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Analyse morphométrique prostatique et des rapports anatomiques péri-prostatiques à l'IRM avant et après traitement partiel par ultrasons-focalisés du cancer de la prostate localisé

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par Denis SEGUIER

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JURY
Président :
Monsieur le Professeur Arnauld VILLERS
Assesseurs :
Monsieur le Professeur Philippe PUECH
Monsieur le Docteur Jean-Christophe FANTONI
Monsieur le Docteur Benjamin VANDENDORPE
Directeur de thèse :
Monsieur le Docteur Jonathan OLIVIER

Travail du Service d'Urologie du CHU de Lille et du Département d'Urologie de l'Hôpital Universitaire de Duke

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MRI analysis of prostate morphometry and periprostatic anatomical relationships before and after partial high-intensity focused ultrasound treatment of localized prostate cancer.

Abstract:

Introduction: Little is known regarding anatomical changes to peri-prostatic tissues after focal high intensity focused ultrasound (HIFU) for localized prostate cancer. We sought to provide a standardized approach to assess prostato-pelvic anatomical morphometric magnetic resonance imaging (MRI) changes post-focal HIFU.

Material and Methods: 38 patients over two institutions (Lille University Hospital and Duke University Hospital) undergoing focal HIFU with pre-and post-treatment (≥6 months) MRI were included. Pre- and post-treatment MRIs were assessed for prostate and treatment region volumes. Prostate-pubic symphysis and prostate-rectum distances were also measured to account for the overall post-treatment prostate-pelvic changes. Within the cohort, two subgroups were identified, those with recurrence (positive biopsy and/or subsequent whole gland treatment) and those without recurrence. Specific MRI features were also described within those two subgroups.

Results:

The estimated median treated-lobe volume was of 16.8 ml (IQR 10.6-21.5) on pre-treatment MRI and of 10.2 ml on post-treatment MRI (IQR 7.2-14.8). Comparison of volume on pre-treatment MRI vs. post-treatment MRI showed a significant difference ($p<0.01$). The median percentage reduction of treated lobe volume for the entire cohort was 28.5% (IQR: 17-47). No significant difference was identified between the non-recurring group and the recurring group for prostate volume and treated lobe-volume both at baseline and after treatment.

The analysis of prostato-rectal measurements was performed for the 17 patients. The mean value of the median prostato-rectal distance was 2 mm (SD 1) in pre-treatment and 1.97 mm (SD 1.1) in post-treatment. No significant difference in either the pre-treatment or post-treatment configuration ($p=0.78$ and $p=0.1$ respectively) between the subgroups of recurring and non-recurring patients were noted. 13 patients concerned by the prostato-rectal analysis were qualitatively classified as presenting an aspect of loss of symmetry in the prostato-rectal space on post-treatment MRI. No significative difference was identified between the recurring and non-recurring group for this parameter.

Conclusion: With this study, standardized method of morphometric alteration post-focal HIFU is demonstrated to be feasible. The presented preliminary data incite further investigations to assess the significance of these findings and clinical implications of this approach in a larger prospective cohort.

1.Introduction

Prostate cancer (PCa) is a frequently diagnosed disease which is responsible for numerous deaths worldwide.[1] In 2020, 1 414 259 individuals were diagnosed with prostate cancer and 375 304 deaths related to PCa were estimated .[2] Those diagnoses also result in a high volume of surgeries from the primary localized setting. The "Haute Autorité de Santé" (Health High-Authority) in France count approximatively 20 000 radical prostatectomy (RP) cases per year in France.[3] In a similar proportion, it is estimated that 90,000 RPs are performed annually in the United States.[4] These figures give us an idea of the public health challenge of managing prostate cancer.

1.1 Focal therapy for localized prostate cancer

In addition to the standard treatments, the last two decades have seen the development of an additional treatment technique particularly dedicated to the management of localized prostate cancer called Focal Therapy (FT).[5] This is defined as an anatomy-based (zonal) treatment strategy that targets the part of the prostate harboring the index lesion (i.e.. the zone comprising the clinically significant cancer).[5,6] This part can either be a quadrant, a lobe or both lobes sub-totally.[7–9] Several types of energy sources have been used so far to perform the focal therapy treatment modality and one of the most established now is high intensity focused ultrasound (HIFU) which will be the focus of our study.[9]

1.2 High-Intensity Focused Ultra-Sound

High-Intensity Focused Ultra-sound (HIFU) has become during the last decades one of the more widely used techniques of thermal ablation (either whole gland or focal).[8,10] This ablation method relies on the use of high-intensity focused ultrasound inducing destruction of tissue by raising temperatures above 60° C.[8] Two precise mechanisms account for the effectiveness of the tissue ablation: one is the thermal effect which consists of induction of a temperature increase above a certain threshold that induces coagulative necrosis of prostate tissue and other the mechanical effect which consists of the creation by ultrasound of a negative pressure on targeted tissue and results in internal cavitation of the tissue and its subsequent destruction. [11,12]

The first historical report of tissue destruction by HIFU occurred in 1944 by Lynn and Putman where they published a case of cerebral lesions treatment by using focused ultrasound.[13] The earliest trace of application in urology dates back to the 1980s with mainly a first usage to treat benign hyperplasia which then slowly transitioned to an oncological application.[12]

Current indication of HIFU use in the FT setting has been notably detailed in the review by Valerio et al. They reported that in the collected studies reviewed, patients had either low, intermediate or high-risk localized prostate cancer with median age of 63 yrs (IQR: 62–70 yr.) and median PSA of 7.3 ng/ml (IQR: 5.8–8.3 ng/ml).[8] This heterogeneity in the profile of patients who have benefited from focal HIFU in the various series of the literature is therefore reflected in the European and American recommendations, which still consider that HIFU in a focal setting cannot be elevated to the rank of a standard treatment option (EAU, NCCN, AUA).[14] The European Urological Association (EAU) thus states that this technique should still be considered experimental and recommends to offer it within the frame of a clinical trial setting or well-

designed prospective cohort study.[15] The National Comprehensive Cancer Network (NCCN) acknowledges the wide availability of data but nonetheless do not recommend focal HIFU as routine primary therapy for localized prostate cancer notably due to lack of long-term data comparing it to standard-of-care procedures (this position also applies to all focal therapy approaches).[16] Specific to HIFU, the NCCN stance is that it can recommend it as a treatment option for local therapy after EBRT recurrence without metastasis noted.[16]

The reported performance for HIFU is considered good overall compared to the standard of care offered at an equally considered state. In a multicenter study providing 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer, Guillaumier et al. reported results for 625 patients, failure-free survival, metastasis-free survival, cancer-specific survival, and overall survival were 88%, 98%, 100%, and 99%, respectively.[17] In their series, the overall rate of urinary incontinence (any pad use) reported in post-treatment follow-up was 2%.[17]

Despite the quality of the existing data and the certain oncological hindsight on this technique, there are still many challenges around the use of HIFU.[18] First, we note that in some manner and as underlined in both European and American guidelines, to this date, there is still a lack of long-term results (> 10 years) to support the oncological efficacy of focal therapy in general and focal HIFU in particular.[15,16] Concerning the question of refining the indication of treatment, it will notably depend on the diagnostic technologic progress which allows, as outlined by Chaussy in his review, to more accurately image and localize tumor lesions and foci.[12]

Technological advancement is considered one of the answers to some of the challenges we evoked previously, as it relies notably on a wider use of pre-treatment planning, particularly

mpMRI pre-planning, and the development of new devices (FOCAL ONE®, SONABLATE®). The advances with those new devices include during treatment US/MRI fusion use, refined real-time imaging and more precise tracking and adjustment of energy delivered.[11,19–21] One of the major challenges around HIFU is post-treatment imaging. It is this point that we will address in more detail and that will be the focus of this study.

1.3 Current limitation in post-treatment assessment after partial HIFU

Despite, the increased interest for FT over time, as evidenced by the increase, year-after-year, in the volume of publications related to this theme (Figure 1), we note several limitations in post-treatment assessment after partial HIFU.

