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Evaluation of functional outcomes following a second focal-HIFU in men with primary localised, non-metastatic prostate cancer; Results from the High Intensity Focused Ultrasound Evaluation and Assessment of Treatment (HEAT) Registry

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Abstract

Objectives

To assess change in functional outcomes after second focal-HIFU compared to one focal-HIFU treatment.

Patients and Methods

In this multi-centre study (2005-2016), 821 men underwent focal-HIFU for localised non-metastatic prostate cancer. PROMS on IPSS, pad usage and erectile function (EF-score) were prospectively collected for up to 3 years. Inclusion criteria were men who had completed at least one follow-up questionnaire.

The primary outcome was comparison of change in functional outcomes between baseline and follow-up after one focal-HIFU or second focal-HIFU using IPSS, EPIC and IIEF questionnaires.

Results

Of 821 men, 654 had one focal-HIFU and 167 had a second focal-HIFU. 355 (54.3%) men undergoing one focal-HIFU and 65 (38.9%) having second focal-HIFU returned follow-up questionnaires, respectively. Mean age and PSA were 66.4 and 65.6 years, and 7.9 and 8.4 ng/ml respectively. After one focal-HIFU, mean change in IPSS was -0.03 (p=0.02) and IIEF (EF-score) -0.4 (p=0.02) at 1-2 years with no subsequent decline. Absolute rates of erectile dysfunction increased from 9.9% to 20.8% (p=0.08), leak-free continence decreased from 77.9% to 72.8% (p=0.06) and pad-free continence from 98.6% to 94.8% (p= 0.07) at 1-2 years, respectively.

IPSS prior to second focal-HIFU compared to baseline IPSS prior to first focal-HIFU was lower by -1.3 (p=0.02), but mean IPSS change was +1.4 at 1-2 years (p=0.03) and +1.2 at 2-3 years (p=0.003) after second focal-HIFU. Mean change in EF-score after second focal-HIFU was -

0.2 at 1-2 years(p=0.60) and -0.5 at 2-3 years(p=0.10) with 17.8% and 6.2% new erectile dysfunction. New pad use was 1.8% at 1-2 years and 2.6% at 2-3 years.

Conclusion

A second focal-HIFU procedure causes minor detrimental effects in urinary and erectile function. Data can be used to counsel patients with non-metastatic prostate cancer prior to considering HIFU therapy.

Key words

Functional outcomes, HIFU, localised prostate cancer

Introduction

Primary focal therapy to treat localised prostate cancer has shown favourable short to medium term oncological and functional outcomes, particularly with regard to urinary and sexual function[1]. Recently published data from the multicentre High Intensity Focused Ultrasound Evaluation and Assessment of Treatment (HEAT) registry on 625 men with largely intermediate and high-risk cancer has shown a 5-year failure free survival of 88% with pad-free incontinence of 98%[1]. 5-year cancer specific survival was 100% supporting the oncological safety of focal therapy as a treatment modality for localised prostate cancer. In this cohort approximately one in five men received a second session of focal-HIFU to treat residual and/or recurrent disease.

We have previously published functional outcomes from a single session of focal-HIFU and focal-cryotherapy and also on functional outcomes following second whole-gland HIFU treatment demonstrating minor detrimental effects[2,3]. However, there is a paucity of data on the effects of a second focal-HIFU on functional outcomes[4]. We present an analysis based on data from the HEAT registry assessing change in urinary function and erectile function parameters in men who underwent a second focal-HIFU.

Patients and Methods

Between November 2005 and November 2016, 821 men underwent HIFU for localised non-metastatic prostate cancer at 6 centres and data collected prospectively within the High Intensity Focused Ultrasound Evaluation and Assessment of Treatment (HEAT) Registry. Eligibility criteria were Gleason 7 or high-volume Gleason 6 disease with maximum cancer core length > 4mm, stage T1c-radiological T3aN0M0 and PSA ≤20ng/ml however some men with disease characteristics outside of these parameters chose to undergo focal-HIFU[5]. All cases were reviewed in a multi-disciplinary meeting and also offered alternative radical treatment options. Androgen deprivation therapy was used in a subset of patients as method to reduce gland volume prior to treatment or used in patients who had deferred treatment.

As reported previously[1], evaluation for focal suitability involved mpMRI to localise lesions and targeted biopsies of Likert score 3-5 lesions combined with systematic or transperineal 5-10mm mapping biopsy. Radioisotope bone scanning and/or cross-sectional CT was used in intermediate or high-risk cases to rule-out distant metastases.

Surgeons were trained as previously outlined via online modules, observation, proctoring by a clinician and mentorship by an expert clinical applications specialist[1]. Hemiablation, wide local ablation, hockey stick, subtotal, focal (quadrant) and lesion control treatment plans were included. The only exclusion criteria was previous use of whole gland therapy. A second focal-HIFU was permitted in our protocol as part of the focal therapy intervention for residual or recurrent disease detected during follow-up. The energy protocol was similar for both primary and redo treatment with treatment in 3 overlapping 3 or 4 cm blocks from anterior to posterior. During treatment the energy level is adapted with step wise ramping based on visual feedback (Ushida changes, near field heating and tissue change monitor readings). The margin was generally 5-10mm and did not differ from primary to second treatment.

