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SHORT COMMUNICATION

Multimodal treatment in focal therapy for localized prostate cancer using concomitant short-term androgen deprivation therapy: the ENHANCE prospective pilot study

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ABSTRACT

Focal therapy (FT) for localized prostate cancer (PCa) is emerging to reduce adverse effects of radical treatments, while maintaining comparable oncological outcomes. However, an area for improvement still exists and a gap in cancer control needs to be filled by complementing FT with additional forms of treatment to minimize failures. Part of the recurrences/persistences after FT may be related to PCa microenvironment favouring tumorigenesis of benign tissue or indolent PCa left untreated. FT-induced inflammation may alter microenvironment in a pro-tumorigenic fashion. On the contrary, androgen deprivation therapy (ADT) modifies PCa microenvironment and suppresses PCa tumorigenesis. So far, ADT has proven effective in combination with radiotherapy, has been evaluated in the context of AS and to reduce prostate volume in the context of whole-gland high-intensity focused ultrasound (HIFU). However, no prospective data exist evaluating FT/ADT combination in terms of cancer control for the treatment of localized PCa. We will perform the ENHANCE pilot study (EvaluatioN of HIFU Hemiablation and short-term AndrogeN deprivation therapy Combination to Enhance prostate cancer control). Twenty men with localized unilateral csPCa will receive HIFU hemi-ablation and concomitant short-term ADT. Oncologic efficacy will be assessed 1-year post-treatment considering the persistence/recurrence of csPCa. Complications and functional outcomes will be evaluated using internationally validated questionnaires. If the hypothesis of an oncological benefit together with no relevant additional toxicity is confirmed, the ENHANCE study will allow an evidence-based starting point for a large randomized controlled trial against the standard of care and/or HIFU hemiablation alone.

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KEY WORDS: Prostatic neoplasms; High-intensity focused ultrasound ablation; Androgens.

In prostate cancer (PCa) treatment we are still far from perfection. However, technological progress is continuously extending our boundaries over their limits.

Thirty years ago, PCa surgery meant impotence in almost all patients, significant incontinence and biochemical recurrence risks. Nowadays, more than 80% of men will be free of disease at 5 years, continent, and with a good chance of preserving erections in case a nerve-sparing

procedure has been performed.[1] Similarly, radiotherapy has dramatically evolved enhancing oncological control and functional results.

Focal therapy (FT) for localized PCa is emerging to further reduce the adverse effects of radical treatments, whilst maintaining comparable oncological outcomes[2, 3] and high interests of the Urological community are present towards this approach.[4]

At a short-to-medium term interval, outcomes are promising, proving its safety and, so far, its effectiveness.[2]

Nonetheless, approximately 20% of men have a positive post-treatment biopsy at 1 year and up to 50% re-treatment rates are described when approaching ten years results.[2, 5] Is this enough or should we seek for a change?

Probably, an area for improvement still exists and a gap in cancer control needs to be filled by complementing the procedure with additional forms of treatment to improve oncological outcomes and minimize treatment failures.

FT failures could be in part attributed to the presence of undetectable (invisible) cancer foci owing to the limitations of the currently available imaging and biopsy techniques.[6, 7] As FT ablates the index/dominant (visible) lesion, 'invisible' foci could be missed, representing an appealing argument against FT given that PCa is a multifocal disease in the majority of men.[6, 7]

Another compelling point is indeed tumor microenvironment, which, in PCa, consists in multiple indirect and direct cellular interactions: tumor cells coevolve dynamically with immune cells, stromal fibroblasts, mesenchymal stem cells and blood vessels.[8, 9]

It is not completely clear whether at least part of FT recurrences may be related to non-aggressive lesions taking the position of an index PCa focus and/or PCa index lesion signaling altering benign tissues behavior, eventually resulting in significant disease.[8, 9]

In this context, FT-induced inflammation may favor tumorigenesis of the untreated surrounding tissues, damaging benign tissues and/or favoring the transition of indolent PCa foci into clinically significant PCa; first, through direct genetic changes; second, through indirect changes, causing microenvironment modifications.[9]

Not unlike the majority of cancer therapies, FT treats the incipient PCa cells/lesion but does not target microenvironment modifications which may constitute an additional and ideal target to enhance oncological control.[9]

Indeed, whether and how we could improve FT results and bring it over its limits is an issue in need of elucidation, also given lack of data about long-term outcomes.

