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REVIEW

MR-Guided High-Intensity Focused Ultrasound: Current Status of an Emerging Technology

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Abstract The concept of ideal tumor surgery is to remove the neoplastic tissue without damaging adjacent normal structures. High-intensity focused ultrasound (HIFU) was developed in the 1940s as a viable thermal tissue ablation approach. In clinical practice, HIFU has been applied to treat a variety of solid benign and malignant lesions, including pancreas, liver, prostate, and breast carcinomas, soft tissue sarcomas, and uterine fibroids. More recently, magnetic resonance guidance has been applied for treatment monitoring during focused ultrasound procedures (magnetic resonance–guided focused ultrasound, MRgFUS). Intraoperative magnetic resonance imaging provides the best possible tumor extension and dynamic control of energy deposition using real-time magnetic resonance imaging thermometry. We introduce the fundamental principles and clinical indications of the MRgFUS technique; we also report different treatment options and personal outcomes.

Keywords Ablation · Cancer · High intensity focused ultrasound · MR-guided intervention · Noninvasive treatment

Introduction

At present, conventional therapy modalities for solid tumors, including malignant and some subtypes of clinically challenging nonmalignant lesions, are represented by open surgery, chemotherapy, and radiotherapy, which carry significant morbidity and mortality and may be associated with long inpatient stays and recovery time [1, 2]. After major technological and clinical research to significantly reduce the adverse effects of conventional treatment and to provide additional therapeutic options, several new modalities have been introduced in the last decades, including radiofrequency, laser, microwave, cryoablation,

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and, more recently, high-intensity focused ultrasound (HIFU) techniques [3–5]. The initial therapeutic trial was carried out in 1942 [6]; the first HIFU application, for neurological disorders in humans, dates back to 1955 by the Fry brothers [7]. However, the actual clinical use of focused ultrasound for ablation therapy was first introduced in China in the 1980s with the development of the biological focal field in 1997 [8].

Ultrasound (US) was the initial form of guidance used; US-guided HIFU therapy has been approved in China, and clinical trials for cancers of liver, kidney, and pancreas are under way in Europe and Asia. Over 20,000 patients with malignant or benign diseases have received this treatment, providing sufficient data to thoroughly document the prevalence of treatment-related adverse events. These results are commonly published in Chinese and are unavailable for scientists outside China [9]. This approach, however, limits treatment to externally targetable lesions and prevents real-time evaluation of procedure success [10]. After the demands for three-dimensional treatment planning and continuous temperature mapping of treated tissue for real-time monitoring of thermal damage in the target zone, magnetic resonance–guided focused ultrasound (MRgFUS) has been developed and successfully tested for noninvasive treatment of various benign and malignant tumors [11]. This review describes the basic principles of MRgFUS therapy, clarifies clinical indications of MRgFUS treatment of various solid tumors, and offers an overview of the clinical experience and research activity of our department.

Technical Principles of MRgFUS Ablation

Magnetic resonance–guided focused ultrasound can be configured as a noninvasive thermal ablation procedure. This category includes energy sources that destroy tissue by using thermal energy. In order to generate thermal damage, pathologic tissue exposure must exceed a temperature threshold; if the ratio of temperature to time does not exceed the threshold, then heated tissue tends to recover vitality. A temperature of >50 °C/10 s ensures coagulative necrosis, as well as 56 °C/1 s [12]. However, most practitioners tend to use higher temperatures (65–85 °C) for few seconds to guarantee complete tissue necrosis. Among the other thermal ablation techniques, MRgFUS is the only therapeutic modality that focuses thermal energy only in the target zone using an extracorporeal transducer, which ablates the target tissue without causing damage to the surrounding area [12]. In routine MRgFUS ablative procedures, multiple focal volumes are tightly packed or even overlapped to assure homogeneous thermal energy deposition and confluent necrosis within the entire targeted area [10]. Acoustic energy is generated by piezoelectric transducers operating at frequency values between 200 kHz and 4 MHz, with an intensity in the focal region on the order of 100–10,000 W/cm^2, with peak compression pressures of up to 70 MPa and peak rarefaction pressures up to 20 MPa [13].

