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Medium term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using HIFU for primary localized prostate cancer

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Abstract

Objective: To report medium-term oncological outcomes in patients receiving primary focal treatment with HIFU for PCa.

Patients and Methods: Consecutive men treated by means of primary focal HIFU for PCa at two centres by 6 treating clinicians were assessed. Patients were submitted to either a focal ablation or hemiablation using HIFU (Sonablate 500). The primary objective of the study was to assess medium-term oncological outcomes defined as overall survival, freedom from biopsy failure, freedom from any further treatment and freedom from radical treatment after focal HIFU. The secondary objective was to evaluate the changes in pathological features among patients treated by means of focal HIFU over time. We also assessed the relationship between year of surgery and 5-years retreatment probability.

Results: One thousand and thirty-two men treated between November 2005 and October 2017 were assessed**.** The median age was 65 yrs and median prostate-specific antigen was 7 ng/ml. The majority of patients had Gleason score of 3+4 or above (80.3%). Median follow-up was 36 months (IQR: 14-64). The overall survival at 24, 60 and 96 months was 99%, 97% and 97%, respectively. Freedom from biopsy failure, defined as absence of Gleason 3+ 4 disease, was 84%, 64% and 54% at 24, 60 and 96 months. Freedom from any further treatment was 85, 59 and 46% at 24, 60 and 96 months, respectively. Roughly 70% of patients retreated received a 2nd focal treatment. Freedom from radical treatment was 98%, 91% and 81% at 24, 60 and 96 months. During the study period we have seen an

increase in the proportion of patients undergoing focal HIFU with Gleason 3+4 disease and with T2 mpMRI staged disease. Finally, we report a reduction over time in the proportion of men undergoing re-treatment within 5-years of first treatment.

Conclusions: Focal HIFU for PCa is a feasible therapeutic strategy with acceptable survival and oncological results, with a reduction in the 5 year retreatment rates over the last decade. Re-do focal treatment is a feasible technique whose functional and oncological outcomes have still to be evaluated.

Introduction

Men with low or intermediate risk prostate cancer often face a choice between active surveillance with the option of deferred radical treatment, and radical treatment using surgery or radiotherapy. In the UK, the number of diagnoses is highest in the 70-74 age range [1], and the proportion of men diagnosed with intermediate risk disease is increasing, whilst low risk disease (Gleason 3+ 3) is decreasing.

Whilst radical treatment of low and intermediate risk prostate cancer is associated with good oncological control, it can be associated with significant side effects, including problems with urinary, bowel and sexual function. [2].

Focal therapy aims to provide oncological control whilst preserving urinary and erectile function[3,4].

A systematic review that included 2350 cases (from 30 studies) treated with focal therapy, reported an overall positive biopsy rate ranging from 3.7 to 23% in a median follow-up range of 0-11.1 years [5]. Azzouzi et al., in a randomized controlled trial comparing focal photodynamic targeted therapy to active surveillance for low risk PCa, reported a lower rate of progression in the former group at 24 months (28% vs 58%) [6]. Despite promising oncological effectiveness of focal therapy, critics have argued that studies have had tendency to include men with low-risk PCa for whom active surveillance might be appropriate. The lack of comparator group analysis, the relatively small study

samples, the short-term follow-up, single centre nature of most studies as well as the paucity of study registration has, to date, limited the strength of the published clinical evidence in terms of case selection and generalizability as well as failure to adjust for any confounding [7]. In terms of informed shared decision making what has been missing so far are outcomes that matter to patients. These comprise: absolute rates of re-treatment, likelihood of deferring or avoiding radical treatment, the probability of overall cancer control and cost-effectiveness. [5].

The University College London Hospital (UCLH) HIFU programme started in 2003 as a whole-gland intervention. The focal therapy programme began two years later in 2005. Today HIFU is almost exclusively used to administer focal treatments, in both primary and salvage settings.

In April 2012 the UK National Institute for Health and Care Excellence (NICE) published an Interventional Procedure Guidance on HIFU (IPG 424) [8], stating that whilst there are no many safety concerns, the evidence on efficacy was limited. It concluded that the procedure could be used within the United Kingdom's National Health Service (NHS) as long as, 'special arrangements for clinical governance, consent and audit or research', were in place.