As per follow-up protocol, 3-6 monthly PSA tests and 1-2 yearly mpMRI were performed. Two increases from the PSA nadir were investigated by biopsy or mpMRI with subsequent biopsy if suspicious lesions were identified. A second focal-HIFU was offered for clinically significant, localised cancer on in-field or out-of-field biopsy or when mpMRI showed Likert

5 lesions in-field associated with rising PSA. Radical prostatectomy or radical radiotherapy were also offered.

PROMS

Patients were asked to complete pre- and post- operative postal PROMS questionnaires (International Prostate Symptom Score (IPSS) and Expanded Prostate Cancer Index Composite (EPIC)) and inclusion criteria for the presented analysis were men who had undergone focal-HIFU for localised non-metastatic prostate cancer and had completed at least one questionnaire after one focal-HIFU and one questionnaire before and after second focal-HIFU. These were categorised into 1-2 and 2-3 year post-treatment time points within the database. Patients were grouped into two cohorts for analysis. First, men having one focal-HIFU and second, men undergoing a second focal-HIFU. Existing institutional ethics committee exemption was granted by the Institutional Joint Research Office. Confidentiality of patients was maintained through allocation of non-identifiable, pseudo-anonymised registry numbers.

Primary outcome

Primary outcome was mean change in functional outcomes in men having one focal-HIFU and those undergoing a second focal-HIFU. This was evaluated using IPSS, pad-free and leak-free status extracted from the EPIC urinary continence domain and a 6 point scale (0-5) based on the response to question 2 from the International Index of Erectile Function (IIEF-5) questionnaire to gauge erectile function (EF) - "When you had erections with sexual stimulation, how often were your erections hard enough for penetration?" [6-8]. This was scored 0-5 (0 - no sexual activity, 1 - almost never/never, 2 - a few times (much less than half the time), 3 - sometimes (about half the time), 4 - most times (much more than half the time) and 5 - almost always/always. Erectile function was analysed by two methods; first, based on change in mean score at specified time points and second, as a binary variable with scores 0-1 constituting erectile dysfunction and scores 2-5 constituting adequate potency. Due to the multicentre nature of the database and numerous outcome measures being collected, no other parameters from the EPIC or IIEF5 questionnaire were recorded.

Variables and Statistical analysis

Data was collected on age, PSA, prostate volume, Gleason grade, combined MRI T-stage, maximum cancer core length (MCCL), use of pre-HIFU hormonal therapy (Bicalutamide 50mg or 150mg) and the extent of ablation (treatment plan). IPSS, pad-free/leak-free status, and erectile function data was collected at baseline, 1-2 years and 2-3 years. A decrease in IPSS score was associated with improved function, decrease in EF and EPIC scores were indicative of worse function. Descriptive statistics were used to describe demographic data and functional outcomes. Mann-Whitney and Fisher's-exact tests were used to compare baseline characteristics between continuous and categorical variables between the two cohorts. Independent T-test, Mann-Whitney and Fisher's tests were used to valuate baseline characteristics. Paired T-tests and McNemar's tests were used in evaluation of functional outcomes at different stages of follow up, the former for IPSS and EF scores, the latter for pad-free, leak-free and erectile dysfunction status. All statistical analyses were undertaken using SPSS v.25 (IBM Corp., Armonk, NY, USA) and R version 3.5.3. Statistical significance was pragmatically set at p-values <0.05 due to multiple testing.

Results

Patient Characteristics

Between November 2005 and November 2016, 821 men underwent focal-HIFU as a primary treatment for non-metastatic prostate cancer: 654 men had one focal-HIFU and 167 had a second focal-HIFU. 355 (54.3%) and 65 (38.9%) men returned follow-up questionnaires respectively and were included in this analysis (Figure 1). Median follow up in the group having one focal-HIFU was 64.9months (IQR 41.9-78.9) and 72.5 months (IQR 65.8-91.0) in the second focal-HIFU group. Groups were comparable at baseline other than the second focal-HIFU cohort having a higher prevalence of T2 disease (74.4% vs 79.9%) (**Error! Reference source not found.**). Both cohorts reported similar baseline functional status prior to any HIFU treatment.

At baseline, IPSS questionnaire data was available in 254 (71.5%) having one focal-HIFU. 48 (73.8%) second focal-HIFU patients provided baseline (before first-focal HIFU treatment) IPSS scores. Continence outcomes were available in 294 (82.8%) of one focal-HIFU group and 61 (93.8%) of second focal-HIFU group with erectile function outcomes available in 161 (45.4%) and 34 (52.3%), respectively.

Functional Outcomes

One focal-HIFU

There was significant improvement in mean IPSS reported at baseline versus 1-2 years post-treatment (-0.03, P=0.02) and a decline in EF score was seen of -0.4 (p=0.02) and -0.4 (p=0.02) respectively. From 1-2 years to 2-3 years after one focal-HIFU no further changes occurred in these domains (Table 2). 77.9% were leak-free continent at baseline, 72.8% at 1-2 years (p=0.06) and 73.5% at 2-3 years (p=0.5) (Figure 2). Pad-free rate at baseline was 98.6%, which fell to 94.8% (p=0.07) at 1-2 years and 95.3% (p=0.2) at 2-3 years (Figure 2). At baseline, 9.9% reported erectile dysfunction compared to 20.8% at 1-2 years and 18.3% at 2-3 years (Figure 2) (baseline vs. 1-2 years [p=0.08] and 1-2 years vs 2-3 years [p=0.7]).