Basic devices use a single-element spherical or flat transducer, moved mechanically to ablate multiple locations, and they can either be fairly large, to allow high-power deep focus for ablation of abdominal organs of deep skeletal sites, or relatively small, to fit into endocavitary sites [14]. Advanced transducers comprise multiple elements that allow greater control of the acoustic field and are necessary to target different locations and to increase the focal volume per sonication, eliminating the need for mechanical motion as a result of the ability to steer the focal point electronically by modulating the phase of the individual driving signals [10]. Compared to US, magnetic resonance imaging (MRI) offers exquisite depiction of fine anatomical details and is the only imaging technique that allows real-time thermal monitoring [15], measuring tissue temperature with a sensibility of ±2 °C. Hence, for both aspects, MRI can be considered more accurate than US as a guidance method for HIFU ablation. Moreover, these advantages can be significantly improved at a higher magnetic field, such as 3 T, where increased signal to noise allows faster imaging at higher resolution, which may improve the definition of tumor margins over 1.5 T [16]. In our institution, all treatments are performed on a 3 T scanner (Discovery 750 General Electric) with a dedicated MRgFUS device (ExAblate 2100, InSightec, Haifa, Israel).

Clinical Applications

Uterine Fibroids: Background

Compared to other treatment options for uterine fibroids, including hysterectomy, myomectomy, and uterine artery embolization, MRgFUS represents a feasible, effective, and completely noninvasive approach that may be alternatively used as a fertility-preserving technique in selected cases [15], although this aspect is as yet not definitively proven. The first feasibility experience of MRgFUS ablation of uterine fibroids dates to 2003 and was performed by Stewart et al. [17], with promising results. Subsequently various clinical trials evaluated the efficacy of MRgFUS in large patient populations, reporting significant reduction of clinical symptoms, with relevant improvement in life quality at 6, 12, and now 24 months [18]; to date, more than 8,500 patients have received MRgFUS worldwide, and only few serious treatment-related complications have been reported; further, acceptance rates from patients are

high [19]. More recent studies report that accurate preprocedural imaging can offer relevant information on MRgFUS outcomes; in 2008 Funaki et al. evaluated 91 patients with symptomatic fibroids treated with MRgFUS, correlating the treatment response of low baseline T2 signal intensity [20]. There is no widely accepted consensus about dimensional inclusion criteria for MRgFUS treatment of uterine fibroids, although leiomyomas should preferably not exceed 10 cm in size and should be preferably localized on the anterior uterine wall [21]. In 2012 Kim et al. introduced an interesting new technique for fibroid ablation, featuring one-layer ablation strategy for lesions larger than 10 cm [22].

Other authors have also reported the feasibility of treating adenomyosis by MRgFUS. In 2006 9 patients with adenomyosis were treated by the Rabinovici team [23], with 1 patient having spontaneous menstrual cycles after MRgFUS and a successful and uneventful pregnancy course. Fukunishi reported on 20 patients treated for adenomyosis with 6 months' follow-up [24]. In light of these data, MRgFUS may be considered a safe and effective method to treat adenomyosis, permitting large ablative volumes to be obtained as well as significant pain relief. However, further trials are essential to evaluate its long-term efficacy, especially because other studies [25] have shown an increase of adenomyoma size at 3–4 months after MRgFUS treatment, for reasons related to tumor size, treatment parameters, operation procedure, and blood supply to target tissue.

