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ORIGINAL ARTICLE

A prospective clinical trial of HIFU hemiablation for clinically localized prostate cancer

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BACKGROUND: Focal therapy is an emerging mini-invasive treatment modality for localized prostate cancer aimed to reduce the morbidity associated with radical therapy while maintaining optimal cancer control. We report the mid-term oncological and functional results of primary hemiablation high-intensity focused ultrasound (HIFU) in a prospective cohort of patients.
METHODS: Over 8 years, hemiablation HIFU was primarily performed in 50 selected patients with biopsy-proven clinically localized unilateral, low–intermediate risk prostate cancer in complete concordance with the prostate cancer lesions identified by magnetic resonance imaging with precise loci matching on multimodal approach. Post-treatment follow-up included regular serial PSA measurements. Biochemical recurrence was reported using Stuttgart and Phoenix criteria. The latter was used as a threshold to offer whole-gland biopsies.
RESULTS: Complete follow-up was available for all patients and the median follow-up was 39.5 months (range: 6–94). Mean nadir PSA value was 1.6 ng ml^{-1}, which represents 72% reduction compared with initial PSA pre-treatment value ($P < 0.001$). Median time to achieve PSA nadir was 3 months. Biochemical recurrence, according to Phoenix and Stuttgart definition, occurred in 28 and 36% of patients, respectively. The 5-year actuarial metastases-free survival, cancer-specific survival and overall survival rates were 93, 100 and 87%, respectively. Out of the eight patients undergoing biopsy, six patients had a positive biopsy for cancer occurring in the untreated contralateral ($n = 3$) or treated ipsilateral lobe ($n = 1$) or bilaterally ($n = 2$). A Clavien–Dindo grade 3b complication occurred in two patients. Complete continence (no pads) and erection sufficient for intercourse were documented in 94 or 80% of patients, respectively.
CONCLUSION: Hemiablation HIFU therapy, delivered with intention to treat, for carefully selected patients affords mid-term promising functional and oncological outcomes. The effectiveness of this technique should be now compared with whole-gland radical therapy.

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INTRODUCTION

The past decade was marked by a widespread use of PSA-based prostate cancer screening. More men with localized prostate cancer are diagnosed and some are unnecessarily treated.[1] This stems mainly from the limited specificity of PSA and the poor sampling of cancers under two-dimensional transrectal ultrasound-guided biopsy.[2] The development of more accurate diagnostic strategies such as multiparametric magnetic resonance imaging (MRI) resulted in more accurate risk stratification based on identification and precise localization of the largest lesion with the highest grade, the so-called index lesion.[3] This is a timely issue given the new evidence suggesting that the natural history of the disease is predominantly driven by this index lesion.[4] Therefore, targeted treatment delivery to the index lesion while sparing other parts of the prostate appeared as a promising concept to avoid unnecessarily harm without compromising cancer control.

Various technologies are applied to treat focal areas of prostate cancer. Among these therapies, high-intensity focused ultrasound (HIFU) emerged as a valid mini-invasive therapy for localized prostate cancer, using focused ultrasound to generate areas of intense heat (85 °C) to induce tissue necrosis. The ability of HIFU to achieve thermo-ablation of targeted prostatic lesion was proven histologically.[5–7] Recent technological advances allowing real-time control and postoperative monitoring of the treated area increased significantly quality control.[8] This energy delivery system originally used to treat the whole prostate can technically be used to treat only parts of the gland. Despite encouraging perioperative, functional and disease control outcomes, a recent systematic review highlighted much of the controversies associated with the preoperative assessment techniques used to accurately localize the disease, the optimal candidates for a focal approach, the postoperative monitoring strategies and the long-term oncological outcomes.[9]

Although the debate about the role of hemiablation HIFU will continue until a randomized trial is conducted, there are clearly benefits to its use that are driving its ongoing implementation. Although it is still early to have a clear idea of how meaningful hemiablation therapy will be for functional and oncological outcomes, preliminary studies are extremely important to help define such a role. Herein, we report our experience with hemiablation HIFU in 50 carefully selected prostate cancer patients with an emphasis on our strategy of combined localization with multiparametric MRI and MRI-targeted biopsy.