Second Focal-HIFU

Men undergoing a second focal-HIFU demonstrated a significant deterioration in mean IPSS score between baseline and after their first focal-HIFU of -1.3 (p=0.02, **Error! Reference source not found.**). Change in mean EF-score was -0.6 (p=0.2) (**Error! Reference source not found.**) with an associated 6.9% rise in reported erectile dysfunction (p=0.43)(Figure 3). There were no changes in rates of urinary leakage (+0.8%, p=0.8) (Figure 4).

Subsequently, a change in IPSS was observed at 1-2 years post-redo treatment of +1.4 (p=0.03) and at 2-3 years of +1.2 (p=0.003) (**Error! Reference source not found.**). Overall IPSS did not change from baseline. Erectile function deteriorated between baseline and final follow-up in this cohort. Mean change in EF-score was -0.2, 1-2 years after second focal-HIFU (p=0.6) and -0.5 after 2-3 years (p=0.1) (**Error! Reference source not found.**). Rates of erectile dysfunction were 30.6% and 19.0% at 1-2 years and 2-3 years follow-up, respectively, compared to 12.8% before second focal-HIFU (Figure 3). 72.9%, 71.4% and 78.9% were leak-free continent before second focal-HIFU, and at 1-2 years and 2-3 years after, respectively (Figure 4).

100%, 98.2% and 97.4% were pad-free continent before second focal-HIFU, and at 1-2 years and 2-3 years after, respectively (Figure 5). The changes in the proportion of men with erectile dysfunction, pad-free incontinence and leak-free incontinence were not statistically significant (p>0.05).

Discussion

This study provides the first analysis of functional outcomes following a second focal-HIFU treatment for primary, non-metastatic prostate cancer. In summary, men who underwent one focal-HIFU had improvement in urinary function with a mean IPSS score decrease of -0.03 after 1-2 years. EF scores deteriorated with a clinically relevant change. This is also highlighted by the fact that in our primary cohort, at baseline 9.9% reported erectile dysfunction, compared to 20.8% and 18.3% post-operatively. Men who underwent second-HIFU showed an initial improvement in their IPSS scores of 1.6 points after first focal-HIFU treatment. Subsequently genitourinary function both declined after a second focal-HIFU treatment with a 1.2 to 1.4 point increase in IPSS and 13.1% to 24.7% reporting new ED since baseline. Rates of new pad-usage were 1.8% to 2.6% after second focal-HIFU.

Overall this data demonstrates a deterioration in urinary and sexual function after a second-HIFU treatment. The effect on urinary function is likely to be related to tissue necrosis or thermal injury to the urethra and striated sphincter at the level of the prostatic apex[9]. With this in mind, appropriate margins can mitigate against adverse outcomes[9]. Potential causes for erectile dysfunction following focal therapy include thermal effects on the neurovascular bundles[10-12].

Systematic reviews assessing return to baseline erectile function after focal or whole gland ablation have previously shown much heterogeneity in outcome measures[13]. The literature suggests that in patients receiving HIFU, return to baseline erectile function occurred by six-months follow-up[13]. In many studies, reported sexual outcomes can be misleading, for example focussing on proportion of men with potency postoperatively rather than evaluating those who experienced a decline in function, the extent of their decline and any association with quality of life outcomes demonstrates a need for standardisation of reporting outcomes. Researchers have highlighted the poor quality, heterogenous findings with short follow up and our study addresses this by utilising validated questionnaires with longer term follow-up. Our results show that a second focal-HIFU for localised prostate cancer treatment has very real effects on erectile function in approximately one in ten men undergoing primary HIFU at 2-3 year follow-up after primary HIFU (Figure 2) and 6% of those undergoing redo-HIFU (Figure 3). It is worth noting that after both primary and redo-

HIFU, rates of erectile dysfunction at 1-2 years improve in the subsequent year of follow-up indicating that early effects of HIFU on potency are transient in a proportion of men. This is important in consenting patients for treatment and in addressing expectations for post-treatment functional outcomes. Furthermore this should be contextualised in reference to alternative treatments e.g. radical prostatectomy or radiotherapy which confer significant side-effects of incontinence in 5-10% and erectile dysfunction in up to 50% of patients [14-17].

When comparing our results to reported studies in the literature, the only comparable paper is that of Berge et al. This analysis, from our own HEAT registry of whole-gland HIFU cases, in patients undergoing redo HIFU suggested equivalence between the rate of adverse events after first and redo treatments and reported worse urinary function in terms of pad and leak status both after initial HIFU treatment and decline in leak-free status after redo whole-gland HIFU- differences not observed in this focal outcomes study.

Evaluation of quality of life outcomes after focal HIFU have previously identified no overall change at 24 months[18]. A phase I/II focal hemiablation study for primary, localised prostate cancer found similar results to our data with no significant difference between baseline, three and six month follow up for erectile function with 90% pad-free and leak-free status at six months[19]. Our findings reflect these outcomes and contribute further to existing literature in demonstrating no change in these domains following a second focal-HIFU.