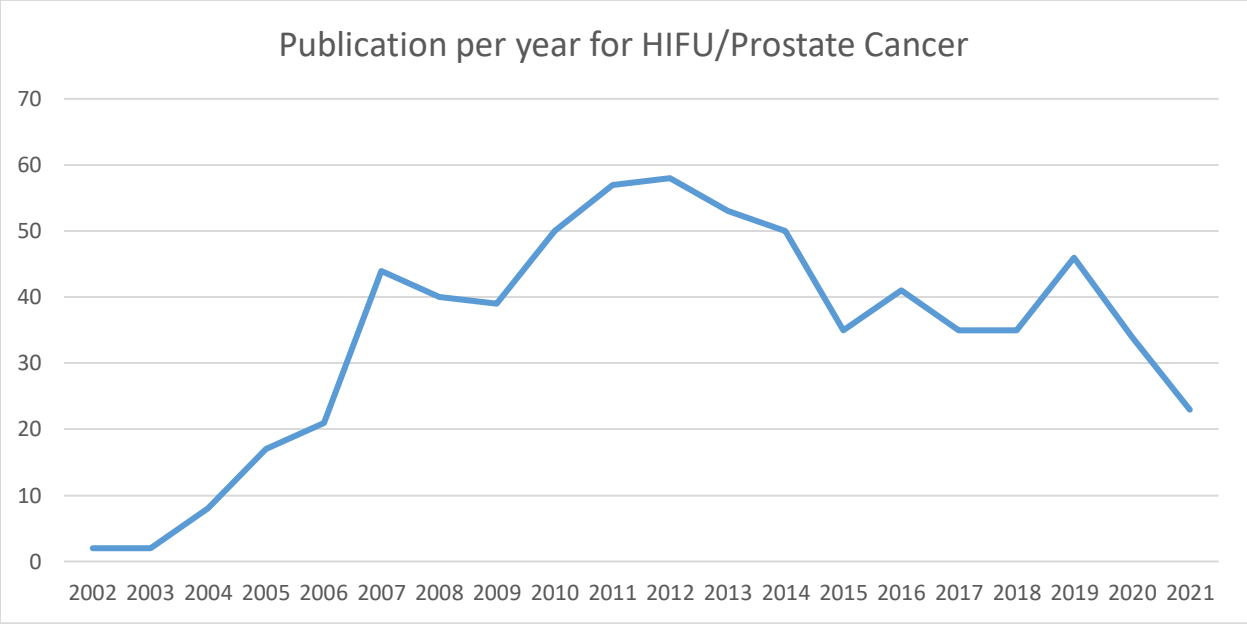

Figure 1: Evolution over time of the volume of HIFU publications in the prostate cancer field of research

One limitation is the lack of standardization in the post-treatment imaging assessment after partial HIFU for localized prostate cancer. This is noted firstly in the absence of guidelines on this point from the referenced learned societies (AUA, EAU, NCCN) and notably in the variability in post-assessment protocols reflected in the multiple systematic review studying partial

HIFU.[15,16,22,23] The scarcity of evidence in the literature is one of the major explanations for the aforementioned lack of standardization. In 2015 Rouviere, particularly emphasized the desperate need for solid evidence in post-treatment imaging and the situation is today similar for the focal treatment setting. What is generally true for all PCa settings happens to also be true in localized disease treated by focal therapy. [24]

Among the limitations to making partial HIFU a standard treatment is the prospect of the lack of knowledge about the ulterior outcome for patients who benefited first from focal and then whole gland salvage. This point has been particularly outlined by Valerio et al. as they stated that "before focal therapy (and thus partial HIFU) becomes an alternative standard option" many issues remain to be addressed and particularly determine which ablative technology has better functional and oncologic outcome, the margin of normal tissue required, and the long-term disease-control outcomes.[23] However, we can point out that the literature includes some proposals to standardize the evaluation of post-treatment recurrence, but evaluations specifically dedicated to the aftermath of focal treatments remain rare. Potretzke et al, for instance, in their review provide insight about post-treatment prostate MRI including expected post-treatment anatomy and imaging characteristics, and the typical appearance of local tumor recurrence after radical prostatectomy, radiation therapy, and focal therapy for prostate cancer. [25] They emphasized how much the multi-parametric MRI approach remains paramount just as in the treatment-naïve gland in post-treatment assessment while providing elements supporting the importance of the dynamic contrast-enhanced MRI sequence for evaluation in this setting.[25] Another example of interest that illustrates the vital role of post-treatment imaging is the development of the use of Gallium-68 prostate-specific membrane antigen positron-emission

tomography (68Ga-PSMA-11 PET/CT). Recent efforts have been directed towards demonstrating the usefulness of this technology as shown in the Pawal et al. study that stated in a series of 247 men this techniques potential effectiveness in detecting the recurrence of PCa to guide the choice of salvage therapy.[26]

All these elements lead us to affirm that there is a need to further study the potential role of imaging, particularly of MRI, in the post-treatment setting after partial HIFU.

1.4 Metric analysis on MRI after partial HIFU, an uncharted territory

Thus, although a certain oncological efficacy of focal HIFU therapy has been demonstrated regarding the selected indications for localized prostate cancer, there are still limitations both on the prospect of long-term efficacy and also on the tools used for post-treatment follow-up and particularly imaging. Concerning post-HIFU imaging as discussed above, little is known about the special features of prostate MRI after treatment with partial gland HIFU ablation.[27]

Notably, to date and to our knowledge, the anatomical changes of the prostate and its relationship to the surrounding organs have not been studied exhaustively.[27] These anatomical modifications resulting from treatment may result in different approaches in therapeutic strategies, especially in the potential subsequent treatment of the entire gland (e.g. surgical difficulty or preservation of organs at risk in radiotherapy).[28,29]

We propose that a systematic approach to these techniques by morphometric analysis (size and location of diseased areas, overall prostate volume and conformation to surrounding pelvic structures) of pre- and post-treatment MRIs would allow a description of the changes in prostatic anatomical conformation induced by partial treatment techniques by focal therapy.

The primary objective of this work is therefore to establish the contribution of morphometric analysis in the evaluation of changes in prostatic anatomical conformation following partial HIFU treatment of localized prostate cancer. The secondary objective focuses on the determination of possible morphometric specificities of patients who have experienced a failure of their first line of treatment with partial HIFU.

2. Material and Methods

2.1 Recruitment, source population and inclusion/exclusion criteria, study design

This study is therefore a retrospective observational cohort study involving human patient data. For this study, the patients analyzed came respectively from the cohorts of patients treated with HIFU for localized prostate cancer at the Lille University Hospital and the Duke University Hospital. Candidates for inclusion were identified within the registries maintained for HIFU patients within these institutions. Inclusion criteria comprised: being over 18 years old, having received HIFU treatment as first-line therapy for localized prostate cancer, and having had a pre-treatment MRI up to 3 years prior to the date of treatment and a post-treatment MRI between 6 and 18 months after treatment. Patients who had received other prior localized treatment or for whom the MRI timing criteria were not met were excluded from the study.

A patient was considered to have a recurrence if he had a post-treatment biopsy demonstrating the presence of significant cancer and/or had received another oncologic treatment following the first HIFU treatment.

2.2. Clinical and bio-pathological data

For each patient included, a precise study of the medical file was carried out and an exhaustive database allowing the establishment of a clinical profile of the cohort was established. All the data recorded are detailed in appendix 1. From this initial collection of pre- and post-treatment clinical data, a profile of the cohort could be established. Those clinical data were collected from computerized medical records to create a project-specific database.

2.3 Treatment modalities and pattern

Patient from both center were treated with Ablatherm® Fusion device (produced by EDAP TMS, Lyon, France).[30] Regarding the treatment template, each patient were treated with a partial template, either hemi-ablation or quadrant ablation pattern. The gross anatomical aspect of those treatment pattern is illustrated in figure 2.

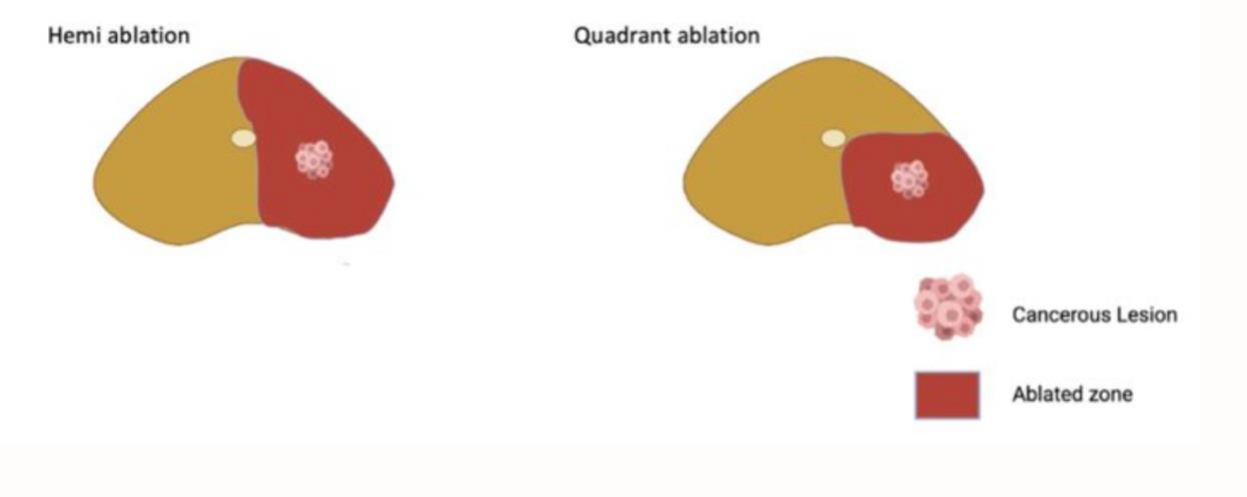

Figure 2. Schematical representation of partial HIFU treatment pattern

2.4 MRI metrics acquisition

2.4.1. Overall MRI protocol

All patients benefited from standard of care multiparametric MRI.[31] Patients treated at Duke University Hospital underwent the examination with an endorectal antenna while the patients treated at Lille University Hospital had a surface antenna. MRI in both centers operated at a strength of 1.5 Tesla.