MATERIALS AND METHODS

We undertook in 2007 a single-center prospective phase IIa feasibility study. Patients with histologically proven prostate cancer were selected if

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Table 1. Patients baseline characteristics

Mean age, years (median) (IQR)	73 (74) (70–77)
Mean PSA, ng ml^{-1} (median) (range)	6.6 (6.3) (3.9–8.3)
Clinical stage	
T1c (%)	16 (32)
T2 (%)	34 (68)
Gleason score	
3+3 (%)	30 (60)
3+4 (%)	14 (28)
4+3 (%)	6 (12)
D'Amico risk classification	
Low (%)	24 (48)
Intermediate (%)	26 (52)
Mean prostate volume, cm^3 (median) (IQR)	31 (27) (20–38)
MRI lesions	62
Base	29
Median peripheral zone	9
Transitional zone	7
Apex	13
Anterior	4
Mean number of lesions per patient	1.2
Mean follow-up, months (median) (IQR)	39 (34) (13–58)

Abbreviations: MRI, magnetic resonance imaging; IQR, interquartile range.

Table 2. Oncologic outcomes

Median ± s.d. PSA nadir, ng ml^{-1} (IQR)	0.91 ± 2.1 (0.52–2.07)
Median time ± s.d. to achieve PSA nadir, months (IQR)	3 ± 5.9 (1–6)
Stuttgart criteria (PSA nadir+1.2 ng ml^{-1}), patients (%)	18 (36)
Phoenix criteria (PSA nadir+2 ng ml^{-1}), patients (%)	14 (28)
Biopsy results, patients	8 (16)
Negative (%)	2 (25)
Positive contralateral (%)	3 (37.5)
Positive ipsilateral (%)	1 (12.5)
Positive bilateral (%)	2 (25)
5-Year actuarial Stuttgart recurrence-free survival rates	45% (CI 95%: 25–64)
Low risk	58% (CI 95%: 33–77)
Intermediate risk	27% (CI 95%: 2–63)
5-Year actuarial Phoenix recurrence-free survival rates	58% (CI 95%: 37–74)
Low risk	75% (CI 95%: 50–89)
Intermediate risk	36% (CI 95%: 5–64)
5-Year actuarial cancer-specific survival rates	100%
5-Year actuarial metastases-free survival rates	93% (CI 95%: 76–98)
5-Year actuarial overall survival rates	87% (CI 95%: 69–95)

Abbreviations: CI, confidence interval; IQR, interquartile range.

the positive biopsy pattern was in complete concordance with the prostate cancer lesions identified by MRI with precise loci matching on multiparametric approach. We included men with localized prostate cancer (clinical stage ⩽T2), a PSA < 15 ng ml^{-1}, a life expectancy of at least 5 years, and a prostate volume < 40 cm^3. We excluded patients who had extra-prostatic extension on multiparametric MRI, suspected regional lymph nodes or distant metastases on cross-sectional imaging or bone scan, and/or previous HIFU or radiation therapy to the prostate. All patients underwent hemiablation using HIFU delivered by the Ablatherm integrated imaging system (EDAP-TMS, Vaulx-en-Velin, France), performed by a single surgeon with a high level of experience in whole-gland HIFU. Hemiablation HIFU was defined as ablation of one lobe of the prostate and not just the index lesion because of device technical limitations. It is, therefore, a region-targeted therapy with emphasis on preserving contralateral neurovascular bundle, bladder neck and external sphincter regardless of individual lesion grade, volume or location and proximity to an ipsilateral neurovascular bundle. Safety margins were defined as follows: ⩾6 mm between the anatomical apex and the lowest section of the treated lobe; and ⩾4 mm when biopsies were positive at the apex. A limited transurethral resection of the only treated lobe was performed at the end of the HIFU session using bipolar resectoscope to prevent early acute urinary retention as well as sloughing of necrotic material requiring prolonged need for indwelling catheter. The details of the HIFU platform and description of the ablation technique in this group of patients have been previously described.[10] Our trial was approved by the Jules Bordet Institute Ethics Review Committee and all patients gave preoperative consent after a detailed discussion on limitations and benefits of hemiablation HIFU for the known clinically unilateral prostate cancer and the need for long-term follow-up with the intention to treat recurrent or progression lesion or *de novo* contralateral disease. Complications were prospectively recorded and graded according to the Clavien–Dindo score.[11] Postoperatively, patients were followed with serial serum PSA determinations and digital rectal examinations at 1, 3, 6 and 12 months and then every 6 months. Given the presence of an untreated half-prostate, an individual PSA nadir was identified in each patient. Biochemical recurrence was reported using Stuttgart (Nadir+1.2 ng ml^{-1}) and Phoenix criteria (Nadir+2 ng ml^{-1}).[12,13] The latter was used as a threshold to offer a new set of bilateral biopsies. Treatment failure was defined as positive biopsy of the treated area independently of the percentage of core involvement or if salvage radiation or hormonal therapy was needed during follow-up. Contralateral positive biopsy was not considered as a clinical failure but as a metachronous development of a contralateral disease and was treated by a secondary contralateral hemiablation according to our protocol. Urinary functional outcomes and erectile function were reported using physician reported rates. Overall quality of life and costs were not reported in this study. Kaplan–Meier analysis was performed to determine biochemical survival with failure defined according to Stuttgart and Phoenix criteria. Local control, morbidity data and functional outcomes are presented with descriptive statistics.