Strengths associated with the present study include the large, prospective, multi-centre design with over 5 years median follow up data available and prospective data collection within a registry, with quality control of data entry. The study considers a relevant patient group as at baseline, the predominant population harboured clinically significant prostate cancer undergoing treatment to avoid clinical progression. Although previous studies have considered oncological and functional outcomes following HIFU treatment in prostate cancer there has been sparse evaluation of functional outcomes after repeat treatment[20].

Limitations include incomplete data acquisition, for example lack of information concerning tumour location within the prostate and specific treatment and energy protocols deployed

during treatment which could have impacted on functional outcomes and recurrence such as apical disease. Verbally speaking though apical disease is a contraindication to HIFU and thus few such patients would have been included in the registry. Although the IIEF5 questionnaire was used, only answers for question two were logged in the database and we lack data on the use of phosphodiesterase-5 inhibitors to determine whether this was a factor effecting reported outcomes. This resulted in a 6-point scale for measuring erectile function and meant that the mean change in terms of absolute values was comparatively small. We acknowledge the presence of potential bias, especially in the second focal-HIFU cohort, when analysing pad-free and leak-free status, secondary to the small number of completed questionnaires within this group. This leaves potential for data to be skewed by not analysing those whose outcomes which were lost to follow-up.

Undertaking multiple analyses and use of statistical significance $p<0.05$ may have resulted in type 1 errors, falsely suggesting that second focal-HIFU has a deleterious effect on IPSS. This, in combination with the small sample size of the second focal-HIFU group, limits precision of results and statistical analyses. We have accounted for this when interpreting the data by assessing the absolute and relative changes rather than relying solely on the p-value. In evaluating function and quality of life there is no agreed definition of what boundary may be considered acceptable, successful or not. To account for this as far as possible we have utilised validated questionnaires to facilitate an overview of such outcomes and facilitate comparison to other studies in the literature[8]. A final limitation lies in attributing causation of worse IPSS scores in the second focal-HIFU cohort to focal therapy. This group underwent longer follow-up as a result of the longer duration of HIFU treatment and thus age-related changes to the prostate gland may have contributed to increases in IPSS and worsening EF scores, confounding conclusions[21].

In conclusion, a second focal-HIFU results in a worsening of urinary function, as measured by IPSS and also in erectile function. Continence, in terms of urinary leakage or pad use, was unaffected. Whilst unable to differentiate from age-related deterioration in urinary function, this data can be used to counsel patients undergoing redo-focal treatment. Further larger, randomised-control studies are required to discern the long-term outcomes and factors predictive for worsening functional outcomes after redo-HIFU therapy.

Conflict of interests:

HU Ahmed proctors for HIFU and cryotherapy and is paid for training other surgeons in these procedures. HU Ahmed is a paid medical consultant for Sophiris Biocorp and Sonacare Inc. Other authors have no conflicts of interest to declare.

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Legends to Illustrations

Figure 1. Patients included in analysis

Figure 2. Leak-free, pad-free and erectile dysfunction status- Primary focal-HIFU Group

Figure 3. Erectile dysfunction in second focal-HIFU group- no significant changes.

Figure 4. Leak-free continence in second focal-HIFU group- no significant changes

Figure 5. Pad-free status in second focal-HIFU group no significant changes

Table 1. Baseline characteristics (before first focal-HIFU) of men undergoing focal-HIFU one or two times. Maximum cancer core length (MCCL)

Mean (SD)	**One focal-HIFU (Cohort 1)**	**Second focal-HIFU (Cohort 2)**	**P**
	N=355	N=65	
Age	66.4 (7.3)	65.6 (7.0)	0.4
PSA before first focal-HIFU	7.9 (5.2)	8.4 (4.2)	0.5
T stage before first focal-HIFU - N (%)			
T1a	1 (0.3)	0 (0.0)	**0.01**
T1c	41 (11.5)	3 (4.6)	
T2	131 (36.9)	13 (20.0)	
T2a	42 (11.8)	9 (13.8)	
T2b	34 (9.6)	16 (24.6)	
T2c	57 (16.1)	14 (21.5)	
T3a	41 (11.5)	9 (13.8)	
T3b	2 (0.6)	0 (0.0)	
No data	6 (1.7)	1 (1.5)	
Gleason Score before first focal-HIFU - N (%)			
3+3	85 (23.9)	16 (24.6)	0.3
3+4	218 (61.4)	35 (53.8)	
4+3	38 (10.7)	12 (18.5)	
4+4	9 (2.5)	1 (1.5)	
No data	5 (1.4)	1 (1.5)	
Prostate volume before first focal-HIFU	41.7 (19.2)	38.9 (18.0)	0.3
+ve biopsy cores before first focal-HIFU	6.7 (7.2)	6.4 (3.5)	0.8
T biopsy cores before first focal-HIFU	31.3 (23.3)	33.1 (19.2)	0.6
MCCL of biopsy before	6.1 (3.1)	6.7 (3.4)	0.2