2.4.2 List of metrics used

This first list established with the research team was the subject of an in-depth methodological discussion with the referring uro-radiologists of the two institutions and the referring urologists for the use of the techniques. In order to facilitate the collection of imaging data and the reproducibility of the method, it was decided to restrict the list of measured criteria to standards previously tested in the literature for prostate-specific measurements.[29,32–35] For pelvic and prostato-rectal conformation measurements, the choice was also made to restrict them in number to limit the intra and inter-patient variability of the measurement and adhere to a simple and easily reproducible geometrical method detailed below.

The definitive list of collected measurements is as follows:

Concerning the pre-MRI data, we collected the prostate volume, future treated lobe volume, the untreated lobe volume , the index lesion volume, the distances (long and short) between the anterior prostate and pubic bone, the distance between the median part of the rectum and the posterior wall of the prostate at mid-gland; for patients who did not benefited from an endo-rectal coil during their MRI acquisition we also realized/obtained standardized measurements of

the distance between the mediolateral point between the anterior rectal wall and the posterior prostate at the mid-gland level.

For the acquisition of these prostatorectal metrics, we proceeded to tracing the lateral tangents between the prostate and the rectum at the medio-glandular level, followed by tracing the tangents of the anterior face of the rectum which realizes the intersection of the median prostatorectal line and the lateral tangents; the mediolateral prostatorectal distance was measured using the orthogonal line passing through the midpoint of the last tangents obtained. The whole measurement technique is summarized in figure 3.

We reproduced the same method of measurement for the post-MRI acquisition minus the index lesion volume assessment (since it was supposedly destroyed in the process of the treatment). Additionally based on the pre- and post-MRI metrics value, we identified a simple calculation to assess the overall change of conformation of the prostate and prostato-rectal space. We, thus, assessed the overall percentage of prostate volume reduction after treatment, the treated-lobe volume reduction, the difference between pre- and post- prostato-rectal distances, and anterior prostate-pubic bone distances.

Finally, in patients who did not have an endorectal coil during their MRI image acquisition, we calculated the variation of median prostato-rectal distance by subtracting the pre-treatment value to the post-treatment value. We also assessed the difference in right and left medio-prostatorectal distances in pre- and post-treatment and then the absolute change in this distance to evaluate the possible loss of symmetry. This loss of symmetry of the prostatorectal space post-treatment was also assessed qualitatively by determining its presence or not.

All measurements were performed using a dedicated prostate image processing software: Invivo DynaCAD Prostate (GE Healthcare©). All metrics were captured on an intranet server dedicated specifically to research with secure and anonymous storage of images used for research purposes. The data collection on MRI was performed by two authors (DS and SK).

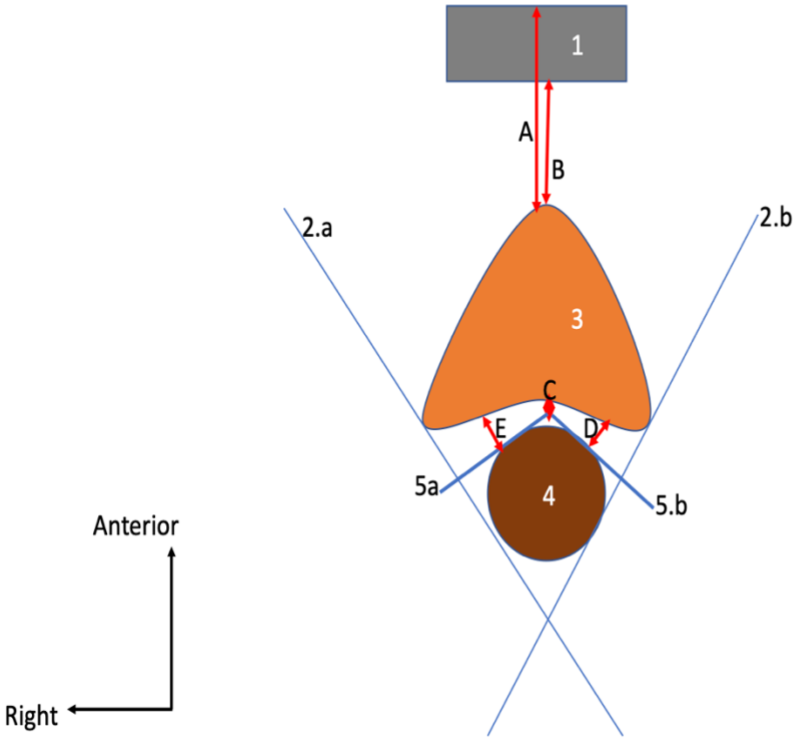

Figure 3. *Anatomical and geometrical repair, axial plane]: 1: pubic bone, 2.a/2.b: prostatorectal lateral tangent, 3: prostate, 4: rectum, 5.a/5.b: Anterior rectal wall tangent. Established measurement (red arrow): A; longer distance between anterior prostate and pubic bone, B: shorter distance between anterior prostate and pubic bone, C: Median distance between rectum anterior wall and prostate posterior wall, D: Left mediolateral distance between rectum anterior wall and prostate posterior wall, E: Right mediolateral distance between rectum anterior wall and prostate posterior wall*

2.5 Endpoints criteria

The primary endpoint for this study was the percentage reduction in volume of the treated lobe. Secondary endpoints for the metrics analysis include: prostate volume variations and post-treatment reduction percentage, variation in prostatorectal distances (median and mediolateral ones) for patients eligible for the measurement, qualitative presence or not of an aspect symmetry loss in the prostatorectal conformation in patients eligible for this description and for the oncological correlation to the metrics, the search for significant differences in the above-mentioned metrics between the group of patients with recurrent cancer and those without recurrence.

2.6 Statistical Analysis

We first performed a description of the whole cohort and the two subgroups (patients with and without recurrence). The variables for these two subgroups were compared. Qualitative variables are described in numbers (percentage) and for quantitative variables, the normality of the data distribution was assessed using the Kolmogorov Smirnov test. Thus, those variables were described as the median [interquartile range (IQR)].

We used a chi-square test for comparison of quantitative variables. If the quantitative variables were normally distributed, comparison of independent groups (recurrent patients versus non-recurrent patients) was performed with a Student's t test and the Mann-Whitney test for non-parametric values. For the comparison of related groups (comparison of pre-treatment variables versus post-treatment variables), a paired-sample Student's t test was performed for the normally distributed values and a Wilcoxon test was performed for the non-parametric ones.

All statistical analyses were performed using SPSS software (version 25.0; IBM, Armonk, NY, USA).

2.7 Ethical framework

This retrospective collection of medical data has received institutional review board approval. The study was registered under the number 110175. The data was stored digitally in a password-protected, anonymized database. The entire research protocol was conducted in accordance with the rules of the Declaration of Helsinki.

3. Results

3.1 Cohort profile

All baseline and follow-up characteristics of the overall cohort and each subgroup are summarized in table. 1.