RESULTS

Baseline characteristics of the study population are summarized in Table 1. Overall, a total of 50 patients (median age 74 years, interquartile range (IQR): 70–77) were enrolled in this study with a mean follow-up of 40 months and a median follow-up of 35 months (IQR: 13–58). 11/50 (22%) patients had a follow-up >5 years. The median value of presenting PSA was 6, 27 ng ml^{-1} (IQR 3.92–8.3 ng ml^{-1}). Patients were stratified to risk groups according to D'Amico classification. All patients had at least one MRI lesion localized in the apex, the base, the median peripheral zone, the transitional zone and the anterior zone of the prostate in 13, 29, 9, 7 and 4 patients, respectively. The median pre- and post-treatment prostate volume was 27 cm^3 and 17 cm^3, respectively. Oncologic follow-up is summarized in Table 2. The median PSA nadir was 0.91 ± 2.1 ng ml^{-1} (IQR: 0.52–2.07) and the median time to achieve nadir was 3 ± 5.9 (IQR: 1–6). The distribution of percentile changes in PSA at 3 months post-operatively was reported using waterfall plot (Figure 1). A PSA nadir < 1 ng ml^{-1} was noted in 30 patients and 41 patients had a PSA nadir/initial PSA $< 50\%$. During follow-up, 18/50 (36%) and 14/50 (28%) patients exhibited PSA elevation ⩾1.2 and 2.00 ng ml^{-1} above nadir, respectively. Out of the 14 patients with PSA ⩾2.00 ng ml^{-1}, five patients were spared biopsy; two patients with metastases and three patients with unrelated severe comorbidities and a short life expectancy. Metastases were considered as a clinical failure and the two patients received androgen deprivation therapy, accordingly. The three patients with severe comorbidities died from unrelated confirmed cause during follow-up. One patient with no PSA elevation above nadir died also during follow-up from a heart attack. One patient with no PSA nadir refused biopsy and was considered as a clinical

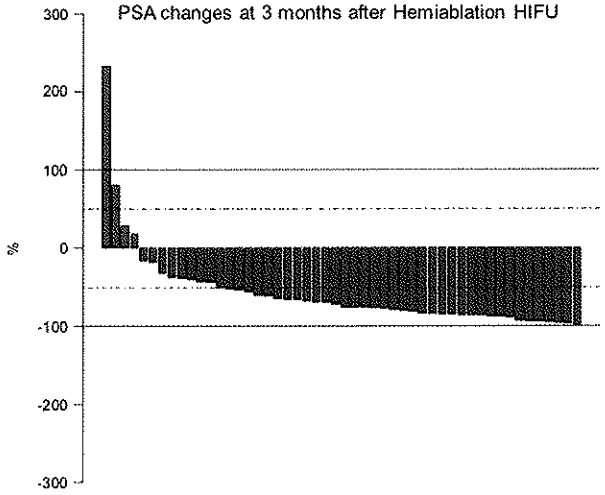

Figure 1. Percentile change in PSA within 3 months postoperatively in patients treated by hemiablation HIFU. HIFU, high-intensity focused ultrasound.