The IDEAL framework for developing surgical interventions describes the manner by which the process of clinical innovation might be reported. It describes the following phases: Idea (1), Development (2a), Exploration(2b), Assessment (3) and Long term monitoring (4)[9]. We report this clinical cohort of the long term monitoring, including the change in use over time in a cohort of over 1000 men who had focal HIFU under the care of one team of clinicians, working within two UK health care settings: NHS and private practice.

1. Materials and methods

1.1. Study population

The study cohort comprised 1032 consecutive patients who had focal HIFU at two centres (University College London Hospital and Princess Grace Hospital) between November 2005 and October 2017. Two surgeons (ME and CM) operated at both centres, and a further 4 surgeons (HUA, MA, LD, CO) operated at UCLH. Data were retrospectively analyzed. This cohort included men who were treated both within National Cancer Research Network (NCRN) approved trials and clinical practice where data were collected.

1.2. Disease localization

Disease was localized using a combination of prostate multiparametric MRI (mpMRI) and biopsy. All patients underwent a 1.5 T or 3.0 T mpMRI study consisting of a T2-weighted imaging sequences, dynamic contrast enhanced and diffusion weighted imaging sequences. No endorectal coil was used. Biopsy strategies changed over time, and included systematic transrectal ultrasound (TRUS)-guided biopsy with additional targeted cores; transperineal template prostate mapping (TPM) biopsies using a 5-mm sampling grid or a modified Barzell approach, and transperineal targeted biopsies with additional systematic sampling. Any man who had an MRI not concordant with initial pathology was offered additional sampling to determine suitability for focal therapy.

1.3. HIFU treatment and follow-up

Patients with either TRUS-guided biopsy or TPM result concordant with a suspicious lesion detected at mpMRI, were offered focal therapy as an alternative to the standard options of radical treatment and active surveillance. Other focal treatments were also available at the two different centres at various time points during this cohort including focal cryotherapy, Nanoknife™ electroporation, photodynamic therapy (Tookad™) and radiofrequency ablation (Encage™).

Men underwent treatment with a transrectal HIFU device (Sonablate 500; Sonacare Inc, Indianapolis, IN, USA). This procedure has been previously described in detail [10]. According to the mpMRI and biopsy report (i.e. lesion volume, extension, Gleason score and number of positive cores) patients underwent either an entire ablation of one prostatic lobe (hemiablation) or the ablation of the index lesion only, identified with a combination of mpMRI and biopsy (focal/quadrant ablation).[11]. A margin of at least 5 mm was adopted around a visible mpMRI-based tumour.

Due to initial experience with whole gland ablation, suprapubic catheterisation was routinely used as a routine for focal treatments. As it became clear that most men re-established voiding less than a week after HIFU, urethral catheterisation was adopted as the standard approach, with removal within 3 to 7 days.

After treatment, PSA was assessed on a 3-4 monthly basis, and an mpMRI was offered at 6 or 12 months. For-cause triggers for an earlier MRI were principally driven by sequential PSA rises. Later MRI scans were requested according to baseline risk and PSA kinetics with routine practice to have an MRI at 1 and 3 years, and additional MRI scans based on PSA changes. Men with a suspicion of residual or recurrent disease on MRI, or those in whom there was an unexplained PSA rise, were offered biopsy assessment. Men with a stable PSA and no concerns on MRI or biopsy could be discharged to their general practitioner for PSA monitoring with a PSA interval (eg 6 monthly) and threshold set for re-referral.

1.4. Variable definition

Baseline variables regarding pre-treatment characteristics including age, PSA value, prostate volume, type of diagnostic biopsy (TRUS-guided vs TPM), number of biopsy cores, number of positive cores, maximum cancer core length (MCCL), mpMRI T stage (T1 vs T2 vs T3), Gleason Score were available for all the patients.

Follow-up data included first PSA after-treatment, percentage of PSA reduction, biopsy failure (defined as the presence of clinically significant PCa at post treatment biopsy). Clinically significant PCa (csPCa) was defined as Gleason score ≥ 3+4. Biopsies were offered systematically to men taking part in NCRN approved studies, and to other men on the basis of concern over mpMRI findings or PSA kinetics. Therefore, follow-up biopsies were not routinely performed across the whole population (41% [424/1032] of patients received a post treatment prostate biopsy) (Table 2). Any additional treatment, including further focal therapy, radical treatment or hormone treatment alone, was recorded.