Uterine Fibroids: Clinical Indications and Personal Experience

ExAblate has been approved by the U.S. Food and Drug Administration (FDA) and has obtained a CE mark approval for treatment of symptomatic uterine fibroids. Some studies have proposed the use of this technique for the treatment of adenomyosis [25]. To date, no precise inclusion criteria have been defined to establish treatment indications and to assess response to treatment. In the majority of cases, the patient is referred for MRgFUS treatment after the assessment of complex clinical and imaging variables, including fibroid size, localization, number, signal intensity on MRI, symptoms, and desire for future pregnancy. The initial trials proving the efficacy and safety of this new approach were restricted to premenopausal women who did not desire future pregnancy [23, 24]; however, because the safety and efficacy of this treatment have been successfully documented, the preservation of fertility in patients with uterine fibroids recently became a theoretical indication for MRgFUS. In particular, a study performed by Rabinovici et al. [15] described 54 pregnancies in 51 women after MRgFUS, with live births in 41 % of them, a 28 % spontaneous abortion rate, an 11 % rate of elective pregnancy termination, and 11 % ongoing pregnancies [23]. Even if it may be speculated that MRgFUS may provide some advantages for fertility preservation compared to the uterine artery embolization, in which embolic particles may damage normal myometrium, in general, the correlation with pregnancy potential is still far from being confirmed. It mostly will depend on patient-related factors, such as age, fibroid location, and volume or presence of other concomitant pathologies causing infertility.

At present, we have treated 75 symptomatic patients (age range 32–49 years) with 89 fibroids (mean lesion size 56 mm; mean volume 87.5 mm^3) on an outpatient basis. Treatment is performed with the patient in the prone position and under light sedation, with active monitoring of vital signs. Rectal and bladder fill (US gel and saline, respectively) is considered after evaluating the position and eventual mobility of the uterus with low-resolution fast-acquired localizer images. If patient positioning and alignment (transducer-fibroid) is considered adequate for treatment, full-resolution T2-weighted images are obtained for ablation planning (Fig. 1). Before the start of treatment, low-energy sonications are delivered to verify the correct position of the focus and the absorption rate of the fibroid. When these elements are verified, the energy can be increased and the real treatment begins. At the end of treatment, T1 fat-saturated postcontrast images are acquired to assess the resulting necrosis within the fibroid (Fig. 2), calculated as nonperfused volume (NPV). Volumetric parameters were calculated by dedicated software (IRM standard Functool 6.3.1, GE Healthcare), defining lesion margins in all layers acquired. The NPV ratio of fibroid is defined as the nonperfused tissue volume divided by the fibroid volume before treatment.

At 3, 6, and 12 months, all treated patients underwent a contrast-enhanced MRI study to evaluate the resulting reduction of NPV ratio, fibroid volume, and diameter. At 12 months, the fibroid size decreased to a mean diameter of 41.2 mm (28.4 %) and the volume to 54.6 mm^3 (45.9 %). In all cases, NPV on posttreatment contrast-enhanced images overlapped with the estimated ablated volume obtained by the software, revealing complete necrosis of the treated region. All treated patients displayed a mild to moderate reduction of leiomyoma size, with significant reduction of fibroid-related symptoms and a better quality of life.

Breast Tumors: Background

In a first feasibility study in 2001, Hynynen et al. [26] applied MRgFUS for the treatment of 11 fibroadenomas under local anesthesia in 9 patients. Eleven lesions were treated; 8 were partially or nearly completely successfully

