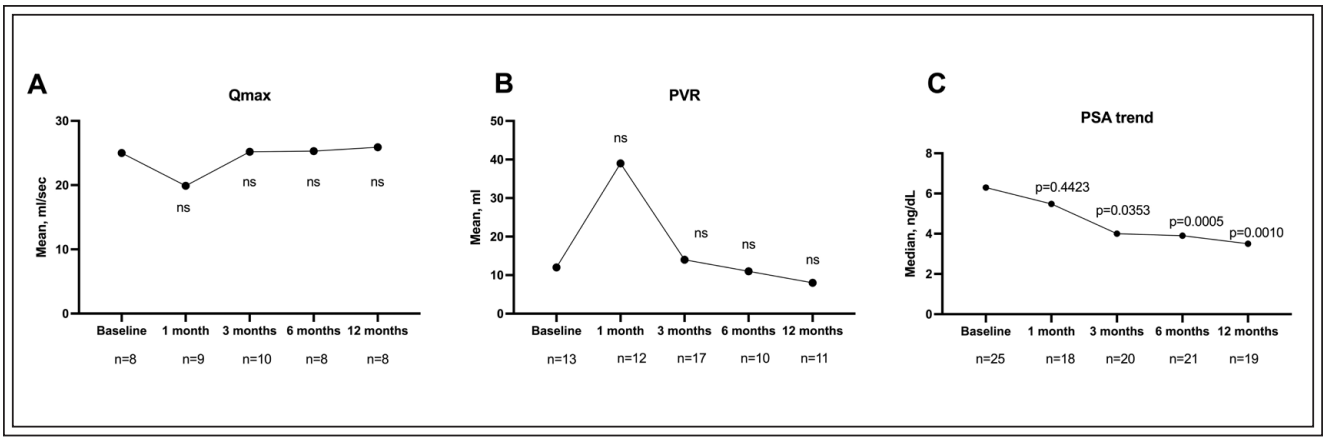

Figure 5. Evaluation of patient functional outcomes.
PVR = post-void residual volume; PSA = prostate specific antigen; Qmax = maximum urine flow rate; IQR = interquartile range; ns = not significant

with a trending decrease to 19.9 mL/sec at 1 month (p = 0.0703) and a return to baseline levels at 3 months and thereafter, Figure 5a. Similarly, PVR volumes trended towards an increased mean volume of 39 mL at 1 month from a baseline of 12 mL, however this was not statistically significant (p = 0.0742) and PVR values further returned to baseline at the 3-month visit, Figure 5b.

Cancer specific outcomes following HIFU treatment are outlined in Table 2. Twelve of 25 (48%) patients had persistence of clinically-significant prostate cancer after systemic control biopsy, with 10 (40%) recurrences being in-field. A total of 8 (32%) patients did not have to undergo any other form of secondary treatment for prostate cancer at a median follow up of 72 months. A total of 8 (32%) patients underwent a second PGA-HIFU treatment in the same field; 4 of the patients who underwent a second in-field PGA-HIFU had another subsequent failure and ultimately underwent salvage therapy. One patient underwent PGA-HIFU for clinically-significant prostate cancer recurrence out-of-field. Thirteen (52%) patients received eventually a radical salvage therapy: 9 received EBRT +/- androgen deprivation therapy (ADT); 4 underwent RARP. Two patients developed metastatic disease. One patient developed metastatic disease at 57 months after PGA-HIFU, after having received salvage EBRT. The other patient developed metastatic disease at 22 months after PGA-HIFU and had local EBRT in the context of oligometastatic disease. Both patients had initially GGG2 disease on their biopsy. There were no deaths at a median follow up of 72 months.