The total number of patients included was 38. 18 were free of cancer recurrence during the time of follow-up, while 20 patients had a recurrence. Among the 38 patients included, 21 had an endorectal coil during both the pre-treatment and post-treatment MRIs. Those patients were excluded from the specific prostato-rectal conformation analysis. Concerning the baseline characteristic of the overall cohort, we note that most of the patients, 30 (83.3%) were of intermediate risk according to the D'Amico classification, most of their index lesions were classified as Gleason grade group 2, (24 patients, 63.2%). There were no significant differences identified at baseline between the group of patients who presented without recurrence after initial treatment and those who had recurrence. During follow-up, there were significant differences in PSA values between the group of non-recurring patients and the recurring ones. The median (IQR) earliest PSA measured for the former was 1.29 (0.9-2.9) and for the latter 4.62 (1.4-7.1), p-value estimated as 0.025. A similar difference was

identified for the latest PSA measured (before the diagnosis of recurrence for the group of recurring-patients and the latest available for the non-recurring group), median (IQR) was 1.5 (0.6-4.9) for the non-recuring-group versus 5.3 (2.3-8.1) for the recurring-group, p-value estimated at 0.048.

Among the group of patients with recurrence, 19 benefited from post-treatment biopsy. One was directly offered treatment based on the rising PSA level. A total of 12 (66.7%) patients presented with in-field recurrences. One patient among this group was lost to follow-up after the diagnosis of his recurrence.

Bio-clinical profile of the cohort				
	Overall cohort (38)	Non-Recurring patients (18)	Recurring patients (20)	p-value (Non-recurring vs Recurring)
Demographic aspect				
Age at treatment, mean(sd)	66 (7,5)	67 (8.1)	64.8 (6.6)	0.233
Charlson Comorbidity Index, mean (sd)	53 (21-53)	37 (21-53)	53 (21-53)	0.379
Oncological data at baseline				
Pre-op Hormonal use (AA or castration), n	0	0	0	NA
PSA, ng/mL, median (IQR)	6 (4.5-10.6)	5.5 (4.5-8.2)	6.8 (4.7-11)	0.349
PSA density	0.15 (0.09-0.27)	0.13 (0.09-0.22)	0.18 (0.09-0.26)	0.35
D'Amico, n (%)	low : 4 (11.1)	2 (12.5)	2 (10)	NA
	intermediate: 30 (83.3)	13 (81.3)	17 (85)	NA
	high : 2 (5.6%)	1 (6.3)	1 (5)	NA
Index lesion GGG, n (%)	1: 9 (23.7)	4 (22.2)	5 (25)	NA
	2: 24 (63.2)	10 (55.6)	14 (70)	NA
	3: 5 (13.2)	4 (22.2)	1 (5)	NA
Treatment pattern, n (%)	Right : 24 (63.2)	11 (61.1)	13 (65)	NA
	Left : 13 (34.2)	7 (38.9)	6 (30)	NA
	Anterior : 1 (2.6)	0 (0)	1 (5)	NA

Oncological data at Follow up				
PSA profile				
Time from treatment to first PSA measurement, median (IQR), month	2 (1-3)	2.3 (1-3)	2 (1-3.7)	0.964
First PSA after treatment, ng/mL, median (IQR)	2.45 (1-5.2)	1.29 (0.9-2.9)	4.62 (1.4-7.1)	0.025
PSA at 6 months, ng/mL, median (IQR)	2.2 (0.7- 5)	0.82 (0.5-2.9)	3.6 (1.8-6.8)	0.018
PSA at 12 months, ng/mL, median (IQR)	2.7 5 (0.7-5.9)	0.7 (0.3-2.6)	5.2 (2.5-7.7)	<0.01
Latest PSA available, ng/mL, median (IQR)	3.3 (1-7.4)	1.5 (0.6-4.9)	5.3 (2.3-8.1)	0.048
Percentage of PSA reduction between pre-treatment and latest measurement, median (IQR)	31 (-2.7-77.8)	73 (23-84)	19 (-36-56)	0.033
Follow-up Biopsy				
Number pts having subsequent biopsy, n (%)	21 (55)	3 (16)	19 (95)	
In-field positive, n (%)	12 (57.1)	0	12 (66.7)	NA
Out-field positive, n (%)	15 (71.4)	0	15 (83.3)	NA
Post-HIFU treatment				
RARP, n (%)	6 (31.6)		6 (31.6)	NA
Radiation, n (%)	5 (26.3)		5 (26.3)	NA
Radiation + ADT, n (%)	3 (15.8)		3 (15.8)	NA
AS, n (%)	1 (5.3)		1 (5.3)	NA
Repeat HIFU, n (%)	4 (31.6)		4 (31.6)	NA

Table 1. Bio-clinical profile of the cohort

3.2 Prostatic metrics

For the overall cohort, the median estimated prostate volume was 43.35 ml (IQR :32.5-52.5) on pre-treatment MRIs and 33.1 ml (IQR 23.6-41.4) on post-treatment MRI. Comparison of matched groups, pre-treatment MRI versus post-treatment MRI, showed a significant difference in prostate volumes between the initial MRI and post-treatment MRI ($p<0.01$). Concerning the treated-lobe volume, the median estimated volume was 16.8 ml (IQR 10.6-21.5) on pre-treatment MRI and 10.2 ml on post-treatment MRI (IQR 7.2-14.8). Comparison of matched groups (pre-treatment MRI versus post-treatment MRI) showed a significant difference in treated-lobe volumes between the initial MRI and post-treatment MRI evaluation ($p<0.01$). The

median percentage reduction of treated lobe volume for the entire cohort was 28.5% (IQR: 17-47).

No significant difference was identified between the non-recurring group and the recurring group for prostate volume and treated lobe-volume both at baseline and after treatment (respectively p=0.65 and p=0.21). There were not differences between those groups in the percentage reduction of treated lobe volume (p=0.3). Results concerning specific prostatic metric findings are available in Table 2 and Table 3 (Overall MRI features and comparison of MRI features pre- versus post-treatment). An example of the set of measurements performed on MRI is shown in Figure 4, which represents the imaging elements of a patient treated by right hemi-ablation.

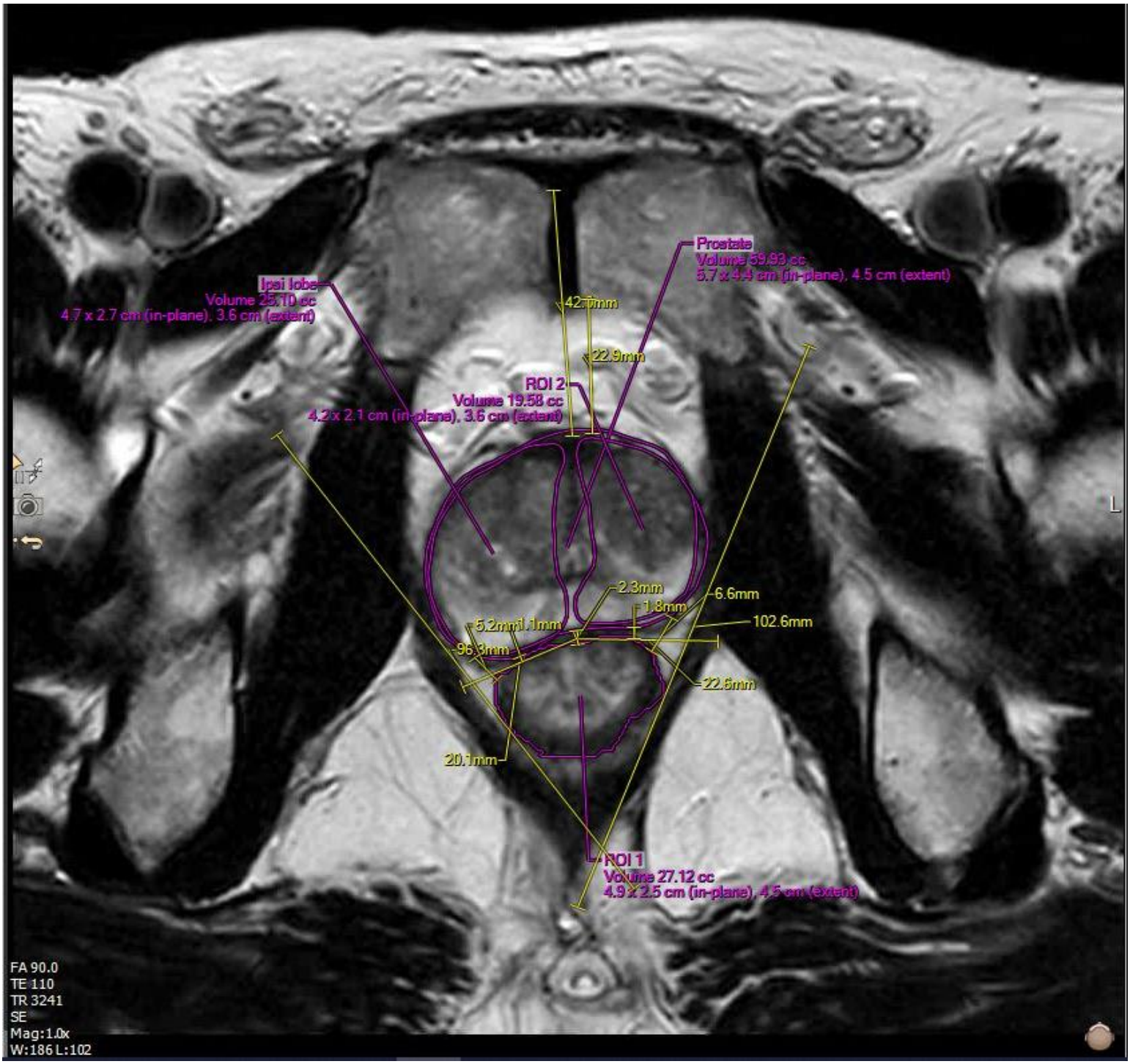

Figure 4.a Pre-treatment MRI measurements for a patient treated by right Hemi-ablation

