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Focal therapy for localized unifocal and multifocal prostate cancer: a prospective development study using real time MR guided Focused Ultrasound

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Abstract. To assess safety and feasibility of non-invasive high intensity 3T MR guided focused ultrasound (MRgFUS) treatment of localized prostate cancer in an exploratory designed study. Men aged 45–80 years were eligible for this prospective study if they had low-risk localized prostate cancer (prostate specific antigen [PSA] ≤10 ng/mL, Gleason score ≤ 3 + 3), with no previous androgen deprivation or treatment for prostate cancer, and who could safely undergo multiparametric MRI (Discovery 750, GE; Gd-Bopta, Bracco) and have a spinal anesthetic. Patients underwent focal therapy using real time MR guided high intensity focused ultrasound (MRgFUS), delivered to all known cancer lesions, with a margin of normal tissue. Primary endpoints were adverse events (serious and otherwise) and urinary symptoms and erectile function assessed using patient questionnaires. 8 men were recruited between June 2011 and June 2012. After treatment, one man was admitted to hospital for acute urinary retention. Another patient had self-resolving, mild, intermittent dysuria (median duration 5.0 days). Urinary tract infection was not reported. Urinary debris occurred in 6 men (75%), with a median duration of 12 days. Median overall International Index of Erectile Function-15 (IIEF-15) scores were similar at baseline and at 6 to 12 months (p=0.060), as were median IIEF-15 scores for intercourse satisfaction (p=0.433), sexual desire (p=0.622), and overall satisfaction (p=0.256). There was an improvement in lower urinary tract symptoms, assessed by International Prostate Symptom Score (IPSS), between baseline and 6 to 12 months (p=0.026). All 8 men with no baseline urinary incontinence were leak-free and pad-free by 9 months. No histological evidence of cancer was identified in 7 of 8 men biopsied at 6 months (87,5%); overall, the entire population (8 patients) was free of clinically significant cancer and had no evidence of disease on multi-parametric MRI at 6 to 12 months. MR guided Focused Ultrasound focal therapy of individual prostate cancer lesions, whether multifocal or unifocal, leads to a low rate of genitourinary side-effects and an encouraging rate of early absence of clinically significant prostate cancer.

INTRODUCTION

Prostate cancer (PC) is one of the most common cancers in the male population worldwide, with recent statistics reporting an incidence of 30% in the United States over the last year [1]. The management of patient with prostate cancer is set to become one of the most challenging public health issues in coming. The problems associated with the diagnosis and management of prostate cancer include over-diagnosis, over-treatment, treatment-related toxicity and escalating, unsustainable costs [2, 3]. At present, radical whole-gland surgery or radiotherapy can result in substantial side-effects, as a consequence of damage to surrounding structures. Whole-gland therapies risk damage to neighboring structures such as the bladder neck, external urinary sphincter, neurovascular bundles, and rectum. These involve urinary incontinence (5–20%), erectile dysfunction (30–70%), and bowel toxicity (5–10%) [4]. Focal therapy for PC is now considered an emerging alternative to active surveillance for the management of low-risk PC, with the overall aim of treating only areas of cancer, minimizing lifetime morbidity without compromising life expectancy. High-Intensity Focused Ultrasound (HIFU) represents an innovative technique that may selectively ablate known disease while preserving existing functions. HIFU features high energy ultrasound focused to ablate target tissue thermally by raising the local temperature over 60 °C, leading to coagulative necrosis [5]. Target tissue destruction is produced by thermal, mechanical, and cavitation effects, that cause a subsequent demarcated region of coagulative necrosis surrounded by normal tissue on microscopic examination [6]. In the last 10 years, the feasibility and the safety of US guided HIFU has been tested in a growing number of clinical studies. More recently, magnetic

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resonance imaging was combined with HIFU principle and was presented as a novel technique for ablation of solid tumors, such as PC. Combining magnetic resonance imaging (MRI) to define the target, to control and monitor the ablation and an ultrasound transducer that controls and delivers the focused ultrasound beam, Magnetic Resonance guided Focused Ultrasound (MRgFUS) allows a noninvasive approach to the treatment of PC. MRI is more accurate than US as it provides high resolution imaging and good anatomical visualization of the target and its surroundings in any orientation for planning treatment and evaluating relative effects, thanks to soft tissue contrast. Moreover, MRI is the only currently available technique with proven capabilities to create quantitative temperature maps during ablative procedure [7, 8]. The aim of our study was to assess safety and feasibility of MRgFUS in patients with localized PC.