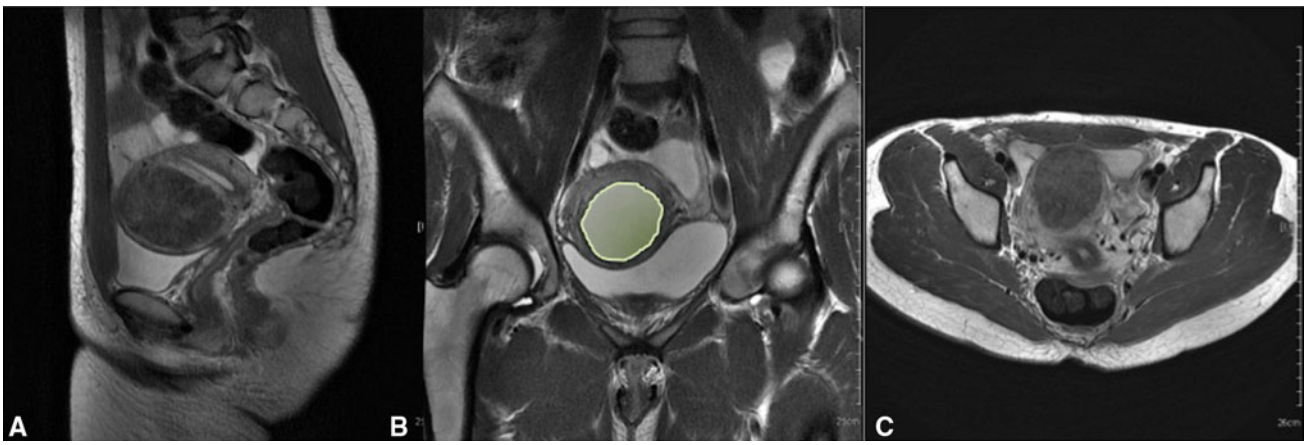

Fig. 1 T2-weighted images used to plan fibroid treatment. Sagittal plane shows a hypointense fibroid of the anterior wall of the uterus (**A**); this plan is used to identify bowel loops with limited energy density line; coronal plane is used to determine the region of treatment (**B**) (*green circle*); axial plane (**C**) is used to identify skin line and possible air bubbles at the skin surface

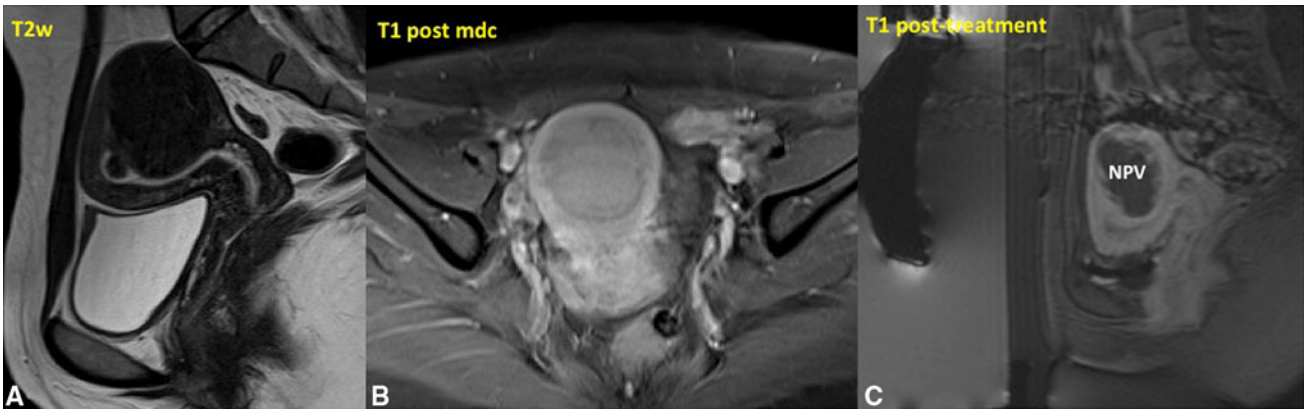

Fig. 2 A 34-year-old woman with metrorrhagia. Before treatment, an intramural hypointense fibroid of the posterior wall of the uterus is identified at T2 sagittal image (**A**); fibroid featured highly perfused behavior at T1-weighted gadolinium-enhanced axial image (**B**). At the end of the treatment, T1-weighted gadolinium-enhanced images are performed to demonstrate the effect of the ablation, verified in this sagittal view as an area on nonperfusing volume (NPV) corresponding to coagulative necrosis (**C**)

treated. After this successful feasibility trial, MRgFUS was applied to the treatment of breast cancer. In a 2003 study Gianfelice et al. [27] treated 12 patients with invasive breast tumors with two different MRgFUS systems before surgery. MRgFUS ablation was well tolerated by all patients without significant complications. After surgical resection, the percentage of necrosis in the treated lesions was between 46 and 88 %, with significant variation from one US treating system to the other. In 2007 Furusawa et al. [28] treated 21 patients with invasive/noninvasive ductal carcinoma with a median diameter of 15 mm; 17 patients were treated once and 4 patients twice. Only one case of recurrence occurred during 14 months' follow-up. In 2005 Wu et al. [29] evaluated long-term clinical results in a group of 22 patients with biopsy-confirmed breast cancer who refused surgical resection (stage I $n = 4$, stage IIa $n = 9$, stage IIIb $n = 8$, stage IV $n = 1$). All patients underwent chemotherapy and radiotherapy after MRgFUS. The tumor had disappeared at contrast-enhanced MRI in 8 patients and had regressed in 14. Local recurrence occurred in 2 patients at 18 and 22 months after treatment, respectively. Five-year disease-free survival and recurrence-free survival were, respectively, 95 and 85 %.