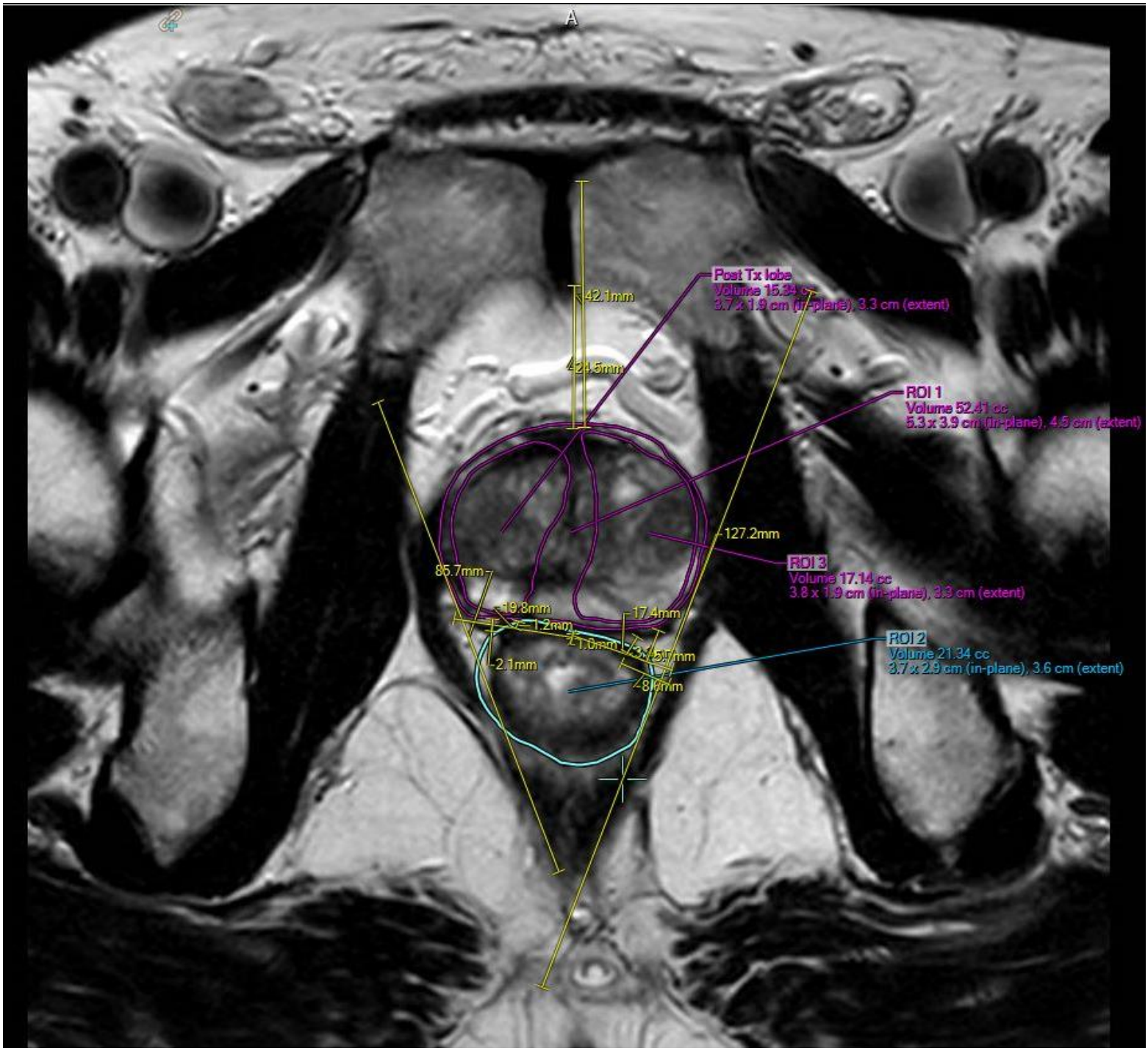

Figure 4b. Post-treatment MRI measurements for a patient treated by right Hemi-ablation

MRI features (Overall Cohort)									
Pre-treatment mpMRI					**Post-treatment mpMRI**				
	Overall cohort	**Non-Recurring Patients**	**Recurring Patients**	**p-value (Non-recurring vs. Recurring)**		**Overall cohort**	**Non-Recurring Patients**	**Recurring Patients**	p-value (non-recurring vs Recurring)
					Time from treatment to MRI, month, mean (sd)	10 (3.7)	NA	NA	NA
Prostate volume, ml,median (IQR)	43.35 (32.5-52.5)	42 (32-48)	46.2 (31-57.2)	0.65	Prostate volume, ml,median (IQR)	33.1 (23.6-41.4)	30.7 (22.2-41.1)	35.3 (25.3-46.3)	0.21
Targeted-Lobe Volume, ml,median (IQR)	16.8 (10.6-21.5)	15.9 (10.5-21)	17.2 (10.7-23.1)	0.55	Treated lobe volume, ml,median (IQR)	10.2 (7.2-14.8)	10.1 (5.9-12.1)	10.4 (7.2-16.9)	0.37
Non-treated lobe volume, mean (sd)	16.5 (6.4)	15.9 (6.3)	17 (6.6)	0.59	Non-treated lobe volume, mean (sd)	14.7 (6.1)	14.2 (6)	15 (6)	0.6
Index lesion Volume, ml,median (IQR)	0.6 (0.3-1.2)	0.68 (0.35-1.6)	0.37 (0.23-0.78)	0.173					
Shortest Mean Distance between Pubic bone and AFMS, mm, mean (sd)	13.8 (5.7)	11.7 (4.8)	15.8 (5.9)	**0.02**	Shortest Mean Distance between Pubic bone and AFMS, mm, median (IQR)	14 (9.8-17)	11.5 (7.6-14.7)	16.2 (12.8-24)	0.001
Descriptive features of MRI changes (Post vs. Pre-treatment MRI)									
	Overall cohort	**Non-Recurring Patients**	**Recurring Patients**	**p-value (Non-recurring vs. Recurring)**					
Reduction percentage of overall	18.4 (13.3-33.4)	27.2 (17.5-36.6)	18.5 (9.5-26)	0.06					

prostate volume, median (IQR)									
Reduction percentage of treated lobe volume reduction, median (IQR)	28.5 (17-47)	41.2 (15-53.6)	26.5 (18.4-35.6)	0.3					
Change in distance between prostate and pubic symphysis, mm, mean (sd)	0.69 (5.2)	-0.7 (4.7)	1.2 (5.5)	0.11					

Table 2. Overall MRI features

Comparison of pre-treatment MRI metrics versus post-treatment MRI metrics			
	Pre-treatment value	Post-treatment value	p-value (Pre- vs. Post-treatment)
Prostate volume, ml,median (IQR)	43.35 (32.5-52.5)	33.1 (23.6-41.4)	<0.01
Treated-Lobe Volume, ml,median (IQR)	16.8 (10.6-21.5)	10.2 (7.2-14.8)	<0.01
Non-treated lobe volume, mean (sd)	16.5 (6.4)	14.7 (6.1)	<0.01
Shortest Mean Distance between Pubic bone and AFMS, mm, mean (sd)	13.8 (5.7)	14.5 (6.3)	0.42
Left mediolateral prostato-rectal distance, mm, mean (sd)	2.7 (1.2)	3.7 (2.2)	0.057
Right mediolateral prostato-rectal distance, mm, mean (sd)	2.5 (1)	3.1 (1.6)	0.14

Table 3. Comparison of pre-treatment MRI metrics versus post-treatment MRI metric

3.3. Peri-prostatic metrics (relation to pubis and rectum)

3.3.1. Prostatopubic distances assessment

The prostatopubic measurements were conducted on the whole cohort. The mean value of the shortest pubic-prostate distances for the overall cohort was 13.8 mm (SD: 5.7) at pretreatment MRI, the median at post-treatment was 14 mm (IQR 9.8-17). At the pre-treatment MRI versus post-treatment MRI comparative analysis, there was no significant difference between the mean distance measured pre-treatment and post-treatment, p=0.42.