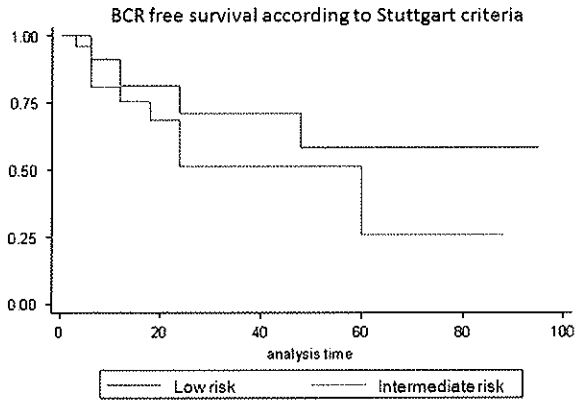

Figure 2. Biochemical recurrence (BCR)-free survival according to Stuttgart criteria.

failure. Finally, eight patients were offered a new set of bilateral biopsies. The results of these biopsies are shown in Table 2. Three patients showed a contralateral significant prostate cancer on biopsies and were treated with a contralateral hemiablation, further follow-up of these patients showed a biochemical response with new PSA nadir. Two patients had bilateral evidence of disease and one patient presented with ipsilateral positive biopsies. These patients were offered salvage radiation therapy with subsequent biochemical responses and new PSA nadirs. The remaining two patients with no evidence of disease on biopsy were followed-up. There was no cancer-related death during the follow-up. The 5-year actuarial Stuttgart and Phoenix recurrence-free survival rates were 45% (confidence interval 95%: 25–64) and 58% (confidence interval 95%: 37–74), respectively (Figures 2 and 3). When stratified according to D'Amico risk classification, patients with low risk had 58% (confidence interval 95%: 33–77) and 75% (confidence interval 95%: 50–89) of biochemical recurrence-free survival rates at 60 months of follow-up, according to Stuttgart and Phoenix, respectively (Figures 2 and 3). For patients in the intermediate risk group, these rates were significantly lower compared with those of the low-risk group ($P=0.007$ for the Phoenix criteria and $P=0.01$ for the Stuttgart criteria). The 5-year estimated overall survival rate, cancer-specific survival rate and metastasis-free survival rate were 87, 100

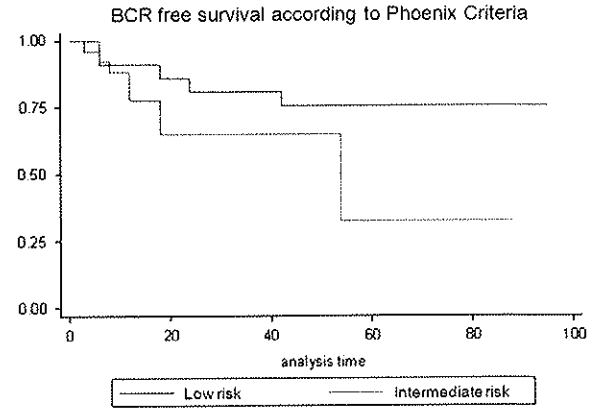

Figure 3. Biochemical recurrence (BCR)-free survival according to Phoenix Criteria.

Table 3. Adverse events and functional outcomes

Acute urinary retention (%)	4 (8)
Urinary tract infection (%)	3 (6)
LUTS (%)	9 (18)
Urethral stricture (%)	2 (4)
Erectile dysfunction	
Preoperatively potent and sexually active (%)	30 (60)
De novo erectile dysfunction (%)	6 (20)
Urinary incontinence	
Transient incontinence	7 (14)
Persistent incontinence	3 (6)

Abbreviation: LUTS, lower urinary tract symptoms.

and 93%, respectively. The incidences of the most frequent complications; namely, acute urinary retention, urinary tract infection, lower urinary tract symptoms, and urethral stricture, were reported in Table 3. A grade 3b complication occurred in two patients who had a urethral stricture managed by endoscopic urethrotomy. No patient presented any grade 4 or higher complication. Urinary functional outcomes were reported using physicians reported rates (Table 3). All patients were continent preoperatively. Seven patients presented with transient incontinence during follow-up from which three patients had persistent incontinence at 12 months postoperatively. The long-term pad-free continence rate was 94%. In preoperatively potent and sexually active patients ($n=30$), six patients (20%) developed postoperative erectile dysfunction.