Breast Tumors: Clinical Indications and Personal Experience

Magnetic resonance–guided focused ultrasound is considered a safe and feasible noninvasive alternative to surgical or radiotherapy treatment of benign and malignant tumors. This treatment is thought to be more psychologically and cosmetically acceptable to patients and more suitable for

treating patients who are at high risk for operation. However, because follow-up studies evaluating the rate of disease progression and recurrence after treatment are still far from being completed, the long-term efficacy of MRgFUS is still under investigation.

At present, we are evaluating the efficacy of MRgFUS treatment in patients with biopsy-proven invasive ductal breast cancer (stage T1M0N0) scheduled for surgical resection. Our single-arm nonrandomized study includes patients with invasive breast cancer proven by 14–20-gauge core needle biopsy, with contrast-enhanced MRI confirming a single focal breast lesion <2 cm in a treatable location and clearly correlated with the histologically proven tumor. Lesions planned for ablation should be located at a minimum of 10 mm distant from untargeted sensitive structures (dermal undersurface, nipple, ribs). Treatment is performed with the patient in the prone position. The breast is placed under moderate compression within a dedicated breast coil. Pretreatment planning is performed on T1-weighted contrast-enhanced sequences, acquired in multiple planes with and without fat saturation pulses (Figs. 3, 4). Similar to what happens for uterine fibroids, low-energy sonications are delivered in order to verify the correct position of the focus and the absorption rate of the lesion before treatment start at full energy. Tumor necrosis is calculated as nonperfused volume (NPV) on contrast-enhanced T1-weighted sequences (Fig. 5). At present we have treated 10 patients; the average number of sonications required to cover the lesions was 48 (range 26–75), resulting in an average treatment time of 2 h 20 min (range 1 h 20 min to 3 h). In 90 % of patients no residual enhancement of ablated lesions was present at MRI. All patients underwent routine breast-conserving surgery within 21 days after MRgFUS treatment; pathological analysis demonstrated the absence of residual cancer after surgical excision in 9 of 10 lesions with a margin of at least 5 mm of normal breast tissue around the necrosis area. In only one case was 15 % of residual tumor volume identified in the necrosis area.

Bone Tumors: Background

Even if the success rate of combined treatment for bone tumors, ranging from surgery to chemoradiation and various forms of percutaneous ablation, is more than acceptable, a significant percentage of patients do not benefit from symptom relief, or they face symptom recurrence in the short term [30, 31]. In these cases MRgFUS can represent a safe and effective approach for both pain palliation and tumor control. To understand the theoretical basis of these two different clinical approaches, it should be taken in consideration that cortical bone has high acoustic absorption and low thermal conduction rates [11]; hence, the focused US energy is absorbed by the cortical surface with no or little penetration into the medullary bone [10]. When pain palliation is the treatment aim, the interaction between focused US and intact cortical bone can be used to produce a temperature increase over the periosteal surface of the target area, finally causing thermal damage to the periosteal nerves, which are responsible for nociception [32]. Gianfelice et al. [33] treated 11 patients with localized painful bone metastases, evaluating symptom relief