1.5. Outcomes

The primary outcome of this analysis was to assess oncological outcomes defined as freedom from any additional further treatment, freedom from radical treatment (defined as radical prostatectomy, external beam radiotherapy and other whole gland therapies), freedom from biopsy failure and overall survival after focal HIFU. We also evaluated the rate of retreatment-free survival according to type of treatment (focal vs hemi), and Gleason score (3+3 vs 3+4 vs ≥4+3).

We report the trend in Gleason score and tumour stage in men having focal HIFU over the inclusion period. To assess for the effect of a learning curve in the domains of patient selection and treatment delivery we evaluated the likelihood of retreatment within 5 years of initial treatment for each of the years that treatments were administered contingent on a minimum of 5-year follow-up (i.e. until 2012).

1.6. Statistical analysis

Statistical analyses comprised four main steps. First, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. Second, Kaplan-Meier curves were plotted to assess survival. Log-Rank test was used to compare

different groups. Third, locally weighted scatterplot smoothing (lowess) was used for graphical representation of the year-by-year trends in pathological characteristics. Finally, multivariable logistic regression analysis (MVA) was performed to test the relationship between year of surgery and 5-years retreatment probability after accounting for the following confounders: PSA, primary Gleason, secondary Gleason, MCCL, number of positive cores and mpMRI T stage (T1 vs T2 vs T3). Lowess smoother function was used to graphically assess the multivariable effect of the year of surgery on the 5-years retreatment probability.

All statistical tests were performed using the RStudio graphical interface v.1.1.383 for R software environment v.3.4.2 (R Foundation, Vienna, Austria). All tests were two-sided with a significance level set at *p-value* <0.05.

2. Results

2.1. Baseline characteristics

Descriptive characteristics and follow-up data are reported in Table 1 and 2, respectively**.** Median age was 65 yr (interquartile range [IQR] range 60-70). Median PSA was 7 ng/ml (IQR 4.9-9.7). Patients were diagnosed either with TRUS (22%) or TPM (78%) and underwent either focal- (71%) or hemi-ablation (29%; specifically, 15% [47/302] of these patients underwent a hemi-ablation that crossed the midline of the prostatic gland). The majority of patients had Gleason score of 3+4 (63%) and T2 stage (78%). Median time to last follow-up was 36 months (IQR 11-64, range 0-131).

2.2. Primary outcome

The overall survival at 12, 24, 60 and 96 months was 99, 99, 97 and 97%, respectively (Figure 1a). Overall, freedom from biopsy failure was 94, 84, 64 and 54%, at 12, 24, 60 and 96 months respectively (Figure 1b). Freedom form any Gleason score PCa was 91, 79, 54 and 41% at 12, 24, 60 and 96 months, respectively (Supplementary figure 1). The freedom from biopsy failure for

patients who received a follow-up biopsy was 86, 69, 44 and 35% at 12, 24, 60 and 96 months (Supplementary figure 2). Rate of freedom from any Gleason score PCa for these patients was 80, 60, 29 and 18% at 12, 24, 60 and 96 months (Supplementary figure 3). Overall, the retreatment-free survival at 12, 24, 60 and 96 months was 98, 85, 59 and 46%, respectively (Figure 1c). Freedom from radical treatment at 12, 24, 60 and 96 months was 100, 98, 91 and 81%, respectively (Figure 1d).

When assessing the rate of retreatment-free survival according to treatment type (focal vs hemi ablation), no significant differences were found between the two groups (Figure 2a). The same analysis according to Gleason score showed a retreatment-free survival rate at 24 and 60 months for Gleason 3+3 vs 3+4 vs ≥4+3 of 86% and 66.5% vs 86.5% and 60.5% vs 77.8% and 37.4%, respectively (Figure 2b). Retreatment rate of the Gleason ≥ 4+3 group was significantly different to men with < Gleason 3 + 4 (all $p<0.001$). There was no significant difference in retreatment rates between Gleason 3+3 and 3+4 ($p=0.13$).