DISCUSSION

At present, focal therapy is considered as an experimental and promising approach given the new genetic and clinical data suggesting that the natural history of the disease is predominantly driven by the index lesion.[3] Therefore, the revolutionary concept of 'less is more' could be applied for the treatment of the majority of prostate cancer patients.[14] Eradicating only the index lesion should result in reduced morbidity, better functional outcomes and similar long-term oncological results compared with treating the whole gland. Our study demonstrates the ability of hemiablation HIFU to offer mid-term disease control in carefully selected patients with localized prostate cancer. It is associated with low rates of urinary functional complications and erectile dysfunction comparable to reported rates in contemporary case series.[9,15–17]

In contrast, our biochemical control rate is lower than the biochemical control rates reported in focal therapy series.[18–20] Interpreting these results should integrate three major principles: optimal patient selection, ability of HIFU to ablate cancer and a good definition of success and failure.

First, optimal patient selection based on identification of high-grade patterns and accurate localization of the index lesion(s) is the principle key to move beyond the proof of concept. In fact, the index lesion volume and the Gleason score are reliable predictors of biochemical recurrence after radical treatment.[21,22] The so-called index lesion(s) represents the area where structural changes of the prostate by the tumor material reach a level of significant functional and metabolic modifications that can be characterized by contouring and hence designed for targeted biopsies and focal treatment.[23] The MRI-targeted approach had resulted in an increased cancer length per biopsy core, a better detection of high-grade and clinically significant cancers and an improved clinicopathological correlation. The absence of an index lesion on multiparametric MRI is associated with an negative predictive value of 93.7–97.5% for clinically significant disease and there is no or only minimal benefit in subjecting these men to biopsy.[24] Understandably, the number of men diagnosed having microfocal cancer lesions that may be clinically insignificant had consequently decreased. Furthermore, tumor multifocality is not predictive of biochemical failure after radical treatment.[22] That is why we selected our patients based on a complete match between the localization of the index lesion on MRI and the positive site of biopsy pattern on biopsy. Nevertheless, it is quite clear that real tumor burden is larger than the index lesion as shown in pathological specimen or as illustrated by metabolic imaging like positron emission tomography for prostate-specific membrane antigen (personal experience).[5,6] Accordingly, a safety area treated widely with energy ablation matches the actual technical limitations of our HIFU device to achieve true focal therapy but would be insufficient if the tumor is near the limits of treatment. We also avoided focal therapy in case of a contralateral disease. Currently, the presence of contralateral indolent disease should not be a contraindication for focal therapy.[25] In our study, five patients (10%) presented contralateral significant disease during follow-up, which represents a clear limitation of the rational of focal therapy.[26] Arguably, two of these patients had a higher Gleason grade than the index lesion. This had already been described in 16% of cases in a report of consensus panel.[27] Furthermore, it had been demonstrated that a microfocal indolent cancer outside the higher grade index lesion had the potential to metastasize several years after the diagnosis.[28] Another limitation could come from our identification of the index lesion based on nonvalidated standards in our early patients before the application of PIRADS score. However, this is not probably the case because of the high experience of our radiologist and his retrospective analysis of these studies in light of the new validated score.

Second, the ability of HIFU to ablate cancer completely on the treated area has been documented, but rates of clinically significant cancer as high as 17% were described in high-risk disease patients.[9] In our study, three patients with a Gleason 4+3 had a residual significant ipsilateral prostate cancer. When considering all patients enrolled in our study, overall positive biopsy rate is 24% if patients meeting the Phoenix criteria who did not undergo biopsy were considered as having a positive biopsy pattern and 12% if only patients with positive biopsy are counted. These results are in line with similar series reporting positive biopsy rates when biopsies were offered only for a cause.[9] Of note, all our patients with positive biopsy had a significant prostate cancer. Furthermore, even when hemiablation is applied, not all lesions can be adequately treated.[29] A safety margin had been defined and respected in our study in order to avoid sphincteric and bladder injury. Predominantly apically located lesions could, therefore, have been inadequately treated. Arguably, one patient with an ipsilateral positive biopsy had a Gleason 3+3 apical lesion.

