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ORIGINAL ARTICLE

Salvage Hemiablation High Intensity Focused Ultrasound for unilateral radio-recurrent prostate cancer



Hémiablation prostatique de sauvetage par des ultrasons focalisés à haute intensité pour des récurrences unilatérales après radiothérapie prostatique

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Hemiablation;
Local recurrence;
Oncological outcomes;
Functional outcomes

Summary

Objective. – To report the oncological and functional outcomes of salvage hemiablation high-intensity focused ultrasound (HIFU) in patients with unilateral radio-recurrent prostate cancer. **Patients and methods.** – Patients with biochemical recurrence (BCR) after primary radiation therapy and evidence of unilateral organ confined recurrence based on a complete match between mpMRI and MRI targeted biopsies were included. Patients with distant metastasis were excluded. Patients were followed with serial serum PSA determinations. BCR were defined using the Phoenix criteria. Complications were graded according to the Clavien score. IIEF-5 questionnaire was used to assess erectile dysfunction. Urinary incontinence was reported using physician reported rates.

Results. – A total of 10 consecutive patients (median age: 71 years, IQR: 69–76) were prospectively enrolled. The median pre-treatment PSA and post-treatment PSA nadir were 3.1 ng/mL (IQR: 1.54–8.59) and 1.52 ng/mL (IQR: 0.76–2.2), respectively. At a median follow-up of 41.5

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(IQR: 18–58) months, 50% of patients experience BCR. BCR free-survival rates at 24 and 36 months were 75% (CI95%: 31–93) and 60% (CI95%: 20–85), respectively. Urinary incontinence grade II occurred in two patients and the remaining patients were pad-free. One patient developed de novo erectile dysfunction requiring PDE5I. The erectile function scores decreased from a mean of 10.1 to 8.7.

Conclusion. – Hemiablation HIFU is an alternative to whole gland therapy in patients with unilateral radio-recurrent prostate cancer, which offers limited urinary and rectal morbidity, and preserves functional outcomes.

Level of evidence. – 3.

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MOTS CLÉS

Cancer prostate ;
Radiothérapie ;
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sauvetage ;
HIFU ;
Hémiablation

Résumé

Objective. – Reporter les résultats oncologiques et fonctionnels de l'hémiablation prostatique de sauvetage par des ultrasons focalisés à haute intensité chez des patients ayant des récurrences unilatérales après radiothérapie prostatique.

Méthodes. – Les patients ayant un cancer de la prostate localisé traités par radiothérapie primaire et présentant une récurrence prostatique unilatérale sans lésions suspectes à distance ont été inclus. Cette récurrence est documentée par une concordance entre la résonance magnétique multiparamétrique et une biopsie ciblée. Les patients sont suivis par des mesures de PSA jusqu'à progression biologique selon les critères de Phoenix. Les complications sont enregistrées prospectivement selon le score de Clavien. Le questionnaire IIEF5 a été utilisé pour déterminer la fonction érectile et la continence a été reportée par les cliniciens.

Résultats. – Dix patients ont été inclus avec une médiane d'âge de 71 ans (IQR : 69–76). La médiane du PSA avant le traitement était de 3,1 ng/ml (IQR : 1,54–8,59). La médiane du PSA après le traitement était de 1,52 ng/ml (IQR : 0,76–2,2). Après un suivi médian de 41,5 mois (IQR : 18–58), la moitié des patients ont présenté une augmentation du PSA au nadir + 2. Le taux de survie sans récurrence était de 60 % (IC95 % : 20–85) à 3 ans. Huit patients étaient parfaitement secs et neuf patients n'avaient aucun changement sur le questionnaire IIEF5.

Conclusion. – L'hémiablation est une alternative thérapeutique chez les patients ayant une récurrence unilatérale après radiothérapie prostatique. Elle offre des résultats oncologiques satisfaisants et altère peu les résultats fonctionnels.

Niveau de preuve. – 3.

