Non-invasive focal therapy of organ confined prostate cancer: Phase I study using MrgFus and excision pathology for efficacy assessment

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Aims and objectives

Aims

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males worldwide [1]. During the last decade, proactive screening for prostate cancer led to a dramatic stage migration resulting in proportionally more men being diagnosed at early stages while the tumor is still organ confined [2]. In the last years, many different minimally invasive procedures have been developed as an alternative option to standard therapies (surgery and radiotherapy); among these therapies, High Intensity Focused Ultrasound (HIFU) emerged as a valid mini-invasive therapy for localized prostate cancer. Over the past 15 years, more than 30,000 Ultrasound (US) guided HIFU ablations of the prostate have been performed worldwide [3]. Wide experience obtained with US-guided HIFU suggests that this kind of focal therapy may become a valid alternative in low-risk prostate cancer, in particular for patients with localized disease (stage T1-T2 Nx-N0 M0), those with disease not suitable for radical prostatectomy or those who refuse surgery. It could also been used as a salvage therapy for locally proven recurrence of prostate cancer after radiotherapy or brachytherapy failures. Even if many authors have reported brilliant results by using US-guidance (e.g. Crouzet et al. presented a multicenter study with 803 patients in which 78 % of these didn't show evidence of residual cancer at the post-treatment biopsy [4]), some relevant limits in treatment efficacy assessment can be found with this approach, substantially related to the intrinsic technical nature of conventional US, not able to provide real-time control on ablative procedure or to define treatment effects with high spatial resolution. In this scenario, MR guidance provides a better contribution to HIFU ablation because of its superior spatial and contrast resolution; moreover, MRI allows a thermometric real-time treatment monitoring. However, at present, the literature reports only animal tests [5] and occasional case descriptions of MRgFUS ablations of prostatic cancer in humans [6-7].

Objectives

Our study aimed to assess safety and effectiveness of non-invasive MR-guided focused Ultrasound Surgery (MRgFUS) treatment of localized prostate cancer in a phase I, treat and resection designed exploratory study.
Methods and materials

Study population

After institutional review board approval, 11 patients with unifocal biopsy proven prostate cancer (low-to-intermediate risk: PSA<12 and Gleason<3+4), confirmed on a previous multiparametric 3-T MRI, also including dynamic contrast enhanced (DCE) imaging (Gd-BOPTA), underwent MRgFUS ablation (ExAblate, InSightec). Patients with a Gleason score # 8, multifocal or bilateral prostate cancer, with a previous pelvic or rectal cancer and with an American anesthesiological (ASA) score # 3 were excluded from the study. All patients were scheduled to a subsequent radical laparoscopic prostatectomy.

MRgFUS procedure

All treatments were performed with an endorectal focused ultrasound ablation system integrated within a 3T MR scanner. The endorectal probe, which contains a 990-elements phased-array focused ultrasound transducer (Figure 1), was inserted into the rectum and filled with degassed water to eliminate residual air within the interface between the prostate and the rectal wall (Figure 2). MRgFUS treatment was carried out on the MR identifiable lesion (<2) using a patient specific energy (3000-8500 J) and real time MR thermometry (Figure 3). Patients were positioned supine on the scanner table under spinal anaesthesia (0.5% iperbaric bupivacaine 2-3ml in association with morphine 25-50mcg) and a 16F Foley catheter was used to ensure urine flow during the procedure. Targeting was confirmed using low-power subtherapeutic sonications monitored with proton resonance frequency (PRF) shift method for MRI thermometry [8], overlapping temperature maps onto anatomic images. After confirmation, treatment started using full-energy sonications in the target area and monitoring in real time each sonication with PRF sequences. Sonicated volumes were considered successfully ablated when the temperature in the target area reached a threshold of 65°C.

Post-procedure

Dynamic contrast enhanced (DCE) imaging after ablative procedure were performed in order to obtain a quantitative Non-perfused volume (NPV); these values were compared with histopathological findings for necrosis assessment.
Fig. 1: On a-b images, endorectal probe containing a phased array focused ultrasound transducer of 990-elements. On c, focused ultrasound ablation system integrated within a 3T MR scanner.

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**Fig. 2**: Morphological T2-MRI acquired before MRgFUS treatment showing the prostatic gland with the target pathological area and the other structures to preserve during procedure, such as rectal wall and neurovascular bundle.

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Fig. 3: Treatment planning: sonication. Dedicated treatment-planning software automatically generates a treatment program, including type and number of sonications required to ablate specific regions.

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Results

No severe complications were observed in all subjects during or immediately after the procedure. The average procedure time was 90 min (range: 60-125). Mean maximum temperature measured in the target lesions was 82 ± 2 °C, with a rectal wall temperature of 35 °C.

Radical Prostatectomy (RP) was performed within a range of 7-15 d (average: 9 d) from MRgFUS. No technical difficulties related to MRgFUS ablation were encountered during surgery.

Results of MRgFUS treatment were assessed by pathological examinations, that demonstrated, in all cases, extensive coagulative necrosis at the site of sonication surrounded by normal prostatic tissue with inflammatory changes; these features were positively correlated with the immediate post-treatment MRI scan and NPV values. At histology 10 patients were free of residual viable tumor within the treated area; the analysis of the whole prostate section specimen of these patients demonstrated extensive coagulative necrosis at the site of sonication surrounded by normal prostatic tissue with inflammatory changes. In the remaining patient, 10% of residual tumor was observed within the NPV. There was a variable amount of isolated cancer tissue (Gleason<6, 3+3) within the non-treated parenchyma that was neither identifiable at MRI nor at biopsy.

Case report

MRgFUS treatment of 71 yo patient with unifocal prostate cancer (Gleason score 6, 3+3, figure 4). On a), PRF real-time thermometry sequence acquired during procedure shows a definite area of temperature increase corresponding to >60 °C (red area). On b), a contrast-enhanced MR imaging (MRI) scan acquired immediately after treatment shows an area of NPV in the target area, corresponding to the exact location of the delivered sonication; MRI exam also shows the absence of rectal wall injuries or side-effects. On c), macroscopic section after radical prostatectomy demonstrates an extensive coagulative necrosis at the site of sonication; the corresponding microscopic image (haematoxylin and eosin stained, d) confirmed tissue necrosis with a peripheral layer of inflammatory infiltrates.
Fig. 4

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Conclusion

Our preliminary experience demonstrated the feasibility of MRgFUS ablation of prostate lesions without significant side effects and/or short-term treatment related complications. Results of our Phase I study suggest that MR guided Focused Ultrasound is a safe and effective modality to determine a > 90% necrosis of identifiable prostate cancer. The treatment is completely noninvasive, with only an endorectal probe insertion, and the required technical background is simple, with a short learning curve for the operator. Devascularization occurring in ablated volumes on contrast-enhanced MRI precisely corresponds to areas of extensive coagulative necrosis as compared to histopathology and validates real-time temperature mapping.

Within the scenario of different therapeutic approaches for localized prostate cancer treatment, including laser, cryoablation, radiofrequency ablation, microwave ablation, and photodynamic therapy (all extensively tested with reduced side-effects) [9], MRgFUS can be introduced as a valid alternative procedure; obviously, more prospective studies will be needed to demonstrate the oncologic effectiveness as well as to validate its durable effect on patient outcomes, and particularly the long-term efficacy of this technique before its introduction in common clinical practice.
References