METHODS AND MATERIALS

Study design and patients

Between June 2011 and June 2012, after an institutional review board approval, 8 patients with unifocal, biopsy-proven prostate cancer, evident on multiparametric magnetic resonance imaging (MRI) were enrolled in a phase I, controlled trial and treated with magnetic resonance-guided focused ultrasound (MRgFUS) ablation. Before the procedure, all patients signed a dedicated written informed consent. All patients included in this study had localized disease (stage T1–T2, Nx–N0, M0, Gleason score ≤ 3 + 3, prostate-specific antigen [PSA] <10 ng/ml), aged 45-80 years, with no previous androgen deprivation or treatment for prostate cancer and evidence of cancer lesions on MRI. We excluded patients who had a Gleason score ≥8, with a previous pelvic or rectal cancer, and with an American anesthesiological (ASA) score ≥3. Men who were unable to have MRI scanning (e.g. severe claustrophobia, permanent cardiac pacemaker, metallic implant) were also excluded. Before treatment, all patients underwent a MRI (Discovery 750, GE) diagnostic exam, in order to define treatment feasibility and to plan the procedure. Target lesions were identified with Turbo Spin Echo T2-weighted, DCE T1-weighted (Gd-Bopta, Bracco), and DWI sequences.

Procedures

All patients enrolled in this study underwent MRgFUS ablation; all treatments were performed using an endorectal focused ultrasound ablation system (ExAblate 2100, InSightec, Haifa, Israel) integrated within a 3T MR scanner (Discovery MR750, GE Medical Systems, Milwaukee, Wisconsin, USA (Fig.1a). Patients underwent spinal anaesthesia (0.5% hyperbaric bupivacaine 2–3 ml in association with morphine 25–50 mcg) and a 16 F Foley urinary catheter was positioned to ensure urine flow during the procedure, in order to reduce prostate movement due to bladder filling. Patients are positioned on MRgFUS treatment table in supine position with slightly elevated legs and bent knees and an endorectal probe, which contains a 990-element phased-array focused ultrasound, is inserted through the patient's anus after lubrication (Fig.1b).

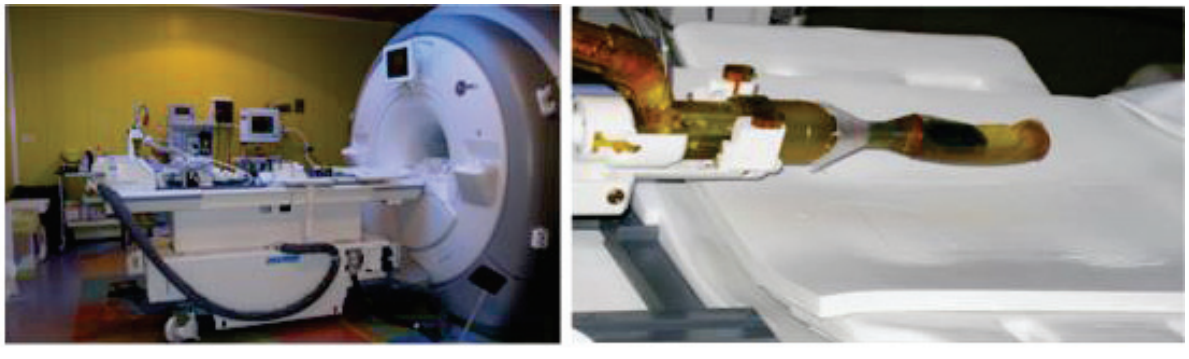

FIGURE 1. (a) The combined ExAblate 2100 and Discovery MR750 MRgFUS system; (b) the table built-in mechanical insertion arm featuring the 990-elemnts phased-array focused ultrasound probe for MRgFUS filled with degassed water at 12° C.