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Introduction

Radiation therapy (RT) is a standard option for the primary management of men with localized prostate cancer (PCa) [1]. A recent analysis from a national community-based PCa registry revealed that approximately 25% of PCa patients in the 36 clinical sites that contributed data to the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry underwent RT as the primary treatment for PCa [2]. Despite improvement in long term survival rates in contemporary series using novel radiotherapy techniques that provide more targeted and escalated doses of radiation to the prostate, up to one third of patients will experience biochemical recurrence (BCR) [3]. The majority of these patients are treated with palliative androgen deprivation therapy (ADT) that can adversely impact the quality of life and increase the risk of cardiovascular events [4]. However, a non-negligible subset of these patients had recurrence limited to the prostate and can be offered salvage local procedures with curative intent [5].

At present, there is no level 1 evidence about the best post-RT salvage procedure and salvage radical prostatectomy (SRP), although challenging, is the recommended standard [1]. However, most urologists are reluctant to offer surgery and prefer to implement less invasive alternatives such as Cryotherapy, Brachytherapy or High Intensity Focused ultrasound (HIFU) [6]. However, by extrapolating from clinical studies involving primary management, each post-radiation salvage whole gland therapy carries higher risks of genitourinary and bowel complications compared to its implementation in the initial management of PCa patients [6].

Recently, focal therapy has been proposed as an effective therapy in patients with clinically significant unilateral PCa that offers limited morbidities and promising functional outcomes and preserves health-related quality of life [7]. Of note, local radio-recurrent PCa is unilateral in two-third of cases [8]. This means that focal salvage therapy could also be investigated in patients with unilateral local radio-recurrent disease. Some researchers had examined

such an approach using Cryotherapy and HIFU [9–15]. They demonstrated that focal salvage therapy is feasible and safe with acceptable short-term oncological outcomes and good functional results. However, all these authors stressed on carefully selecting patients before offering focal salvage therapy. The selection process should incorporate the most effective method to exclude distant metastasis at the time of treatment and the most accurate diagnostic strategy to identify local recurrence. In the present study, we report our experience with salvage hemiblention HIFU in carefully selected patients with unilateral radio-recurrent PCa with an emphasis on our strategy of combined localization with mpMRI of the prostate and MRI targeted biopsy.

Patients and methods

Between 2013 and 2016, 10 consecutive patients with a BCR defined using Phoenix criteria (nadir + 2 ng/mL) [16] after primary RT underwent mpMRI of the prostate, bone scan and pelvic computed tomography. Patients with organ confined unilateral recurrence based on a complete match between mpMRI and MRI targeted biopsy and no evidence of regional or distant metastases were included. All patients included had a life expectancy > 5 years. Our study was approved by the local ethics review committee and all patients gave pre-operative consent.

Multiparametric MRI and biopsies

Patients underwent a mpMRI of the prostate on a 3 Tesla magnet Verio system (Siemens A.G., Erlangen, Germany) using an external multichannel phased array coil and an endorectal coil (Medrad Inc.). The conduct and reporting of mpMRI were conformed to European Society of Urogenital Radiology recommendations in the Prostate Imaging Reporting and Data System version 1 document [17]. Of note, examinations were interpreted by a trained radiologist with 20 years' experience. Patients with suspected radio-recurrent disease on mpMRI underwent MRI-targeted biopsy. The details of our biopsy platform (Medison/koelis® Urostation) and the description of our biopsy technique have been previously described [18].

HIFU hemiblention

All the procedures were performed under spinal anesthesia by a single high volume surgeon using the Ablatherm® Integrated Imaging device (EDAP TMS, Vaulx-en-Velin, France). The details of our HIFU platform and description of our hemiblention techniques have been previously described [19]. It is noteworthy to recall that hemiblention refers to ablation of one lobe of the prostate and not just the index lesion because of device technical limitations. Safety margins in patients with a radio-recurrent disease were defined as follows: ≥ 4 mm between the anatomical apex and the lowest section of the treated lobe. If biopsies were positive at the apex, the firing lesions were held close to the sphincter. A limited transurethral resection was performed at the end of the HIFU session [20].