This seemingly baffling scenario is not without possible answers, one of them being Androgen deprivation therapy (ADT). ADT modifies tumor microenvironment in an antitumorigenic way and suppresses PCa growth and progression.[10]

From an oncological perspective, ADT has been reported to increase the overall survival in men with localized intermediate- to high-risk PCa when combined with external beam radiation therapy (EBRT) or radical prostatectomy.[11] D'Amico *et al.* randomly compared combined EBRT and 6-month ADT to EBRT alone for localized unfavorable PCa and reported an 8-year overall survival improvement with the combination therapy.[12] The ROGT 94-08 randomized trial comparing EBRT alone to EBRT with 4-months ADT in 1979 PCa patients showed a disease free and overall survival improvement at 10-years (hazard ratio for death with radiotherapy alone, 1.17; P=0.03).[13]

From a functional perspective, several groups already used short-term ADT for whole gland HIFU with the purpose of reducing the prostate volume and postoperative urinary symptoms,[14-16] reporting no relevant toxicity. Short-term ADT has been also investigated in the context of active surveillance[17] and other trials are under way.[18]

From a biological perspective, recent findings support the use of an ADT-based multimodal approach in the context of FT. Mice bearing PCa xenografts showed improved cancer control of FT and ADT combined compared with one of the two alone.[19] Immuno-histochemical and morphometric analysis of microcirculatory networks proved HIFU and ADT allow higher reduction of microvessels density both in tumor and non-tumor glands in comparison with HIFU monotherapy. Furthermore, retention of microcirculation in residual non-tumor glands was associated with a higher probability of PCa, thus supporting

a possible role for neoadjuvant ADT as an accessory mechanism to modulate retained PCa elements and prostatic microenvironment.[20]

However, to date, there is no prospective data assessing the role of HIFU FT/ADT combination for the treatment of localized PCa in terms of cancer control.

We will soon perform the ENHANCE (EvaluatioN of HIFU Hemiablation and short term AndrogeN deprivation therapy Combination to Enhance prostate cancer control) pilot, open-label, single-arm study to assess the oncologic efficacy and safety, in terms of functional outcomes and morbidity, of HIFU hemi-ablation in combination with concomitant short-term ADT for the treatment of low- to intermediate-risk localized PCa, including unilateral csPCa patients (detailed study protocol available at Clinicaltrials.gov - Identifier: NCT03845751).

Our aim is to examine the hypothesis that combining the focal effects of HIFU with the systemic effects of ADT might eradicate PCa cells by targeting the "visible" index foci (through HIFU) and tumor microenvironment, knocking down the "invisible" foci and aberrant PCa related signaling (through ADT), consequently minimizing treatment failures.

Research protocol was approved by the Comité d'Evaluation des Protocoles et d'Aide à la Recherche (CEPAR), Institut Mutualiste Montsouris, Paris (France), on April 12th 2019, as a proof of ethics approval by an independent committee (Institutional Review Board), reference number no. 2019-03.

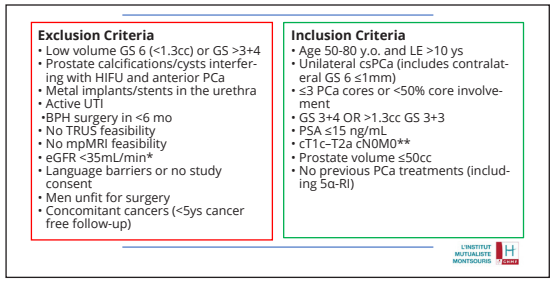

Figure 1.—Main ENHANCE Inclusion and Exclusion Criteria.
*As unable to tolerate Gadolinium contrast agents (mpMRI); Men not reaching an androgen castration status at three months post-ADT administration will be included in the trial but not in the final analysis; **staging will be performed according to the EAU Guidelines.
LE: life expectancy; GS: Gleason Score.

Inclusion and exclusion criteria are displayed in Figure 1. The study will follow the IDEAL criteria for reporting surgical innovations (Stage 1 IDEAL recommendations).

Twenty men will receive short-term ADT, 3-month depot of 22.5 mg of leuprolide acetate and bicalutamide 50 mg once per day for 3 months, starting one month prior to the sched-

TABLE I.—*Patients evaluation protocol at baseline and during the 12 months follow-up. ^mpMRI will be conducted according to international standards (b value of at least 1400 and PIRADS-v2 criteria). Both mpMRI performed at our institution and outside our institution will be included if performed according to the required standards. Two expert radiologists will independently double report mpMRI, blinded to each other and to clinical data. Prostate biopsies will be reported according to the START criteria - MRI-targeted prostate biopsy (3 cores per each target lesion + 12 random cores) or transperineal template mapping biopsies.*