first focal-HIFU			
Maximum percentage core involvement on biopsy before first focal-HIFU	54.8 (26.6)	52.9 (24.9)	0.6
Biopsy Type- N (%)			
TPM	260 (73.2)	48 (73.8)	0.3
TRUS	89 (25.1)	16 (24.6)	
TURP	1 (0.3)	0 (0.0)	
No biopsy, MRI only	0 (0.0)	1 (1.5)	
No data	5 (1.4)	0 (0.0)	
Pre-operative hormonal therapy before first focal-HIFU- N (%)			
No	293 (82.5)	57 (87.7)	0.2
Yes	62 (17.4)	7 (10.8)	
No data	0 (0.0)	1 (1.5)	
HIFU Modality- N (%)			
Hemi	82 (23.1)	17 (26.2)	0.06
Focal	243 (68.5)	37 (56.9)	
Hockeystick	6 (1.7)	0 (0.0)	
Lesion Control (focal- quadrant)	20 (5.6)	9 (13.8)	
Lesion control (hemi)	4 (2.2)	2 (3.1)	
Biopsy invasion before first focal-HIFU - N (%)			
None	191 (53.8)	31 (47.7)	0.2
Perineural	107 (30.1)	17 (26.2)	
Lymphovascular	1 (0.3)	0 (0.0)	
No Data	56 (15.8)	17 (26.2)	

Table 2. Change in IPSS, EF-score (as per response to IIEF5Q2)- One focal-HIFU Group

	Group Mean IPSS (SD)		Group Mean EF-score (SD)	
Baseline (before first focal-HIFU)	9.47 (5.9)		3.9 (1.3)	
1-2y after one focal-HIFU	9.44 (6.3)		3.5 (1.6)	
2-3y after one focal-HIFU	9.6 (6.2)		3.8 (1.5)	
	Change in mean	**P Value**	**Change in mean**	**P Value**
Baseline vs 1-2y after one focal-HIFU	-0.03	**0.02**	**-0.4**	**0.02**
Baseline vs 2-3y after one focal-HIFU	0.1	0.8	-0.2	0.6
1-2y after one focal-HIFU vs 2-3y after one focal-HIFU	0.2	0.2	0.3	0.2

Table 3. Change in IPSS, EF-score (as per response to IIEF5Q2)- Second focal-HIFU Group

	Group Mean IPSS (SD)		Group Mean EF-score (SD)	
Baseline (before first focal-HIFU)	9.5 (6.6)		4.1 (1.3)	
1-2y after first focal-HIFU	7.9 (5.5)		3.3 (1.5)	
2-3y after first focal-HIFU	8.2 (4.8)		3.6 (1.3)	
Before second focal-HIFU	8.2 (5.4)		3.5 (1.4)	
1-2y after second focal-HIFU	9.6 (5.8)		3.3 (1.7)	
2-3y after second focal-HIFU	9.5 (5.5)		3.0 (1.4)	
	Change in mean	**P Value**	**Change in mean**	**P Value**
Baseline (before first focal-HIFU) vs before second focal-HIFU	-1.3	**0.02**	-0.6	0.2
Baseline (before first focal-HIFU) 1-2y post second focal-HIFU	+0.1	0.36	-0.8	**0.005**
Baseline (before first focal-HIFU) 2-3y post second focal-HIFU	0.0	0.37	-1.1	**0.008**
Before second focal-HIFU vs 1-2y post second focal-HIFU	1.4	**0.03**	-0.2	0.6
Before second focal-HIFU vs 2-3y post second focal-HIFU	1.2	**0.003**	-0.5	0.1
1-2y post second focal-	-0.1	0.06	-0.3	0.6