TABLE 2. **Overall patient outcomes post-PGA-HIFU treatment**

Cs-PCa outcome	**Number of patients (%)**
Residual ≥ GG2 at control biopsy	12/25 (48%)
Residual ≥ GG2 at control biopsy in-field	10/25 (40%)
Underwent EBRT +/- ADT	9/25 (36%)
Underwent RARP	4/25 (16%)
Underwent 2nd PGA-HIFU in-field	8/25 (32%)
Underwent 2nd PGA-HIFU in-field and another secondary salvage treatment	4/25 (16%)

PGA-HIFU = partial gland ablation-high intensity focal ultrasound; Cs-PCa = clinically-significant prostate cancer; GG = Gleason grade; EBRT = external beam radiation therapy; ADT = androgen deprivation therapy; RARP = robotic-assisted radical prostatectomy

Discussion

This study presents patient-reported functional outcomes (erectile, urinary and QoL) of an initial cohort of patients who underwent PGA-HIFU at a single center. Despite the small sample size, we observed a minor, transient, but significant, deterioration of erectile function (as per IIEF-15) and urinary function at 1 month (as per IPSS and EPIC – urinary function domain scores). Erectile and urinary function scores both returned to baseline at the 3-month visit and thereafter. Men did not report an adverse impact on QoL (as per FACT-P, VAS and EQ-5D) despite the transient erectile and urinary functional deterioration.

The literature surrounding functional outcomes associated with PGA-HIFU is relatively sparse, with few prospective studies reporting these functional outcomes only as secondary endpoints.

In a large prospective series of 189 men undergoing HIFU for localized prostate cancer, there was no change in IPSS scores at 12 months.[12] In this cohort, Dellabella et al reported a slight impact on IIEF-15 at 12 months, with improvements at 24-26 months.[12] Of note, this cohort included men receiving focal ablation, hemi-ablation and whole-gland ablation cases. A prospective study by Ahmed et al included 41 patients receiving focal therapy for localized prostate cancer and observed a transient deterioration of IIEF-15, IPSS and EPIC-urine scores at 1 month, with a gradual return to baseline by 12 months.[10] These results are consistent with the trend of deteriorated erectile and urinary function at 1 month and subsequent normalization that we report. A pooled analysis of 3 prospective studies demonstrated significant deterioration of IIEF-15 scores at 1 and 3 months.[11] A large retrospective series composed of 100 men undergoing hemi-ablation in the United States showed no difference in IIEF-5 and IPSS scores when comparing baseline scores to best score within 2 years; the completion rate of functional questionnaires in this series was 47%.[13] Although these were the first set of patients undergoing PGA-HIFU at our center, our results are comparable with the available literature.

It is important to interpret the current study with the context that this represents our initial experience with PGA-HIFU at our institution. We previously reported that in a separate cohort of men that underwent PGA-HIFU following this initial set of patients in the current study, systematic control biopsy identified the persistence of clinically significant cancer in 31% of patients.[14] In the current cohort, the clinically-significant prostate cancer rate at systemic biopsy was 12/25 (48%). Therefore, the results of this study do not demonstrate an improvement in both functional and oncological outcomes that would otherwise be expected to occur with an operator-dependent learning curve. Eight (32%) patients with clinically-significant prostate cancer underwent a re-HIFU treatment within the same field. However, re-HIFU achieved oncologic resolution (as determined by subsequent biopsy) for half of the patients, with the remaining half undergoing another salvage treatment. Finally, 48% of the patients eventually received another salvage therapy (EBRT or RARP) due to either in-field or out-of-field recurrence. The PGA-HIFU performed at our center does not meet the criteria for a hemi-ablation, as the anterior zone is not included, with a median treated prostate volume of 33.3% (IQR 21.1-40.1%), Table 1.[14] While the functional outcomes of this initial PGA-HIFU cohort are promising, the oncological outcomes are suboptimal.