2.3. Change in baseline characteristics of the population over time

The trend of Gleason score treated over time is shown in Figure 3a. We observed that Gleason 3+4 represented the majority of the cases treated over the duration of our study, starting from 50%, steadily increasing until roughly 75% in 2017. Patients with Gleason 3+3 diminished in prevalence over time, and the proportion of men attributed Gleason ≥ 4+3 remained stable over the period of study.

The trend of T stage treated over time is depicted in Figure 3b, with the majority of men having T2 disease, a reduction over time of men with T1 disease and a steady rate of T3 disease.

Multivariable analysis in men with at least 5 years of follow-up does suggest a learning curve in patient selection and treatment delivery, as later year of surgery was significantly associated with a lower probability of 5-year retreatment (OR: 0.77; 95% CI: 0.67-0.89; $p<0.001$). We believe that the learning curve has 2 components: firstly, learning about the capabilities of HIFU technology to ablate

cancer in some anatomical areas of the gland. For example, extreme apical tumours are more likely to be undertreated given the lack of a 5mm margin. Secondly, learning about the intrinsic disease characteristics: large volume tumour crossing the midline, or bilateral Gleason 3 + 4 would no longer be offered focal therapy, where previously they may have been offered an extended hemi-ablation.

Furthermore, PSA (OR: 1.07; 95% CI: 1.01-1.12), T2 stage (OR: 3.75; 95% CI: 1.63-9.82) and T3 stage (OR: 5.0; 95% CI: 1.9-14.9) reached independent predictor status (all $p<0.02$) (Table 3) for the probability of undergoing a re-treatment within 5-years of the primary treatment.

Finally, we depicted the multivariable effect of the year of surgery on the 5-year retreatment rate (Figure 4). The likelihood of retreatment reduces with later year of surgery, as described in Table 3. Specifically, in 2007 the multivariable predicted probability of being retreated within 5 years was roughly 50%, decreasing to around 30% in 2012.

3. Discussion

Focal therapy has gained interest as a treatment option for clinically localized PCa with the aim of decreasing the side effects associated with radical treatment whilst offering greater oncological control than active surveillance [6], and allowing delayed radical treatment if needed. Early studies have shown promising results in terms of post treatment side effects and related quality of life [3,4,12], but longer term data are required [7].

The aim of this analysis was to evaluate medium-term outcomes in a cohort of men treated at 2 expert centres using focal HIFU. To our knowledge this is the largest cohort of patients (n=1032) treated with focal therapy using HIFU as energy source with intermediate follow up (median: 36 months; IQR: 14-64; range: 0-131).

First, in our study the overall survival of patients treated with focal HIFU was 99, 99, 97 and 97% at 12, 24, 60 and 96 months, respectively (Figure 1a), in keeping with the low mortality expected from studies of men with low and intermediate risk prostate cancer [13].

Second, the rate of detection of clinically significant cancer post treatment was 6, 16, 36 and 46% at 12, 24, 60 and 96 months – this is shown in the rate of biopsy-free failure across the whole cohort in figure 1b. When looking at the rate of biopsy failure exclusively in men who received a follow-up biopsy, the rates of clinically significant disease detection were 14, 31, 56 and 65% at 12, 24, 60 and 96 months – this is shown in supplementary figure 2). Residual or recurrent disease after focal therapy can be due to a number of factors, and is affected by the follow up protocol for the cohort. As there was no routine biopsy requirement for all men in the cohort, these data may underestimate the presence of Gleason > 3 + 4 disease. Positive histology after treatment can occur either in the treated area, or in a new location, which could have been undersampled prior to treatment, or arisen de novo following treatment.

Shah et al. in a review of histological outcomes after focal treatment, reported the presence of PCa in 22% of patients treated with focal HIFU at post-treatment biopsy (follow-up range 6-12 months) [14]. It is noteworthy as the majority (63%) of those positive biopsies, were either insignificant (54%) or from the untreated part of the prostate (9%) [14]. In a recent systematic review the overall presence of significant and insignificant cancer was 0% (IQR: 0–13.5%) and 23.3% (IQR: 10.4%– 38.1%), respectively, with a median follow-up of 12 months [3]. In our study 74% (189/255) of patients had PCa with Gleason 3+4 at biopsy failure, while 20%, 5% and <1% had Gleason 4+3, 4+4 and 4+5, respectively.