Follow-up

Patients were followed with serial serum PSA determinations at 1, 3, 6, and 12 months and then every 6 months. Patients experiencing BCR according to Phoenix criteria were offered bone scan, pelvic CT and mpMRI of the prostate. Patients with no evidence of regional or distant metastases underwent 68Ga-PSMA positron emission tomography (PET) hybrid imaging. Only patients suspected to have local recurrence underwent subsequent MRI targeted biopsy. Patients with histologically confirmed local recurrence were offered a redo-HIFU particularly when the recurrence is in the untreated contralateral lobe. Complications were graded according to Clavien score [21]. IIEF-5 questionnaire was used to assess erectile dysfunction [22]. Urinary incontinence was reported using physician reported rates and graded according to Stamey into three grades [23].

Results

Baseline and tumor characteristics of the study population are summarized in Table 1. Median time between primary radiation therapy and focal salvage HIFU was 4.2 years (IQR 2.8–6.1). ADT was used concomitantly to radiation therapy in 3 patients. At the time of salvage therapy, none of our patient was on ADT and total testosterone was in the normal range. All patients had a histologically confirmed organ confined unilateral radio-recurrent clinically significant PCa without evidence of regional or distant metastases on conventional imaging. Only one patient had a Gleason 6 cancer, but cancer length was > 5 mm and the patient was treated, accordingly. The oncologic outcomes after salvage hemiblention HIFU are summarized in Table 2. All patients experienced a PSA nadir in the postoperative setting. At a median follow-up of 41.5 (IQR: 18–58) months, 5/10 (50%) of patients experienced BCR according to Phoenix criteria. Local recurrence was identified in two patients at MRI. One of these had a suspicious bilateral recurrence with distant metastasis identified on bone scan and the other one had ipsilateral disease with no evidence of metastasis on 68Ga-PSMA. The latter patient underwent an MRI targeted biopsy and was subsequently treated by SRP. The operative specimen showed a clinically significant cancer located at the ipsilateral apex. The procedure was challenging but with no perioperative complications. PSA was undetectable after the operation but the patient developed urinary incontinence. Two patients developed only distant metastases and one patient had a BCR without evidence of clinical recurrence on 68Ga-PSMA. All patients with distant metastases were offered ADT. The only patient with rising PSA and no evidence of recurrence was offered surveillance. BCR free-survival rates at 24 and 36 months were 75% (CI95%: 31–93) and 60% (CI95%: 20–85), respectively. The procedure was well tolerated in the urinary and gastro-intestinal domains. At the end of the follow-up, two patients presented urinary incontinence grade II and the remaining patients were pad-free and leak-free. One patient developed de novo erectile dysfunction requiring PDE5I. The erectile function scores decreased from a mean of 10.1 to 8.7. There were no rectal toxicities at total cohort follow-up.

Table 1 Baseline and tumor characteristics of 10 patients with organ confined unilateral radio-recurrent prostate cancer before treatment by hemiablation HIFU.

	Radiation therapy	Salvage focal HIFU
Median age (IQR), years	68 (65–73)	71 (69–76)
PSA pre-treatment, ng/mL	7.2 (5–11)	3.1 (1.54–8.59)
Gleason score		
≤ 6	2	1
3 + 4	5	4
4 + 3	1	2
4 + 4	1	2
4 + 5	1	1
D'Amico risk group		
Low	2	1
Intermediate	3	4
High	3	4
Unknown	2	1
Median prostate volume (IQR), mL	37 (21–47)	20 (8–22)

Table 2 Oncologic outcomes of 10 patients with organ confined unilateral radio-recurrent prostate cancer after treatment by hemiablation HIFU.