HIFU vs 2-3y post second focal-HIFU				

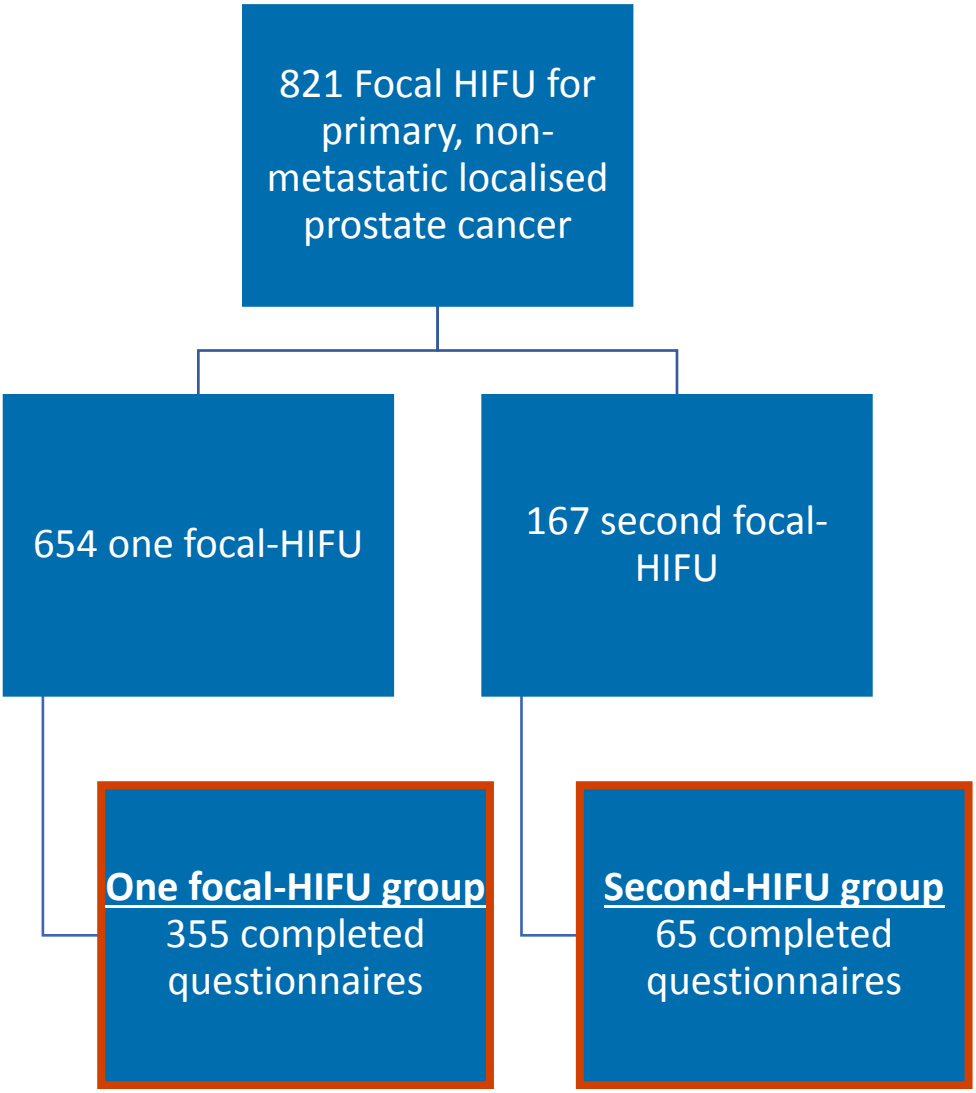

Figure 1. Patients included in analysis

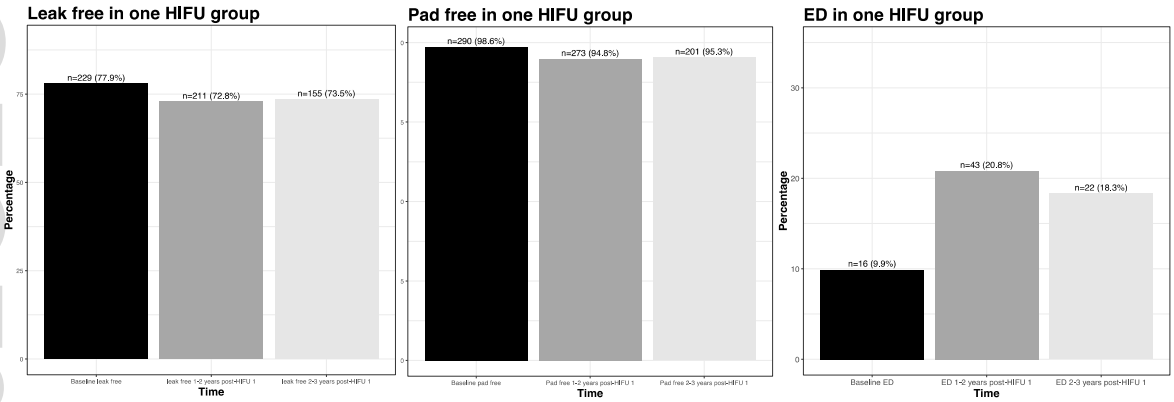

Figure 2. Leak-free, pad-free and erectile dysfunction status- Primary focal-HIFU Group