Donaldson et al., in a consensus conference, reported that the panellists were uncertain about whether post-treatment biopsy should also routinely sample the untreated gland [15]. In our study, follow-up biopsies were performed mostly ‘for-cause’ and the majority of patients had targeted sampling of MRI-suspicious areas. This might explain the considerable rate of presence of any PCa in post treatment biopsies (77%; 325/424) (Table 2). It is still not clear whether patients with a post-treatment positive biopsy have poorer oncological outcomes and studies evaluating the presence of positive biopsy after radiotherapy showed discordant results [16,17].

Third, the overall retreatment rate showed that 98, 85, 59 and 46%, of patients were free of any further treatment at 12, 24, 60 and 96 months, respectively. Previous studies providing retreatment data, reported rate of any retreatment ranged from 5% to 10.3% with a median follow-up range of 12-38 months [18–20]. Interestingly, among the 271 patients who underwent a retreatment, 193 (71%) chose a repeat focal HIFU. Moreover, 51 out of 193 (26%) patients retreated with HIFU, underwent a second retreatment, with 74% of men not having had further treatment to date.

There is a philosophical debate about whether a retreatment rate of this order is reasonable, given lower re-treatment rates for radical treatment. However, the preservation of urinary and sexual function is seen to a much greater extent in focal treatment than radical treatment, and many men consider this trade off a valuable option for them. Previous studies assessing the role of re-do whole gland HIFU, concluded that retreatment is associated with a small increase in urinary side effects but further deterioration in potency from the initial treatment effect [21]. Nonetheless, the functional outcomes of re-do focal HIFU have yet to be addressed.

According to our results, re-do HIFU is a feasible retreatment strategy which should be taken into account when a second treatment is necessary.

In terms of retreatment rates, in this study we provided data regarding the radical treatment rate, defined as radical prostatectomy, external beam radiotherapy and other whole gland therapies. In the context of focal therapy follow-up, a whole gland treatment is proposed either for a disease upgrade to high risk PCa or for a multifocal/bilateral csPCa which could not be controlled with a further focal approach. For these reasons, the rate of radical treatment after focal therapy might be considered a reliable outcome which mirrors the local control of the disease provided by a focal therapy strategy. In our study, overall rate of radical treatment was 0, 2, 9 and 19% at 12, 24, 60 and 96 months. Guillaumier et al. recently published a report of oncological and functional outcomes on a cohort of 625 men across 9 centres. This report differs in that it is done by one team of surgeons operating at 2 centres, and the number of men is increased. Guillaumier et al. reported a failure-free survival after primary focal HIFU (defined as freedom from radical or systemic therapy, metastases,

and cancer-specific mortality) of 99%, 92% and 88 at 1, 3 and 5 years[12]. These rates are, as expected, concordant with the rate of radical treatment-free survival provided in the current study. Many concerns exist regarding the feasibility of radical prostatectomy after focal therapy. Nonetheless, results reported by studies evaluating outcomes of salvage radical prostatectomy after focal therapy seem to be promising [22,23]. In particular, Nunes-Silva et al. reported a match analysis of two groups submitted to radical prostatectomy and salvage radical prostatectomy after focal therapy. The authors reported a comparable rate of complications and incontinence. However, patients assigned to salvage radical prostatectomy had lower rate of erectile function recovery and a higher probability of biochemical recurrence within 2 years of follow-up [22].

In a sub-analysis we assessed the retreatment-free survival curves according to treatment type and Gleason score. In this study patients had been treated either with a focal ablation or with a hemiablation. Whether to treat the entire lobe affected by PCa or to restrict the treatment to the index defined at mpMRI concordant with the presence of PCa, is the results of a pre-operative assessment in which multiple features of the disease are taken into account (i.e. Gleason score, MCCL, volume of the index lesion and number of positive cores). So far, to our knowledge, no studies have directly compared the two techniques. In this study we reported that, focal- and hemiablation have similar rate of retreatment-free survival. Tailoring the extension of the treatment to the disease's features seemed to be a feasible approach.