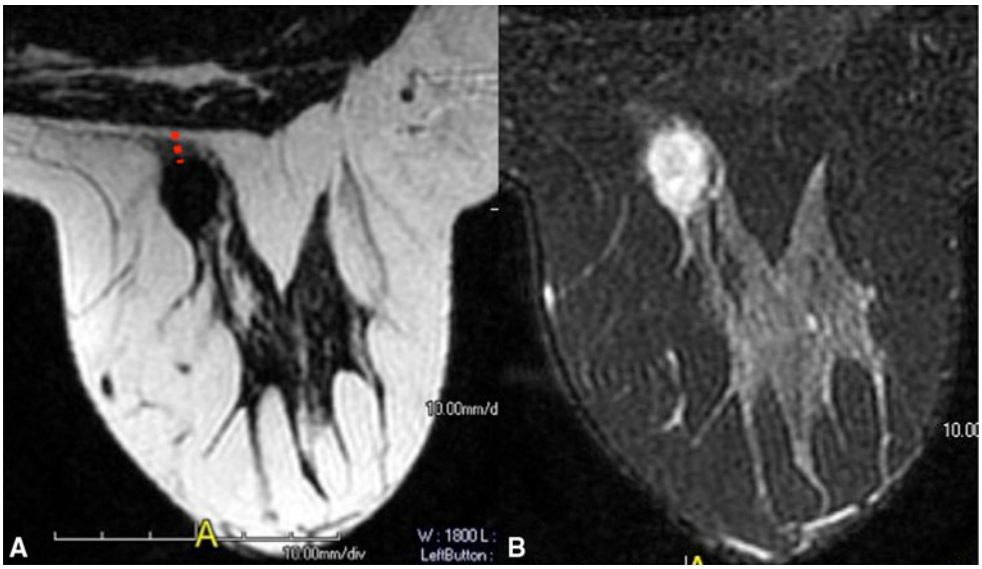

Fig. 3 A 45-year-old woman with ductal cancer (T1 N0 M0) of the left breast. At pretreatment planning, (**A**) T2-weighted axial image shows the nodule and its distance from the pectoralis muscle (*red dashed line*), and (**B**) T2-weighted axial image with fat saturation shows high-signal intensity of the pathologic nodule