Median ± SD PSA nadir, ng/ml (IQR)	1.52 ± 2.1 (0.52–2.07)
Median time ± SD to achieve PSA nadir, months (IQR)	1 ± 1.9 (1–3)
Phoenix criteria (PSA nadir + 2 ng/ml), patients (%)	5 (50%)
Multiparametric prostate MRI (n = 5)	
Positive	2
Negative	3
Metastases on bone scan and/or pelvic CT	3
68Ga-PSMA PET imaging (n = 2)	
Positive (site)	1 (prostate, Fig. 1)
Negative	1
Biopsy results (n = 1)	
Clinically significant disease	1
Clinically insignificant disease	0
No cancer	0
24 months actuarial Phoenix recurrence free survival rates	75% (CI95%: 31–93)
36 months actuarial Phoenix recurrence free survival rates	60% (CI95%: 20–85)

Discussion

Local recurrences after primary PCa therapy lead to disease progression and at time death. Therefore, complete local tumor eradication is mandatory to improve long-term cancer control. SRP is the most studied procedure with reported 10-year BCR free survival rates ranging from 28% to 53% [24]. Cancer specific survival and overall survival rates as high as 80% were also reported [25]. However, morbidity of such an approach could be quite high with up to 1/3 of patients experiencing grade 3 and 4 complications [26]. Additionally, the surgical technique is challenging and functional outcomes are poor [27]. Thus, the majority of surgeons prefer to manage these patients expectantly and to offer ADT for metastasis [28]. By doing so, most of these patients will live more than 10 years but some of them will also progress and succumb to their disease. That's why some surgeons have used energy-based modalities but retrospective case series reporting on salvage Cryotherapy, HIFU or brachytherapy for radio-recurrent PCa yielded lower oncologic outcomes

compared to SRP [6]. Therefore, the need for a minimal invasive approach that exhibit a favorable balance of harms and benefits opened the door to apply focal therapy as an alternative salvage treatment of recurrent disease after RT. Eisenberg and Shinohara were the first to report results of focal Cryotherapy in properly selected patients with a unilateral focus of disease recurrence after radiotherapy [12]. A recent observational study of the Cryo On-Line Data (COLD) Registry suggested that patients treated with focal cryotherapy were at lower risk of urinary incontinence, erectile dysfunction, urinary retention, and recto-urethral fistula compared to their peers treated with whole gland Cryotherapy [13]. Oncologic outcomes appeared also comparable to whole gland cryotherapy with BCR free survival rates varying between 47% and 54% at 5 years [9,14]. Recently, a pilot study examined 39 patients with organ confined radio-recurrent PCa treated by focal HIFU [10]. The authors reported at a median follow-up of 17 months a BCR free survival rates of 69% and 49% at 12 and 24 months, respectively. The procedure was well tolerated with only one



Figure 1. A 68Ga-PSMA PET/CT obtained in a 56 years old patient presenting with a BCR (PSA=3,8 ng/ml) 13 years after external beam radiation therapy. Coronal views demonstrate a suspicious hypermetabolic lesion in the apical right prostatic lobe and no evidence of regional or distant metastases.

patient developing a recto- urethral fistula that was managed conservatively. In a prospective two-center study that examined 48 patients, Baco et al. demonstrated local recurrence in 17% of their patients [11]. The patient and cancer characteristics as well as the morbidity, the functional and oncologic results of these different studies are summarized in Table 3. In the present study, local recurrence was documented in one patient and suspected in another one. Three patients presented metastasis in the relative short follow-up period. Of note, these patients had not been primarily investigated by 68Ga-PSMA and could have presented micrometastatic disease at the time of staging. Despite a decrease in their PSA, these patients probably did not benefit from salvage treatment. Therefore, a better selection of patients based on the most effective method for metastatic evaluation is mandatory in future studies. In total, 5 patients were free of BCR at the end of follow-up. Another point is the early achievement of PSA nadir that provides immediate feedback on treatment efficacy and allows identification of patients with residual cancer. These patients could be offered another curative treatment even in the salvage setting. In total, ADT was avoided in 70% of patients. Additionally, 60% of patients had an effective PSA nadir and could be considered cured. However, a longer

follow-up is necessary to ascertain this hypothesis. Furthermore, the treatment was safe and relatively well-tolerated. Our functional outcomes were in line with those reported in contemporary series [10,11] with only two patients developing moderate urinary incontinence.