In a recent consensus meeting [24], the panelists agreed that focal therapy is an acceptable strategy for tumours of up to, and including Gleason 4+3 with no clear agreement on the size of the tumour. Nonetheless, treatment of Gleason $\geq$ 4+4 was discouraged [24]. In our study patients with Gleason $\geq$ 4+3 had a significantly higher retreatment rate as compared to lower Gleason categories. As a potential explanation, Le Nobin et al., suggested that higher grade tumours need a significantly higher margin around the mpMRI visible lesion to achieve complete ablation [25]. For these reasons, focal therapy for men with Gleason score $\geq$ 4+3 disease should not be routinely offered. On the contrary, there was no significant difference between men with Gleason 3+ 3 and Gleason 3 + 4 disease. This most likely reflects the fact that the majority of men treated with Gleason 3 + 3 disease

had visible disease on MRI, suggesting the presence of Gleason 3 + 4 disease. Men were offered repeat biopsy to determine this, but not all men accepted this, and treatment of Gleason 3 + 3 disease was permitted.

Fourth, when assessing the trend of pathological characteristic of patients over time (Figure 3a-b), we observed a steady increase in the proportion of Gleason 3+4 and T2 treated over the other categories, with a growing tendency to treat men with MRI visible Gleason 3 + 4 disease. Men with Gleason 3 + 3 disease are increasingly proposed for active surveillance and also are ever more likely to accept this strategy.

Finally, there is an improvement in the oncological outcomes over time, in terms of 5 year retreatment rates, falling from 50% for men treated in 2007 to 30% for men treated in 2012 (figure 4). We believe that this represents both the change in selection criteria, and in treatment delivery over time. Firstly, lesions very close to the apex are, nowadays, less likely to be treated with a focal approach because covering the whole lesion whilst sparing the sphincter is technically challenging and the risk of partially treated disease is higher. Secondly, the increasingly inclusion of patients with a visible lesion at MRI over the study period (Figure 3b) allowed the operator to more accurately select the area to treat with an appropriate margin. Thirdly, HIFU systems have been significantly improved over the years with subsequent improvement in long-term oncological outcomes [26]. Lastly, as in all other surgical procedures, the effect of the operator learning curve is likely to play a role.

We recognize the limitations of this report. First, it is based on retrospective data of a clinically managed cohort rather than a prospective study with mandated biopsy follow up. Nonetheless, Anglemyer et al, supported the reliability of retrospective studies demonstrating that observational reports did not significantly differ if compared to randomized control studies in terms of results [27]. Second, in the context of pre-assessment, data regarding pre-treatment mpMRI report were not available. Consequently reporting and accounting for mpMRI lesion locations and volume was not possible. Third, data regarding disease localization at biopsy histological report were not

available, therefore we were not able to account for the eventual presence of untreated disease. In this context, also data regarding post-treatment biopsy PCa location were not available, making the discrimination between in-field and out-of field recurrence impossible to figure. Moreover, as aforementioned, follow-up biopsies were not routinely done. Most part of patients underwent a "for-cause" biopsy due to rising PSA or a prostate MRI suggestive of residual or recurrent disease. For these reasons, rate of biopsy failure must be interpreted with caution, nonetheless it mirrored the clinical practice over the study period. Finally, in this study we provided survival outcomes with long-term figure (up to 96 months). Although the median time to last-follow up in this study was 36 months (IQR: 14-64), up to 14% (n=149) of patients had a follow up greater than 80 months. Given the call for mid-, long-term oncological outcomes in the field of focal therapy [7] we deemed that data presented in this study might provide the reader useful clinical information regarding the efficacy of focal HIFU. Moreover, in regards to the medium-term outcomes presented in the current study, the follow-up protocol for men after HIFU included discharge to local hospitals or primary care when the mpMRI and PSA were stable after at least 5 years from latest treatment. Recommendations for PSA frequency and a re-referral threshold for PSA were given, and men were referred back at this threshold for a further MRI and biopsies where indicated. Data were not always available on those men who were managed locally, but the risk of treatment failure for those men continuing to be managed locally would be likely to be lower than for those referred back in. The chosen methodology to censor the Kaplan Meier from those data could have induced a negative bias, potentially overestimating rates of failure. For clarity we also report, in table 2, that 73.7% of the whole cohort was free from further treatment.