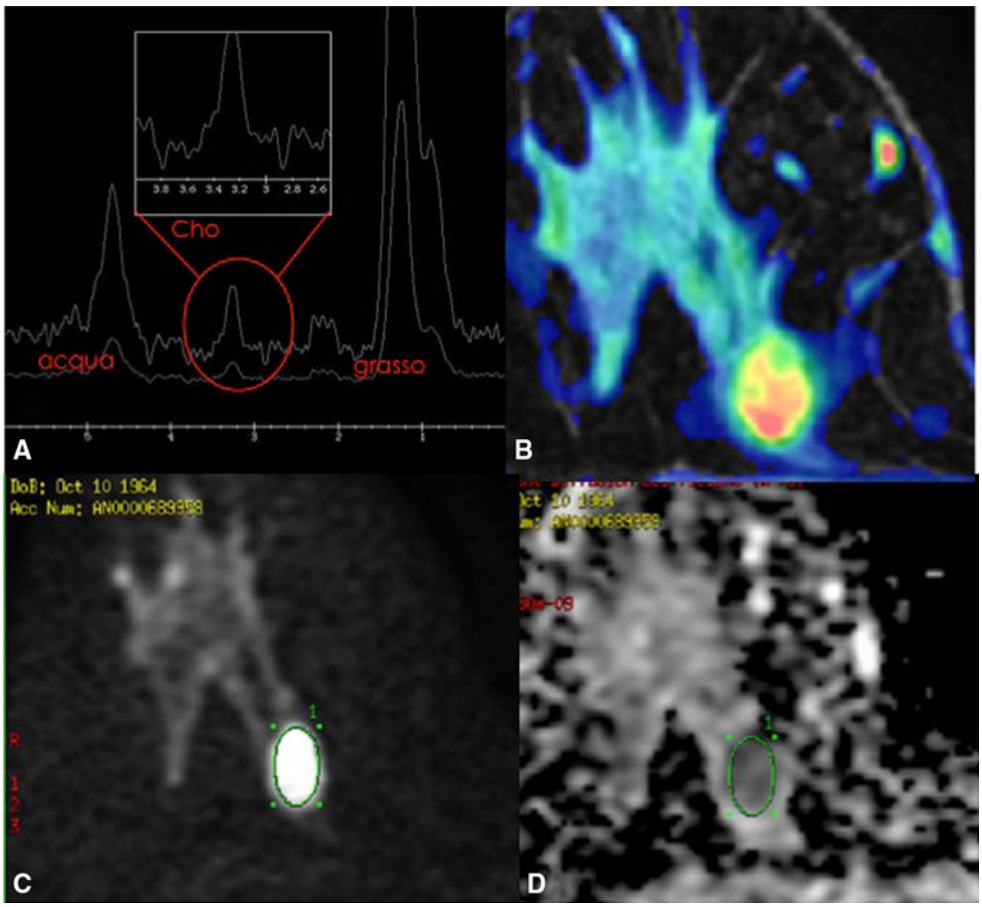

Fig. 4 **A** Pretreatment evaluation completed with MR spectroscopy. **B** Dynamic gadolinium-enhanced T1-weighted images for perfusion. **C** Diffusion-weighted image for molecular restriction. **D** Apparent diffusion coefficient map. All are indicative of malignancy

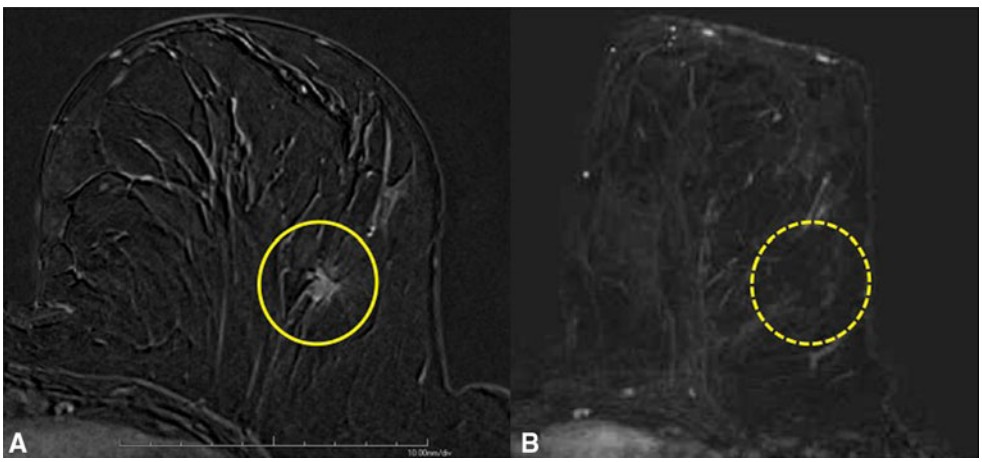

Fig. 5 **A** Gadolinium-enhanced T1 GRE fat-saturated axial image shows the malignant highly vascular nodule. **B** After MRgFUS treatment, no residual enhancement of ablated lesion is detectable

with a 0–10 pain score and reporting progressive pain reduction in treated regions and a decrease in pain medication use during a 3-month follow-up period. Another multicenter study, performed by Liberman et al. [34], followed up 39 patients with painful bone metastases; they demonstrated significant reductions in pain scores during the 3-month follow-up. Furthermore, MRgFUS can be a feasible option to obtain pain palliation in patients with benign bone tumors (such as osteoid osteoma) or nontumoral conditions. A clinical trial performed in St. Mary's

Hospital (London, United Kingdom) is evaluating the safety and efficacy of MRgFUS for the treatment of low back pain due to facet joint arthropathy or degenerative arthritis, with 15 patients successfully treated with 62 % pain decrease and disability decrease of 55 % [35]. On the other hand, when tumor control or tumor debulking is the primary clinical intent, focused US should be applied over a damaged (severely thinned or eroded) bony cortex, thus allowing thermal damage to lesions located deep into the medullary bone. Ablation of deep bone lesions under US guidance was performed by Weeks et al. [35] in combination with chemotherapy in 80 patients with different primary bone tumors (60 with stage IIb disease and 20 with stage III disease; Enneking staging system). Follow-up images demonstrated completely ablated malignant bone tumors in 69 patients and greater than 50 % tumor ablation in the remaining 11 patients.