The baseline and post-treatment values for the non-recurrent and recurrent groups were significantly different, respectively, on pre-treatment MRI 11.7 (SD 4.8) vs. 15.8 (SD 5.9) p=0.02 and on post-treatment MRI 11.5 (IQR 7.6-14.7) vs. 16.2 (IQR 12.8-24), p=0.001.

The mean change in prostatopubic distance (short distance comparison) was 0.69 mm in the entire cohort. There was no significant difference in this distance variation between the recurrent and non-recurrent groups. All detailed results concerning the prostatopubic distance assessment are available in Tables 2 and 3.

3.3.2 Prostatorectal conformation assessment

The detailed analysis of prostatorectal measurements was performed only on the 17 patients in the cohort who did not have an endorectal coil during their MRI image acquisition. The mean value of the median prostatorectal distance was 2 mm (SD 1) in pre-treatment and 1.97 mm (SD 1.1) in post-treatment. Comparison of these distances for the recurrent and non-recurrent groups showed no significant difference in either the pre-treatment or post-treatment configuration (p=0.78 and p=0.1 respectively).

Regarding the subcohort "patients without endorectal antenna", the matched analysis (pre vs. post treatment analysis) of the right and left mediolateral measurements did not identify a significant difference between the mean value of its measurements at pre-treatment MRI compared to post treatment MRI. For the left distance the mean pretreatment was 2.7 mm (SD 1.2) and post-treatment 3.7 mm (SD 2.2), p=0.057 and the mean right mediolateral distance pre-treatment was 2.5mm (SD 1) versus 3.1mm (SD 1.6) in post-treatment, p=0.14.

The mean distance variation of the medial prostatorectal measurement in the whole subcohort "patients without endorectal antenna" was -0.03mm (SD 1.2); it was 0.9 (SD 1.5) for patients without recurrence and -0.3 (SD 1) for patients with recurrence. The difference between the latter two groups was not significant, the corresponding p-value being 0.08.

The mean change in the difference in right and left mediolateral distances between pre- and post-treatment was 0.37mm (SD 2.6) for the same subcohort. When comparing the group of non-recurring and recurring patients, the identified values were -0.4 (SD 4.1) for the patients without recurrence and 0.6 (SD 2) for the patients with recurrence. The difference between the latter two groups was not significant, the p-value being equal to 0.5.

A total of 13 of the 17 patients concerned by the prostatorectal specific measurements were qualitatively classified as presenting an aspect of loss of symmetry in the prostatorectal space on post-treatment MRI. No significative difference was identified between the recurring and non-recurring groups regarding this parameter.

All results concerning the prostatorectal conformation are summarized in Table 4.

Prostatorectal MRI features (Non-endorectal coil patients, N=17)									
Pre-treatment mpMRI					**Post-treatment mpMRI**				
	Overall cohort (17)	Non-Recurring Patients (4)	Recurring Patients (13)	p-value (Non-recurring vs. Recurring)		Overall cohort (17)	Non-Recurring Patients (4)	Recurring Patients (13)	p-value (non-recurring vs Recurring)
Distance between prostate posterior surface at mid-gland and anterior rectal wall mm, mean (sd)	2 (1)	1.9 (1.4)	2 (1)	0.78	Distance between prostate posterior surface at mid-gland and anterior rectal wall mm, mean (sd)	1.97 (1.1)	2.8 (1.8)	1.7 (0.7)	0.1
Left mediolateral prostato-rectal distance, mm, mean (sd)	2.7 (1.2)	2.9 (2)	3.2 (1.7)	0.7	Left mediolateral prostato-rectal distance, mm, mean (sd)	3.7 (2.2)	4.2 (3.8)	3.6 (1.7)	0.7
Right mediolateral prostato-rectal distance, mm, mean (sd)	2.5 (1)	2.6 (0.9)	2.3 (0.7)	0.1	Right mediolateral prostato-rectal distance, mm, mean (sd)	3.1 (1.6)	4.8 (1.2)	2.6 (1.6)	0.01
difference between left-right mediolateral prostato-rectal distance (pre), mm,mean (sd)	0.2 (0.9)	-0.3 (1.3)	0.3 (0.7)	0.2	difference between left/right left-right mediolateral prostato-rectal distance, mean,(sd)	0.6 (2.7)	-0.6 (4.5)	0.95 (2)	0.3
Descripitive features of MRI changes (Post vs. Pre-treatment MRI)									
	Overall cohort	Non-Recurring Patients	Recurring Patients	p-value (Non-recurring vs. Recurring)					
Median prostato-rectal variation, mm, mean (sd)	-0.03 (1.2)	0.9 (1.5)	-0.3 (1)	0.08					
Variation of the difference in left-right mediolateral prostato-rectal distance, mean, sd	0.37 (2.6)	-0.4 (4.1)	0.6 (2)	0.5					
Presence of an aspect of prostatorectal space symmetry loss n (%)	13 (76)	4 (100)	9 (70)	0.21					

Table 4. Prostatorectal MRI features

4. Discussion

4.1 Key points

This study provides interesting answers to the question of post-partial HIFU MRI aspects from a morphometrics view point. Despite a certain lack of power that did not allow us to reach statistical significance for all points/features evaluated, we were notably able to demonstrate that in our cohort there was a median reduction of nearly 30% in the volume of the treated lobe between pre-treatment and post-treatment MRI (IQR 17-47). The difference between the estimated mean treated lobe volumes on pre- and post-treatment MRI was significant, with a median volume of 16.8 ml (IQR 10.6-21.5) on pre-treatment MRI versus 10.2ml (7.2-14.8) on post-treatment MRI. These results are consistent with the few preexisting studies addressing this matter in the literature.[29,33,36] Thus, we could notably mention the recent example of the study by Schaudinn et al. who observed in a small cohort of non-recurrent patients treated lobe shrinkage in 93% of the cases with an average percent volume change of -37% (range: -70% to +108%).[29]

Beyond this main result, which is consistent with the literature, one of the important strengths of this study lies in the proposal of an innovative, standardized and reproducible method of measuring periprostatic relations. To our knowledge, this is a novel work that quantitatively measure and allows one to account extensively for the prostatorectal conformation on MRI before and after treatment. We notably demonstrated in our study the feasibility of gaining assessable measurements such as the mean distance variation of the medial prostatorectal measurement that we estimated being of -0.03mm (SD 1.2) for the sub-cohort of eligible patients in this analysis. The mean measurement was estimated to be 0.9 mm (SD 1.5) for

patients without recurrence and -0.3 mm (SD 1) for patients with recurrence. In a similar fashion, we also provided the mean change in the difference in right and left mediolateral distances between pre- and post-treatment which was 0.37mm (SD 2.6). In the comparative study of the subgroups (recurrent versus non-recurrent), none of the values compared were statistically significantly different, but there was a tendency towards significance, especially when comparing the variations in median prostatorectal distances, respectively for the non-recurrent versus recurrent groups; 0.9mm (SD 1.5) versus -0.3 (SD 1), p=0.08.

4.2 Main limitations

Naturally, this work suffers from biases that can be considered limiting in the scope of interpretation of the results. The retrospective nature of the study led to a certain limitation in the use of available data, clinical data may have been missing, and the data used may suffer from a certain heterogeneity inherent to the nature of the study design. Although the exploitation of MRI data was entirely exhaustive, the recording of clinical data may have suffered from some attrition due to memory bias (data not recorded in the patient file, loss to follow-up patients, referral to an external institution). In particular, we were not able to exploit all the data recorded during HIFU because of the lack of access to the data stored in the machines used for the treatment. Another main limitation related to the retrospective nature of the study is the width of the time frame for postoperative MRI, as a reminder, the time frame for postoperative MRI is 10 months (SD 3). This relative heterogeneity certainly also participates in the variability of the compiled results and calls for a careful clinical interpretation of our results. The scope of interpretation of our study was also limited by the modest size of the cohort (38 patients) and especially for the prostatorectal analyses where, for the reasons

mentioned above, it could only be conducted on 17 patients of the cohort. This small cohort size certainly contributes to the lack of significance of the comparisons established for the recurrent and non-recurrent patient sub-cohorts.