Evaluation	Baseline	1 month	2 months	3 months	6 months	12 months
History and PE	√	*		√	√	√
PSA	√		√	√	√	√
Mp-MRI^ (and PV)	√			√	*	√
Biopsy	√			*	*	√
Testosterone	√		√	√	√	√
IIEF-5	√			√	√	√
ICSmaleIS questionnaire	√			√	√	√
IPSS	√			√	√	√
Clavien Dindo	√	√		√	√	√
CTCAE v5	√	√		√	√	√

PE: physical examination; PV: prostate volume; PSA: prostate specific antigen; IIEF-5: International Index of Erectile Function-5; ICSmaleIS: International Continence Society, male Incontinence Symptoms - continence will also be evaluated considering the number of pads used per day); IPSS: International Prostate Symptom Score; CTCAEv5: Common Terminology Criteria for reporting Adverse Events.
√Indicates routinely performing the concerned evaluation; *indicates performing the concerned evaluation when necessary (mp-MRI and subsequent prostate biopsy are performed before 12 months if biochemical recurrence occurred according to the Phoenix criteria: PSA rise by 2ng/ml or more over the PSA nadir value).

uled HIFU hemi-ablation (Focal ONE HIFU device - EDAP TMS, Lyon, France).

Follow-up protocol and outcomes assessment will include clinical history and examination, digital rectal examination, PSA, specified validated questionnaires and tests which are detailed in Table I.

The primary outcome will be the proportion of treatment failures at 12 months (Figure 2), identified as men harboring csPCa, based on transperineal template mapping biopsies and/or multiparametric magnetic resonance imaging (mpMRI)-targeted biopsies and defined according to any Gleason Score ≥7, high-volume (>1.3 cc) Gleason Score 6, ≥7 mm of PCa in any core and/or ≥20% of positive cores.

Other relevant outcome measures will include: 1) erectile function at 12 months compared to baseline using IIEF-5 Score, defining potency as IIEF-5 ≥22 with/without PDE-5 inhibitors; 2) Continence at 12 months measured by International Continence Society, male Incontinence Symptoms questionnaire and number of pads used per day, considering continent pad-free, leak-free men; 3) Morbidity/treatment toxicity as graded by Clavien-Dindo classification, recorded according to the EAU guidelines on reporting complications and the Common Terminology Criteria for reporting Adverse Events (CTCAE v5); 4) proportion of men requiring salvage secondary PCa interventions due to biochemical recurrence (Phoenix criteria). Changes of free and total PSA, testosterone, prostate volume and Voiding function (IPSS Score) will be also assessed.

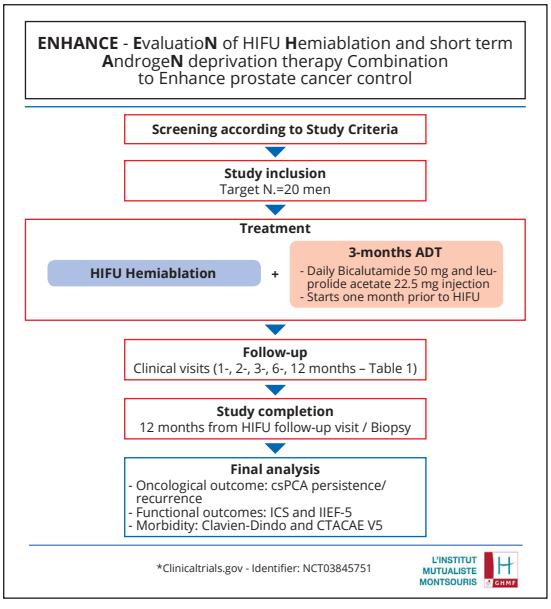

Figure 2.—Study flowchart summary.

Upon conclusion of this study, we expect to clarify the potential role of the multimodal approach involving short-term ADT and HIFU Hemi-ablation for the treatment of localized PCa and to record possible treatment-related side effects. If an oncological benefit together with no relevant additional toxicity is confirmed, the ENHANCE study will allow an evidence-based starting point for a large randomized controlled trial against the standard of care and/or HIFU hemi-ablation alone.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions.—Giancarlo Marra, Paolo Dell'Oglio, Mohammed Baghdadi, Rafael Sanchez-Salas: development of the research protocol; Giancarlo Marra, Rafael Sanchez-Salas: in charge of the experimental phase; Giancarlo Marra: preparation of the manuscript; Xavier Cathelineau: contribution to reviewing the research protocol, supervision of the protocol; Rafael Sanchez-Salas and Xavier Cathelineau: contribution to the reviewing of the manuscript. All authors read and approved the final manuscript.

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