The coil balloon was inflated to achieve tight contact with the entire circumference of the rectal wall and filled with degassed water to eliminate residual air within the interface between the prostate and the rectal wall. The physician identifies the focus area to be targeted and then manually draws the contours of the target area (ROT—region of treatment) and the safety regions that should be spared, like the rectal wall, urethral sphincter, neurovascular bundles, and the bladder wall. A dedicated treatment-planning software automatically generates a treatment program, including type and number of sonications required to ablate specific regions. A central location in the ROT is sonicated using low thermal dose, generating sub-lethal sonification, monitored with PRF shift method for MRI thermometry overlapping temperature maps onto anatomic images, to reconfirm targeting anatomical. After confirmation, treatment started using full-energy sonications in the target area and monitoring in real time each sonication, to achieve temperatures between 65 C° and 85 C° at focal point. Treatment was considered complete once the lesion and tumor-free margins have been completely ablated with a evidente non-perfused area at MRI: the ablated region is evaluated with T2-weighted and T1-weighted contrast enhanced sequences in order to assess lesion necrosis and immediately identify possible side effects on surrounding tissues (Fig. 2). After treatment patients were examined and monitored for adverse events for 3 hours prior to discharge.

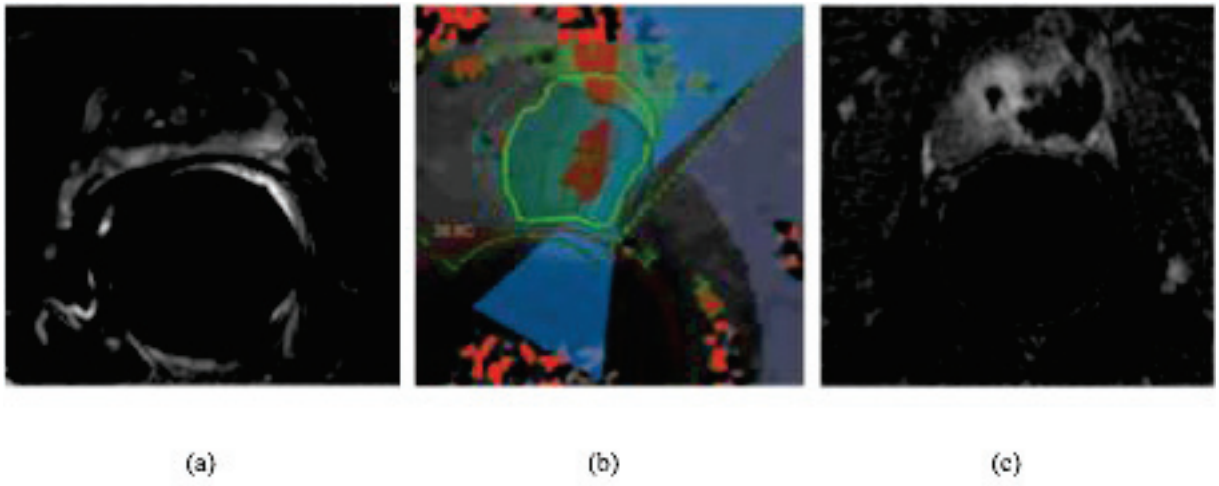

FIGURE 2. (a) Gleason 6 (3 + 3) tumor of the left prostatic lobe in a 63 years old patient is detected as a homogenous focus of low signal intensity on a transverse T2-weighted MR images; (b) real time monitoring allows continuous control of temperature variations while sonications are performed under MR guidance; (c) Axial T1-weighted Gradient Echo images after injection of gadolinium, performed after MRgFUS treatment shows tissue necrosis in the area of ablation.

RESULTS

The mean procedure time was 84 min (60-120). Mean maximum temperature measured in the target lesions was 81 +/- 2 °C, with a rectal wall temperature of 35 °C. The number of sonications ranged between 7 and 11, with a mean duration time for sonication of 13 seconds. All patients removed their catheter after 14 days according to our departmental protocol: one man had acute retention of urine after removal of the catheter. Another patient had self-resolving mild intermittent dysuria but required no pads (median duration 5.0 days). All 8 men with no baseline urinary incontinence were leak-free and pad-free by 9 months. Urinary tract infection was not reported. Urinary debris occurred in 6 men (75%), with a median duration of 12 days. No rectal adverse events were observed. Overall, International Index of Erectile Function-15 IIEF-15 scores were similar at baseline and at 6 to 12 months ($p=0.060$), as were median IIEF-15 scores for intercourse satisfaction ($p=0.433$), sexual desire ($p=0.622$), and overall satisfaction ($p=0.256$), indicating normal erectile function with erections sufficient for penetration at baseline in all man. There was an improvement in lower urinary tract symptoms, assessed by International Prostate Symptom