Third, the definition of success and failure constitutes another major challenge in focal therapy. Clearly, patients who developed metastasis would be considered as a clinical failure but the absence of PSA nadir and the relative short duration between treatment and diagnosis of metastases would rather be in favor of a micrometastatic disease present at the moment of staging and treatment. In fact, it is well known that, unlike radiation therapy, early achievement of PSA nadir following ablation therapies provides immediate feedbacks on treatment efficacy.[30] Understandably, the absence of a PSA nadir following treatment will identify patients with residual cancer. This was the case for our two patients. In the future, recent advances in molecular imaging will have a role in better selecting these patients before undergoing focal therapies and will decrease clinical failure rates.[31] In addition, most of contemporary studies had misused Stuttgart and Phoenix criteria to define biochemical failure. In our opinion, it will be more appropriate to use the latter criteria as a threshold to offer biopsy rather than to define recurrence that is routinely applied in our practice. These thresholds should be defined to avoid unnecessary patient anxiety, non-justified explorations and repeated biopsies. A therapeutic approach that aims at reducing morbidity should not be hampered by the weight of procedures needed for validation of the methodology in light of data showing tissue ablation after radical prostatectomy.[5,6] In our study, these thresholds were more frequently reached in the group of patients with intermediate risk of prostate cancer compared with their lower risk siblings. This is in accordance with contemporary data demonstrating that tissue under ablation in aggressive prostate cancer tumor may be inadequately ablated.[32,33] However, numerous factors such as the proportion of initial PSA due to tumor, the amount of residual prostate tissue, the progression of BPH, the amount and extent of TURP and prostate volume are considered significant confounders that influence post-treatment value of PSA and PSA kinetics. Excellent cancer-specific survival rate, in our study, could not be considered as a clinical success given the short follow-up, the high percentage of low-risk patient and the small number of patients. The need for secondary contralateral focal therapy in three patients should be considered as a failure of the treatment approach rather than a clinical failure as these patients showed no ipsilateral cancer on biopsies. Although we cannot rule out the presence of a significant disease at the beginning of the treatment, this eventuality is less likely because these patients were carefully selected with a complete match between MRI images and biopsy results. However, these patients could have a small amount of multifocal disease from the beginning that progressed afterwards. These patients were subsequently treated with contralateral hemiablation and showed a biochemical response with a new PSA nadir.

In total, only three patients showed a residual tumor in the treated lobe and were correctly treated by salvage radiation therapy. These cases represent true failure of the treatment. As stated in a consensus panel meeting in 2010 even when HIFU is correctly applied, not all lesions can be adequately treated. The reason for this remains, however, unclear. Lesions with higher Gleason score are associated with increased neoangiogenesis. This could be responsible for a heat sink phenomenon that is tissue cooling by blood flow that causes thermal loss. The tissue under ablation in high-grade tumor may be inadequately ablated and is a high-risk site for persistent residual progressive disease and metastatic spread. Furthermore, despite being called hemiablation, significant portions of the prostate are left untreated to avoid sphincteric and bladder base injury. Of note, one of these patients had a recurrence in the apical zone.

Finally, no rectal toxicities were reported and the strategy was well tolerated in the genitourinary functional domains. It is

noteworthy to mention that the application of a limited TURP may have contributed to the toxicity seen above and beyond that of hemiablation HIFU. However, the absence of standardized instruments to assess functional outcomes represents a clear limitation of our study.

CONCLUSION

Our study suggests that hemiablation HIFU is a valid mini-invasive focal therapy strategy, feasible in day-to-day practice with satisfactory functional outcomes. Appropriate patient selection, good clinical experience with HIFU and a large-scale randomized prospective trial with at least 10 year of follow-up is needed to obtain sufficient metastases and cancer-related death to prove non-inferiority over radical treatments.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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