Lastly as a limitation, we want to underline that the interobserver variability was not assessed in this study even though for the MRI measurement, the two authors who performed it were not blinded from each other and each one of them reviewed the data collection performed by the other. However, we note that when the inter-observer correlation was evaluated in the literature, it was reported as very high as seen in the study of Kirkham et al. where the correlation coefficient was $r>0.9$.[33]

The nature of the biases detailed above leads us to interpret with caution the correlation to a clinical significance of the results, it is therefore difficult to establish a direct link between these metrics and the good realization of the HIFU treatment, its effectiveness and the potential prediction of possible post-treatment recurrence.

4.3 Next steps and ulterior perspective

4.3.1 Consolidating the evidence

The main interest of our study is to produce a reproducible method of morphometric evaluation of prostate MRI performed after focused ultrasound treatment of localized prostate cancer. The results, although non-significant for a part and suffering from the limitations detailed above, lays the foundation for further studies. Replication of this methodology in a prospective study with a larger cohort would allow further testing of the hypothesis of the correlation between the metrics and the correct conduct of the treatment and its effectiveness. As also mentioned by Rouvière and Kirkham, respectively, a prospective protocol would allow all patients to be

assessed at a fixed time point and would decrease the heterogeneity of results.[27,33,36] The conduct of multivariate analysis within a prospective study would also make it possible to establish the links between the various parameters and to refine the clinical relevance attributed to them.

4.3.2 Extension to the use of other MRI data, the example of contrast-enhanced sequences

As a further perspective on the use of these results, we can also highlight the possibility of their correlation to the use of contrast-enhanced sequences. Previous studies have made descriptions of prostate appearance on contrast-enhanced sequences on post-HIFU MRI, including Hötker who described specific aspects of early versus late post treatment MRI.[28] In their study, rim enhancement of the ablation zone and hypointense rim around the ablation zone on T2-weighted images were found at earlier times after ablation (respectively; 18-22.5 days vs. 409-593 days and 53-57.5 days vs. 279-409 days).[28] However, they only described these aspects, no correlation was established with other MRI features (post treatment prostate volume) or treatment performance aspects such as correlation to devascularization of the treated area. In a similar fashion in a setting of biochemical recurrent patients, Rouviere et al also exploited so benefit of contrast-enhanced sequence.[37] They analyzed at post-treatment MRI 77 lesions and described which sequence element allowed to identify it, among them some were detected only on DCE images (n = 52), T2w images (n = 2) or both (n = 23). Again, these results were only correlated with post-treatment clinical elements (here the result of the biopsy confirming the diagnosis of recurrence). Therefore, it seems interesting to us to consider a study compiling the morphometric elements as we have described them and the contrast-enhanced sequences in order to, among other things, help predict the good devascularization of the treated areas (which

is strongly correlated to the effectiveness of the treatment carried out) and, more broadly, to establish the correlations between these different parameters and the general outcomes of the treatment.

4.3.3 Morphometric data as potential additional tools in clinical decision making

Beyond the simple replication of the methodology used in this work in a more solid design (prospective multicentric with large cohort), the integration and correlation of morphometric elements extended to other dimensions of the management of localized prostate cancer could give them a new light. Among other observations, a correlation with post-treatment anatomopathological results could make it possible to establish a link between changes in the volume treated and the presence of necrosis. This approach has already been partially considered by Rouvière who assessed correlation between post-HIFU MRI findings and the proportion of necrosis on follow-up biopsies, unfortunately in this study no correlation could be established between those parameters[36].

The integration of morphometric data can also be integrated as part of the planning of retreatment after initial HIFU failure. Indeed, although in our study no specific MRI features could be specifically correlated to a recurrent or non-recurrent disease status, morphological changes induced by focal therapy may have an impact on the oncological and functional outcome of salvage treatments.[38,39] This is a critical point in decision making since, as Ribeiro et al. demonstrated in their multicenter study, the initial treatment can have an impact on the outcome of salvage treatment (in this case prostatectomy), they notably reported in their multivariable analysis that men who benefited from salvage whole-gland surgery after focal therapy experienced a higher risk of biochemical recurrence (HR 0.36, 95% CI 0.16-0.82,

p=0.02).[39] Thus, morphometric data could eventually be used to refine possible indications for salvage treatment. A recent example of this perspective comes from the study of Thompson et.al who evaluated the oncological and functional results after salvage prostatectomies after partial HIFU.[40] Their criteria for selecting patients for salvage prostatectomy included the notion of "surgical resectability" on MRI, although in this study it was not clearly defined by objective or measurable criteria. It seems to us that the morphometric evaluation on MRI has a potential role in the refinement of these criteria and could eventually help to judge, among other things, the surgical resectability in the hypothesis of the necessity of a surgical salvage treatment.

A similar reflection can be conducted in the hypothesis of post-HIFU salvage radiotherapy, where again post-initial treatment and pre-salvage treatment evaluation is crucial. This is highlighted in the Hardenberg study, which evaluated the triggers and oncologic outcome of salvage radical prostatectomy, salvage radiotherapy and active surveillance after focal therapy of prostate cancer.[41] They emphasized the need to keep in mind that in post-FT the peripheral zone was subject to periprostatic adhesions that could increase the toxicity of a possible salvage radiotherapy option.[38,41] Here again, the precise description of these periprostatic changes was lacking and it is reasonable to conceive how a morphometric analysis such as the one initiated in our study would elucidate this point.

Ultimately, and despite the biases inherent to the design of this study, it opens perspectives of interest for the use of imaging data after partial treatment with HIFU and invites the conduct of studies on larger cohorts in more methodologically robust designs to refine the results adumbrated here.

Conclusion

This study supports the feasibility and usability of morphometric data obtained on pre- and post-HIFU MRI. It tends to show that simple parameters such as the estimation of the reduction of the treated lobe volume or the variations of symmetry of the prostatorectal space can subsequently be used as an indicator of the quality and the effectiveness of the treatment conducted and also as a potential tool to guide the clinical decision of salvage treatment in the event that it is needed. This tendency cannot be affirmed based on our only study because of its inherent bias but opens the perspective of further work on larger prospective cohorts in order to deepen its meaning and to judge in fine the clinical relevance of its morphometric measurements.

REFERENCES

1. Cancer today. http://gco.iarc.fr/today/home.
2. Giona, S. The Epidemiology of Prostate Cancer. in *Prostate Cancer* (eds. Bott, S. R. & Ng, K. L.) (Exon Publications, 2021).
3. La prostatectomie totale robot-assistée, une technique possible mais sans valeur ajoutée démontrée par rapport aux autres modalités opératoires. *Haute Autorité de Santé* https://www.has-sante.fr/jcms/c_2732432/fr/la-prostatectomie-totale-robot-assistee-une-technique-possible-mais-sans-valeur-ajoutee-demontree-par-rapport-aux-autres-modalites-operatoires.
4. Lowrance, W. T. *et al.* Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States. *J. Urol.* **187**, 2087–2092 (2012).
5. Donaldson, I. A. *et al.* Focal Therapy: Patients, Interventions, and Outcomes—A Report from a Consensus Meeting. *Eur. Urol.* **67**, 771–777 (2015).
6. Arcot R & Polascik TJ. Evolution of Focal Therapy in Prostate Cancer: Past, Present, and Future. *Urol. Clin. North Am.* **49**, 129–152 (2022).
7. Postema, A. W. *et al.* Standardization of definitions in focal therapy of prostate cancer: report from a Delphi consensus project. *World J. Urol.* **34**, 1373–1382 (2016).
8. Valerio, M. *et al.* New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. *Eur. Urol.* **71**, 17–34 (2017).
9. Hopstaken, J. S. *et al.* An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years? *Eur. Urol.* **81**, 5–33 (2022).
10. Shoji, S. *et al.* Analysis of oncological outcomes of whole-gland therapy with high-intensity focused ultrasound for localized prostate cancer in clinical and technical aspects: a retrospective consecutive case-series analysis with a median 5-year follow-up. *Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group* **38**, 1205–1216 (2021).
11. Chaussy, C., Thüroff, S., Rebillard, X. & Gelet, A. Technology insight: High-intensity focused ultrasound for urologic cancers. *Nat. Clin. Pract. Urol.* **2**, 191–198 (2005).
12. Chaussy, C. G. & Thüroff, S. High-Intensity Focused Ultrasound for the Treatment of Prostate Cancer: A Review. *J. Endourol.* **31**, S30–S37 (2017).
13. Lynn, J. G. & Putnam, T. J. Histology of Cerebral Lesions Produced by Focused Ultrasound. *Am. J. Pathol.* **20**, 637–649 (1944).
14. Bates, A. S. *et al.* A Systematic Review of Focal Ablative Therapy for Clinically Localised Prostate Cancer in Comparison with Standard Management Options: Limitations of the Available Evidence and Recommendations for Clinical Practice and Further Research. *Eur. Urol. Oncol.* **4**, 405–423 (2021).
15. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5.
16. Referenced with permission from the NCCN Clinical Practice for Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer Version 4.2022 — May 10, 2022 NCCN.org NCCN Guidelines for Patients® available at www.nccn.org/patients.
17. Guillaumier, S. *et al.* A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. *Eur. Urol.* **74**, 422–429 (2018).
18. Schulman, A. A., Tay, K. J., Robertson, C. N. & Polascik, T. J. High-intensity focused