Score (IPSS), between baseline and 6 to 12 months (p=0.026). Dynamic contrast-enhanced T1-weighted sequences acquired immediately after treatment, in order to visualize lesions necrosis and to assess the integrity of adjacent tissues, showed an excellent correlation with thermal damage maps. The entire population (8 patients) was free of clinically significant cancer and had no evidence of disease on multi-parametric MRI at 6 to 12 months. Moreover, no histological evidence of cancer was identified in 7 of 8 men biopsied at 6 months (87,5%).

DISCUSSION

Currently, the management of low risk PC remains controversial [9, 10]; approximately 29 % of patient referred to active surveillance, 33 % to radiotherapy and 39 % to radical prostatectomy (RP) [11]. In most of the cases, RP is curative and in several centers represents the first-line treatment choice, even if associated with higher morbidity as compared to other therapeutic options [12]. Recently, treatment approaches that do not involve an intervention, i.e. active surveillance, or percutaneous techniques that preserve existing functions and selectively ablate target lesions in prostate glands, are significantly growing in popularity and clinical acceptance. Crioablation, Laser, radiofrequency, microwave have been extensively tested as a focal therapies for treatment of localized PC, showing some limits inherent to their technique. Imaging guidance is imperative in all these types of treatment. Between the various imaging modalities, MRI -especially multiparametric MRI- is the most sensitive and specific imaging technique for prostate cancer [13]. In cryosurgery, tumor tissue is ablated by freezing. In prostate cryosurgery, the correct needle positioning is essential to freeze as much of the tumor as possible and to avoid damaging the surrounding tissues to prevent complications. This is currently, possible performing cryosurgery under MRI guidance instead of transrectal ultrasound guidance. To date, only limited data about MRI-guided cryosurgery study of the prostate are available [14]. During the Laser Ablation Treatment, a laser fiber is positioned in the tumor under imaging guidance (ultrasound or MRI) destroying the tissue by the raising of the temperature than 60°C. At present, studies reporting on MRI-guided prostate laser ablation are scarce because it is an emerging technique. During radiofrequency ablation (RFA), a needle electrode, that produces electromagnetic waves, needs to be inserted into the tumor tissue. The waves cause friction within the tissue that raises the temperature and causes cell death [15]. Clinical experience performing MRI-guided RFA of the prostate is still very limited, probably because of technical difficulties. The major drawbacks of MRI-guided RFA are possible interference with the radiofrequency pulses of the MR system and the large image artifact (up to eight times its original size) caused by the radiofrequency electrode. Microwave ablation is almost identical to RFA. A drawback of this technique is that the electromagnetic waves can interfere with the radiofrequency signals used for MRI, which can cause noise in the MR images. Compared with the aforementioned techniques, focused ultrasound MRgFUS is the only real noninvasive ablation technique. Of the available techniques, we consider MRI-guided focal ablation the most sophisticated focal therapeutic option in the prostate cancer management. It appears to be fast and feasible because of the sharply defined ablation zone, few anticipated low adverse events and complications (in any cases cleared up in a few days), quick recovery of patients and possibility to repeat the procedure. In this contest, results of our Phase I study suggest MR guided Focused Ultrasound as a safe and effective modality, reporting necrosis percentage >90% after ablation . No residual viable tumor tissue was evidenced in the ablation area or along the safety margins at subsequent MRI exams. Moreover, histological examination revealed no evidence of cancer in 7 patients and a residual tumor in the remaining one patient, at 6 month. The increased popularity of HIFU relies on many factors, and it appears highly attractive as a minimally invasive treatment that entails no incision or puncture; moreover it is bloodless, can be carried out on an outpatient basis, and is repeatable. The clinical outcome of HIFU treatment has improved significantly over the years as a result of technical, imaging, and device developments. In this scenario, MR guidance is certainly the most significant change. Our preliminary experience demonstrated the feasibility of MRgFUS ablation of prostate lesions without significant side effects and/or short-term treatment related complications. Despite initial results on humans where feasibility and safety appear highly promising, MRgFUS is still under investigation, and more studies are needed to demonstrate the oncologic effectiveness as well as to validate its durable effect on patient outcomes.

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