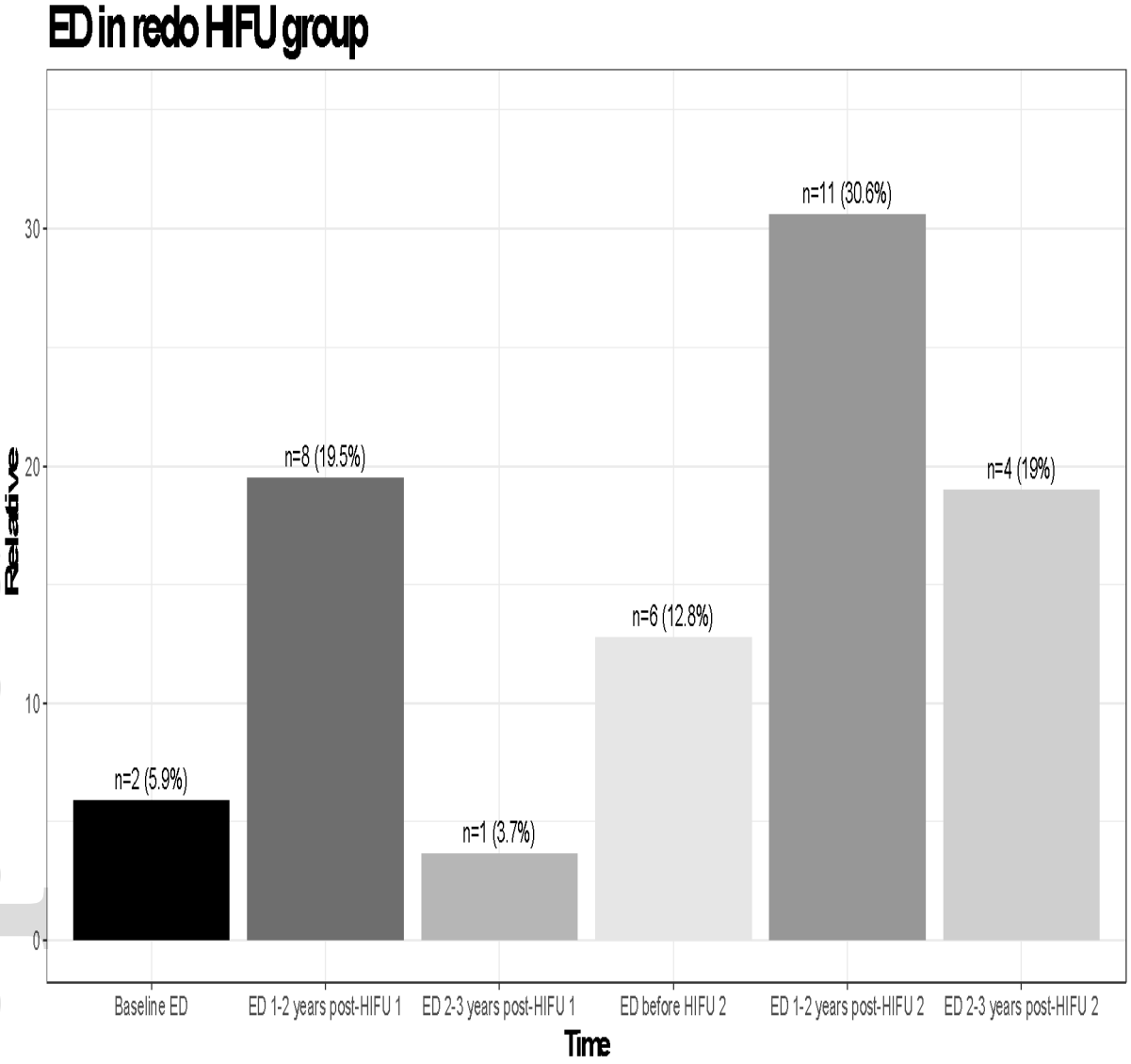

Figure 3. Erectile dysfunction in second focal-HIFU group- no significant changes.