ultrasound for focal therapy: reality or pitfall? *Curr. Opin. Urol.* **27**, 138–148 (2017).
19. EDAP TMS - Global leader in therapeutic ultrasound. https://us.edap-tms.com/home/us.
20. Medical Device Manufacturer | Sonablate Corp. | Charlotte. https://www.sonablate.com/.
21. Connor, M. J., Gorin, M. A., Ahmed, H. U. & Nigam, R. Focal therapy for localized prostate cancer in the era of routine multi-parametric MRI. *Prostate Cancer Prostatic Dis.* **23**, 232–243 (2020).
22. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part II: Principles of Active Surveillance, Principles of Surgery, and Follow-Up | Journal of Urology. https://www.auajournals.org/doi/10.1097/JU.0000000000002758.
23. Valerio, M. *et al.* The role of focal therapy in the management of localised prostate cancer: a systematic review. *Eur. Urol.* **66**, 732–751 (2014).
24. Rouvière, O. Prostate cancer: Post-treatment imaging-a desperate need for solid evidence. *Nat. Rev. Urol.* **12**, 307–308 (2015).
25. Potretzke, T. A., Froemming, A. T. & Gupta, R. T. Post-treatment prostate MRI. *Abdom. Radiol. N. Y.* **45**, 2184–2197 (2020).
26. Lawal, I. O. *et al.* Pattern of Prostate Cancer Recurrence Assessed by 68Ga-PSMA-11 PET/CT in Men Treated with Primary Local Therapy. *J. Clin. Med.* **10**, 3883 (2021).
27. Rouvière, O., Gelet, A., Crouzet, S. & Chapelon, J.-Y. Prostate focused ultrasound focal therapy—imaging for the future. *Nat. Rev. Clin. Oncol.* **9**, 721–727 (2012).
28. Hötker AM *et al.* Temporal changes in MRI appearance of the prostate after focal ablation. *Abdom. Radiol. N. Y.* **44**, 272–278 (2019).
29. Schaudinn A *et al.* High-intensity focused ultrasound (HIFU) hemiablation of the prostate: Late follow-up MRI findings in non-recurrent patients. *Eur. J. Radiol.* **144**, 109957 (2021).
30. Ablatherm Fusion. https://us.edap-tms.com/us/products/prostate-us/ablatherm-hifu-us.
31. Rouvière, O. *et al.* Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol.* **20**, 100–109 (2019).
32. Kimple, R. J., Wallen, E. M., Pruthi, R. & Marks, L. B. A simple algorithm to assess patient suitability for Calypso-seed implantation for four-dimensional prostate localization. *J. Appl. Clin. Med. Phys.* **11**, 3107 (2009).
33. Kirkham, A. P. S. *et al.* MR Imaging of Prostate after Treatment with High-Intensity Focused Ultrasound. *Radiology* **246**, 833–844 (2008).
34. Burtnyk, M., Chopra, R. & Bronskill, M. Simulation study on the heating of the surrounding anatomy during transurethral ultrasound prostate therapy: a 3D theoretical analysis of patient safety. *Med. Phys.* **37**, 2862–2875 (2010).
35. Sumitomo, M. *et al.* Anterior perirectal fat tissue thickness is a strong predictor of recurrence after high-intensity focused ultrasound for prostate cancer. *Int. J. Urol. Off. J. Jpn. Urol. Assoc.* **17**, 776–782 (2010).
36. Rouvière, O. *et al.* MRI appearance of prostate following transrectal HIFU ablation of localized cancer. *Eur. Urol.* **40**, 265–274 (2001).
37. Rouvière, O. *et al.* Prostate cancer transrectal HIFU ablation: detection of local

recurrences using T2-weighted and dynamic contrast-enhanced MRI. *Eur. Radiol.* **20**, 48–55 (2010).
38. Riviere, J. *et al.* Salvage radiotherapy after high-intensity focussed ultrasound for recurrent localised prostate cancer. *Eur. Urol.* **58**, 567–573 (2010).
39. Ribeiro, L. *et al.* Is the Toxicity of Salvage Prostatectomy Related to the Primary Prostate Cancer Therapy Received? *J. Urol.* **205**, 791–799 (2021).
40. Thompson, J. E. *et al.* Peri-operative, functional and early oncologic outcomes of salvage robotic-assisted radical prostatectomy after high-intensity focused ultrasound partial ablation. *BMC Urol.* **20**, 81 (2020).
41. von Hardenberg, J. *et al.* Triggers and oncologic outcome of salvage radical prostatectomy, salvage radiotherapy and active surveillance after focal therapy of prostate cancer. *World J. Urol.* **39**, 3747–3754 (2021).

AUTEUR : Nom : SEGUIER **Prénom : DENIS**

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Titre de la thèse : Analyse morphométrique prostatique et des rapports anatomiques péri-prostatiques à l'IRM avant et après traitement partiel par Ultrasons-Focalisés du cancer de la prostate localisé

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Cadre de classement : *Onco-urologie*

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Mots-clés : Cancer de la Prostate, Analyse Morphométrique, IRM, Ultrasons focalisés, HIFU

Résumé :

Introduction : La littérature est limité sur la description des modifications anatomiques des tissus péri-prostatiques après un traitement par ultrasons focalisés de haute intensité (HIFU) pour un cancer de la prostate localisé. Nous avons cherché à fournir une approche standardisée pour évaluer les changements anatomiques morphométriques prostato-pelviens par imagerie par résonance magnétique (IRM) après un HIFU focal.

Matériel et méthodes : 38 patients répartis sur deux établissements (CHU de Lille et CHU de Duke) ayant bénéficié d'HIFU focaux avec IRM pré et post ablation (≥6 mois) ont été inclus. Les IRM pré et post-traitement ont été évaluées pour les volumes de la prostate et de la région de traitement. Les distances prostate-symphyse pubienne et prostate-rectum ont également été mesurées pour tenir compte de l'ensemble des modifications prostate-pelviennes post-traitement. Au sein de la cohorte, deux sous-groupes ont été identifiés, ceux avec récidive (biopsie positive et/ou traitement ultérieur de la glande entière) et ceux sans récidive.

Résultats : Le volume médian estimé du lobe traité était de 16,8 ml (IQR 10,6-21,5) à l'IRM avant traitement et de 10,2 ml à l'IRM après traitement (IQR 7,2-14,8). La comparaison du volume sur l'IRM avant traitement et sur l'IRM après traitement a montré une différence significative ($p<0,01$). Le pourcentage médian de réduction du volume du lobe traité pour l'ensemble de la cohorte était de 28,5 % (IQR : 17-47). L'analyse des mesures prostato-rectales a été effectuée pour les 17 patients. La valeur moyenne de la distance médiane prostato-rectale était de 2 mm (SD 1) avant le traitement et de 1,97 mm (SD 1,1) après le traitement. 13 patients concernés par l'analyse prostato-rectale ont été qualitativement classés comme présentant un aspect de perte de symétrie dans l'espace prostato-rectal à l'IRM post-traitement. Aucune différence significative n'a été identifiée entre le groupe récurrent et non-récurrent pour ce paramètre.

Conclusion : Cette étude démontre la faisabilité d'une méthode standardisée d'évaluation des altérations morphométrique post-focale HIFU. Les données préliminaires présentées incitent à poursuivre les recherches pour évaluer la signification de ces résultats et les implications cliniques de cette approche dans une cohorte prospective plus importante.

Composition du Jury :

Président : Pr. Arnauld Villers

Assesseurs : Pr. Philippe Puech, Dr. Jean-Christophe Fantoni, Dr. Benjamin Vandendorpe

Directeur de thèse : Dr. Jonathan Olivier