In this study we prospectively collected QoL information on the first 25 patients undergoing PGA-HIFU. We used multiple evidenced-based questionnaires to measure patient-reported outcomes over the first 12 months after treatment. We identified a deterioration in urinary and erectile function at 1 month, with subsequent normalization, and no effect on overall QoL at any moment. There are limitations to this study. Firstly, the small sample size of this cohort impacts our statistical analyses, and thus, our results should be interpreted within this context. Furthermore, there was attrition of the cohort at the 12-month mark as only 15-16 individuals continued to participate in completing the questionnaires. Secondly, all patients received an alpha-blocker for 1 month following their treatment, which may have partially masked the full extent of any short term functional deficits in urinary function. Thirdly, we did not prospectively collect data regarding adverse events secondary to the PGA. In addition, the QoL data was not collected in patients receiving a second PGA-HIFU treatment. Fourthly, the patients in this cohort were treated with Ablatherm for the first 10 cases and with FocalOne for the last cases, making the assessment of oncological outcomes difficult in this study. Lastly, this study reflected the early experience with HIFU within a single center. Larger, prospective cohorts with long term follow up periods are still needed to clarify the potential role PGA-HIFU can offer in localized prostate cancer.

Conclusion

Our initial cohort of 25 patients who underwent PGA-HIFU at our center presented a minor and transient, but significant, deterioration in erectile and

urinary function at 1 month after PGA-HIFU, which subsequently returned to baseline at the 3-month visit and remained stable up to 12 months. Despite the transient erectile and urinary function deterioration, men did not report worsening of QoL at any time point following PGA-HIFU. PGA-HIFU can be an attractive intermediate management strategy to maximize functional parameters but requires thorough monitoring and consideration of radical options in the setting of recurrence.

Disclosures

Dr. Sanchez-Salas reports having participated in clinical trials with EDAP-TMS. □

References

1. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010;28(1):126-131.
2. Resnick MJ, Koyama T, Fan KH et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013;368(5):436-445.
3. Valerio M, Ahmed HU, Emberton M et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. *Eur Urol* 2014;66(4):732-751.
4. Eggener SE, Scardino PT, Carroll PR et al. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. *J Urol* 2007;178(6):2260-2267.
5. El Fegoun AB, Barret E, Prapotnich D et al. Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. *Int Braz J Urol* 2011;37(2):213-219;discussion 20-22.
6. van den Bos W, Muller BG, Ahmed H et al. Focal therapy in prostate cancer: international multidisciplinary consensus on trial design. *Eur Urol* 2014;65(6):1078-1083.
7. Orczyk C, Emberton M, Ahmed HU. What tumours should we treat with focal therapy based on risk category, grade, size and location? *Curr Opin Urol* 2015;25(3):212-219.
8. Eastham JA, Auffenberg GB, Barocas DA et al. Clinically localized prostate cancer: AUA/ASTRO guideline, part I: introduction, risk assessment, staging, and risk-based management. *J Urol* 2022;208(1):10-18.
9. Ziglioli F, Baciarello M, Maspero G et al. Oncologic outcome, side effects and comorbidity of high-intensity focused ultrasound (HIFU) for localized prostate cancer. A review. *Ann Med Surg (Lond)* 2020;56:110-115.
10. Ahmed HU, Hindley RG, Dickinson L et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol* 2012;13(6):622-632.
11. Yap T, Ahmed HU, Hindley RG et al. The effects of focal therapy for prostate cancer on sexual function: a combined analysis of three prospective trials. *Eur Urol* 2016;69(5):844-851.
12. Dellabella M, Branchi A, Di Rosa M et al. Oncological and functional outcome after partial prostate HIFU ablation with Focal-One((R)): a prospective single-center study. *Prostate Cancer Prostatic Dis* 2021;24(4):1189-1197.
13. Abreu AL, Peretsman S, Iwata A et al. High intensity focused ultrasound hemigland ablation for prostate cancer: initial outcomes of a United States series. *J Urol* 2020;204(4):741-747.
14. Rompré-Brodeur A, Marcq G, Tholomier C et al. Role of systematic control biopsies following partial gland ablation with high-intensity focused ultrasound for clinically significant prostate cancer. *J Urol* 2021;206(5):1177-1183.