Meanwhile we acknowledge several limitations to our study. First, control biopsy was not performed systematically in a protocol based scenario but offered only in patients who experienced BCR with no documented distant metastases. This could have overestimated local control but it would be difficult to convince our ethical board to subject all patients to an invasive diagnostic procedure when its results would not alter the treatment decision-making. Second, another limitation is the absence of a validated definition of failure for HIFU in general and for focal therapy in particular. While we did use Phoenix criteria to define a threshold to offer biopsy, this definition was not used to define failure in our study. Third, despite the fact that all our patients were selected based on a complete match between mpMRI and MRI targeted biopsy, 68Ga-PSMA was not used to rule out metastatic spread before inclusion. In our case series, patients who developed metastasis shortly after the treatment were considered as clinical failures but the relative short duration between treatment and diagnosis of

Table 3 Published series of focal salvage treatment for unilateral radio-recurrent prostate cancer.

First author (year)	Number of patients	Design of the study	Follow-up (range), months	Median age	PSA before salvage treatment (range), ng/mL	Proof of local recurrence	Metastatic Evaluation	BCR criteria after salvage treatment	BCR-Free Survival Rates	Continenence rate	Potency rate	Recto-urethral Fistula rate
Yong-Hong (2013)	91	R	15 (1–97)	71.7	4.8 (0–926)	NA	NA	Phoenix criteria	1-year: 95.3% 3-year: 72.4% 5-year: 46.5%	94.5%	50%	3.3%
Bomers (2013)	10	P	NA	67	NA	MRI targeted biopsy	Whole body MRI	NA	NA	NA	NA	0%
Wenske (2013)	55	R	47.8 (1.6–203.5)	66	7.0 (1.2–185.8)	TRUS guided biopsy	Bone scan + abdominopelvic CT scan	Phoenix criteria	5-year: 47% 10-year: 42%	NA	NA	5.5%
De Castro Abreu (2013)	25	R	31 (4–90)	71	2.8 (0.1–8.2)	TRUS guided biopsy	Bone scan + abdominopelvic CT scan or MRI	Phoenix criteria	5-year: 54.4%	100%	28.6%	0%
Eisenberg (2008)	19	R	18 (6–33)	70.6	3.3 (0.28–8.96)	TRUS guided biopsy	Bone scan + abdominopelvic CT scan	Phoenix criteria	1-year: 89% 2-year: 79%	94.7%	40%	0%
Ahmed (2012)	39	R	17 (10–29)	70.5	4.6 (0.02–27.9)	MRI targeted biopsy	Bone scan	Phoenix criteria	1-year: 69% 2-year: 49%	87%	NA	0.03%
Baco (2013)	48	P	16.3 (10.5–24.5)	68.8	14.2 (2.9–70)	MRI targeted biopsy	Bone scan + abdominopelvic CT scan or MRI	Phoenix criteria	1-year: 83% 2-year: 52%	75%	NA	0%
Present study	10	P	21.5 (8–28)	71	3.1 (1.54–8.59)	MRI targeted biopsy	Bone scan + abdominopelvic CT scan	Phoenix criteria	1-year: 75% 2-year: 60%	80%	NA	0%

metastases would rather be in favor of a micrometastatic disease present at the moment of staging. Fourth, the cohort was small with a short follow up and no control group to assess collateral damage and functional and oncologic outcomes.

Conclusion

Our study suggests that hemiablation HIFU can be an alternative strategy for patients with radio-recurrent unilateral PCa. Appropriate patient selection based on a strategy combining mpMRI and MRI targeted biopsy as well as 68Ga-PSMA and a large scale prospective trial with at least 5 years of follow-up is needed to obtain a clear idea of how meaningful hemiablation therapy will be for functional and oncological outcomes in the salvage setting.

Disclosure of interest

The authors declare that they have no competing interest.

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