In conclusion, this study involved a large retrospective series of patients treated with primary focal HIFU. Focal therapy for PCa using HIFU as energy source is a feasible therapeutic strategy with acceptable survival and oncological results at medium term, at least for patients with up to intermediate risk disease. For men treated in the later part of the cohort, a retreatment probability of 30% at 5 years was seen, with the majority of these men having repeat focal treatment. Re-do focal

treatment is a feasible technique whose functional and oncological outcomes are being studied. Moreover, the oncological control of the disease improved over the time, meaning that better patient selection and surgeon expertise are crucial in application of focal HIFU.

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Figures legend

Figure 1: a) Overall survival; b) Biopsy failure-free survival; c) Retreatment-free survival; d) Radical treatment-free survival

Figure 2: a) Retreatment-free survival according to the type of focal therapy strategy ; b) Retreatment-free survival according to Gleason score

Figure 3: a) Trend of Gleason score treated over time; b) Trend of T stage treated over time

Figure 4: Trend of multivariable 5-years retreatment probability over time

Supplementary figure 1: Any Gleason score biopsy failure-free survival

Supplementary figure 2: Biopsy failure free-survival in men receiving a follow-up biopsy

Supplementary figure 3: Any Gleason score biopsy failure-free survival in men receiving a follow-up biopsy

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Table 1: Descriptive characteristics of 1032 patient having primary focal HIFU for prostate cancer

Variables	**Overall (n=1032)** **n (%)**
Age at treatment (yrs)	
Median	65
IQR	60-70
PSA value (ng/ml)	
Median	7
IQR	4.9-9.7
Prostate volume (cc)	
Median	36.5
IQR	28-48
Number of biopsy cores	
Median	25
IQR	12-44
Number of positive biopsy cores	
Median	5
Range	3-8
Maximum cancer core length (mm)	
Median	6
IQR	4-8
T Stage	
1	78 (7.6)

2	802 (77.7)
3	123 (11.9)
Biopsy Type	
TRUS	230 (22.3)
TPM	802 (77.7)
Gleason Score	
3+3	203 (19.7)
3+4	654 (63.4)
4+3	159 (15.4)
4+4	16 (1.6)
Treatment type	
Focal	730 (70.7)
Hemi	302 (29.3)
Percentage of PSA reduction (%)	
Median	60
IQR	30-80

IQR: interquartile range; PSA: prostate specific antigen; TRUS: transrectal ultrasound guided biopsy; TPM: transperineal template prostate mapping

Table 2: Follow-up data of 1032 patient having primary focal HIFU for prostate cancer

Variables	Overall (n=1032) n (%)
Retreatment	
No	761 (73.7)
Yes	271 (26.3)
Number of retreatment	
One	271
Two	71
Three	18
Type of 1st additional treatment	
Focal HIFU	193
Focal Cryotherapy	12
EBRT	9
Radical prostatectomy	30
Whole gland HIFU	4
ADT	20
Other	3
Radical Treatment	
No	964 (93.4)
Yes	68 (6.6)
Patient receiving a FU biopsy	424 (41.0)
Patients with any PCa found at FU biopsy	325 (31.5)
Biopsy Failure	
No	777 (75.3)
Yes	255 (24.7)
Gleason at biopsy failure	

n, % on overall	
3+4	189 (18)
4+3	52 (5)
4+4	12 (1)
4+5	2 (<1)
Time to Retreatment	
Median	26
IQR	13-46
Time to Radical treatment	
Median	34
IQR	14-60
Time to Last FU	
Median	36
IQR (range)	14-64 (0-131)

FU: Follow up; EBRT: external beam radiotherapy; ADT androgen deprivation therapy; Biopsy failure: presence of csPCa at FU biopsy

Table 3: Multivariable logistic regression model predicting 5-year retreatment probability after focal HIFU for prostate cancer

Predictors	**Multivariable analysis**	
	OR (95% CI)	**p-value**
Year of surgery (yos)	0.77 (0.67-0.89)	<0.001
PSA	1.07 (1.01-1.12)	0.015
Primary Gleason score	1.76 (0.88-3.5)	0.1
Secondary Gleason score	0.96 (0.60-1.54)	0.8
MCCL*	1.05 (0.98-1.12)	0.18
Number of positive cores	1.01 (0.97-1.03)	0.9
T stage		
T1	Ref	-
T2	3.75 (1.63-9.82)	0.003
T3	5.0 (1.9-14.9)	0.002

* MCCL: maximum cancer core length