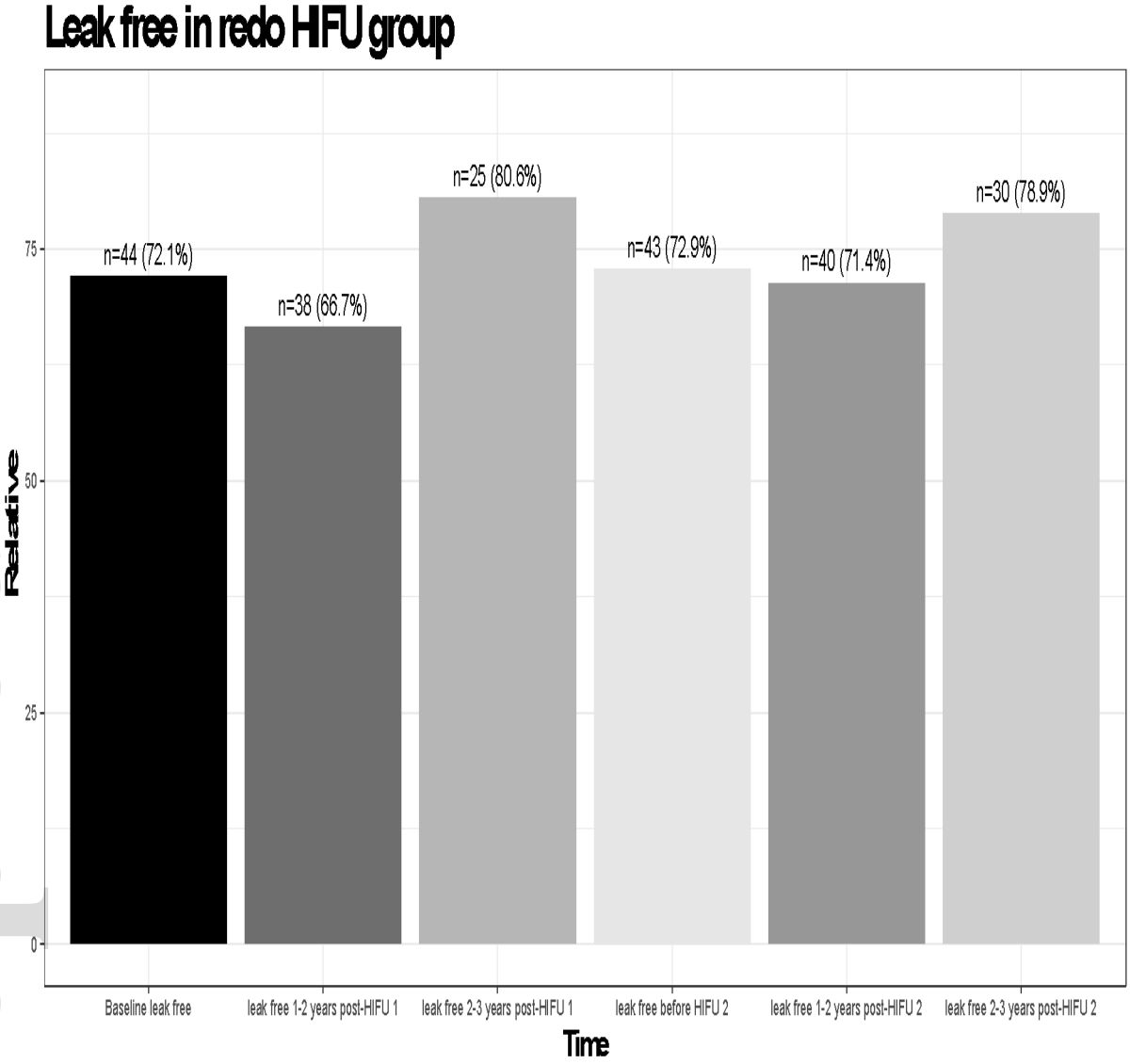

Figure 4. Leak-free continence in second focal-HIFU group- no significant changes

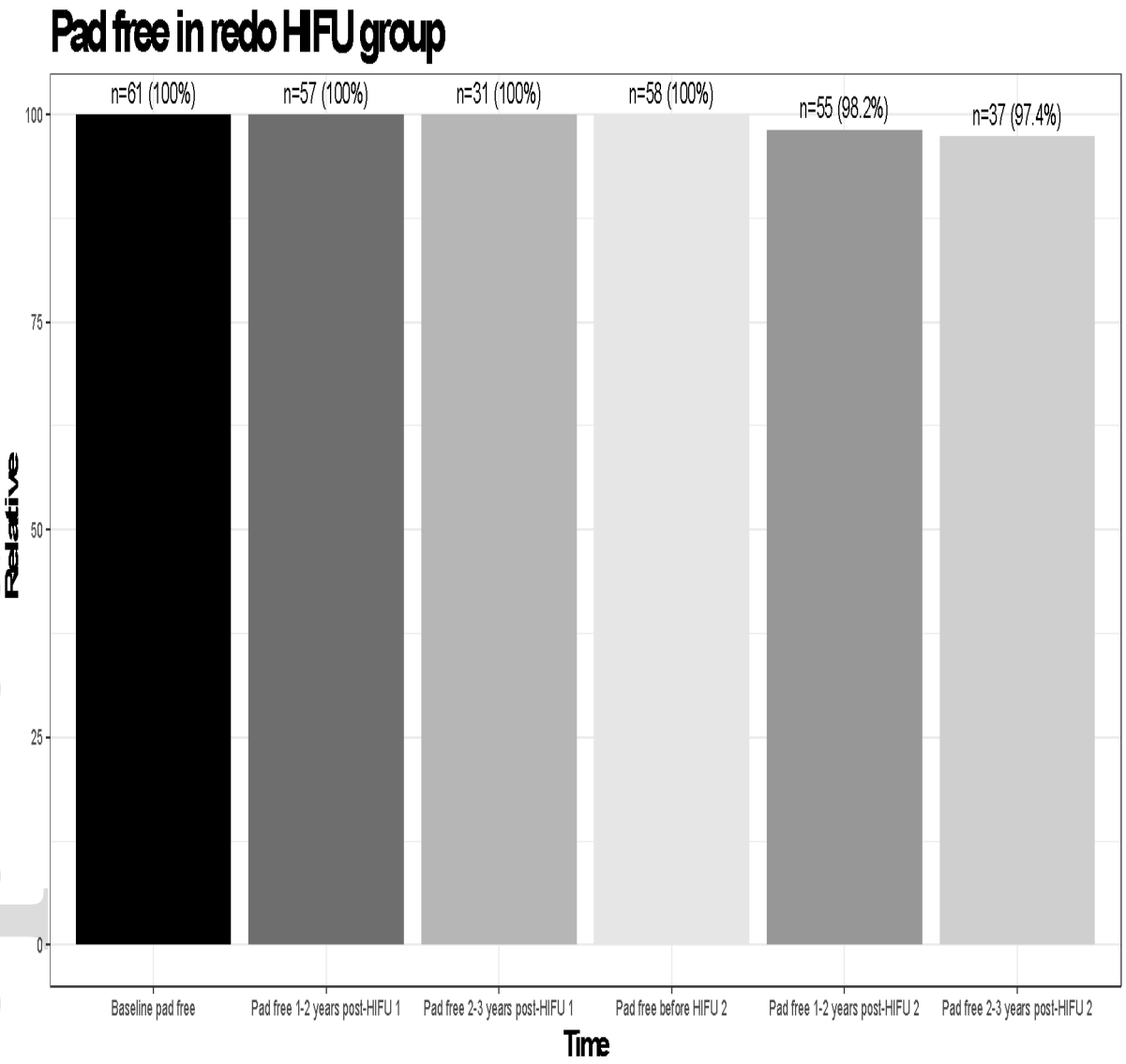

Figure 5. Pad-free status in second focal-HIFU group no significant changes