Bone Tumors: Clinical Indications and Personal Experience

Magnetic resonance–guided focused ultrasound is clinically approved in the European Union for palliative treatment of bone lesions, while FDA-accepted, MR-guided high-intensity focused US ablation is provided to patients with bone metastasis who have exhausted or refused all other pain palliation methods, including external beam radiotherapy. If compared to other nonsurgical treatment options for both pain palliation and tumor control, and most of all with radiotherapy, a relevant advantage of MRgFUS ablation is represented by the fact that treatment can be repeated indefinitely until the clinical aim is achieved, without issues related to radiation absorption or other toxicity effects. Similar considerations could be applied to the treatment of benign bone lesions that often represent a clinical challenge for surgeons. Nevertheless, most of the MRgFUS treatments are carried out in a single stage, requiring further interventions only in a minor population.

In our department, we are evaluating the safety and efficacy of MRgFUS treatment for pain palliation in patients with both benign (osteoid osteoma, osteoblastoma, aneurismal bone cyst) and malignant (metastases, primary bone tumors) lesions. Patients are variably positioned according to tumor location, and general, epidural, or peripheral anesthesia is chosen on the basis of different parameters (lesion location, patient age, clinical condition). In all cases pretreatment planning is performed with T2-weighted MR sequences acquired in multiple planes with and without fat saturation pulses (Fig. 6). Treatment is started after delivering low-energy sonications to verify the correct position of the focus; the ablation is therefore performed over the periosteal surface for osteoid osteoma and bone metastases with intact cortex (Fig. 7), or through the eroded cortex in cases of lytic metastases (Fig. 8). Although MR thermal maps cannot be measured directly inside the bone itself (as a result of the low MR signal from the cortical zone), heating due to conductive processes from the bone surface within the adjacent soft tissue is measurable and considered adequate for treatment monitoring. With regard to the ablation of osteoid osteoma, 9 consecutive patients with limited joint function and reduced quality of life due to painful osteoid lesion confirmed at workup MR and CT have been treated. In all subjects, symptoms were assessed before and 1–3 months after treatment on a 0–10 pain scale; in 8 of 9 (83 %) patients, complete clinical success after the MRgFUS procedure was reported, while a single patient with atypical medullary osteoid osteoma experienced symptom recurrence and underwent surgery with intralesional curettage 9 months after the MRgFUS procedure. No treatment-related complications were observed during or after the procedure. With regard to the treatment of painful bone metastases, we have so far performed 18 MRgFUS ablations of lesions from different known primary tumors. Patients included in the study were all receiving chemotherapy and could not undergo other pain palliation treatment, or they had exhausted or refused other therapy options. To evaluate treatment efficacy in terms of pain palliation, the Brief Pain Inventory—Quality of Life (BPI-QOL) criteria were used to calculate pain severity score. To evaluate treatment efficacy in terms of local tumor control, lesion changes were evaluated according to MD Anderson (MDA) criteria. The pain severity score changed significantly from a baseline average of 7.1 ± 2.08 (4–10) to 1 ± 1.1 (0–3) at 3 months' follow-up. In particular, at the end of the protocol, 13 of 18 (72.2 %) patients reported a 0 score for pain severity without medication intake, consisting of a complete response to treatment. CT examinations performed at 3 months' follow-up revealed an increase of bone density with restoration of the cortical border in 5 of 18 (27.7 %) patients. According to MDA criteria, we observed a complete response to treatment in 2 of 18 (11.1 %) patients, a partial response in 4 of 18 (22.2 %) patients, stable disease in 10 of 18 (55.6 %) patients, and progressive disease in 2 of 18 (11.1 %) patients.

Prostate Cancer: Background

Over the past 15 years, more than 30,000 US-guided HIFU ablations of the prostate have been performed worldwide [36]. In 2011 Crouzet et al. presented long-term results of a European multicenter study with 803 consecutively treated patients with US-guided HIFU, including data from 2 years' posttreatment prostate-specific antigen follow-up [37]. In

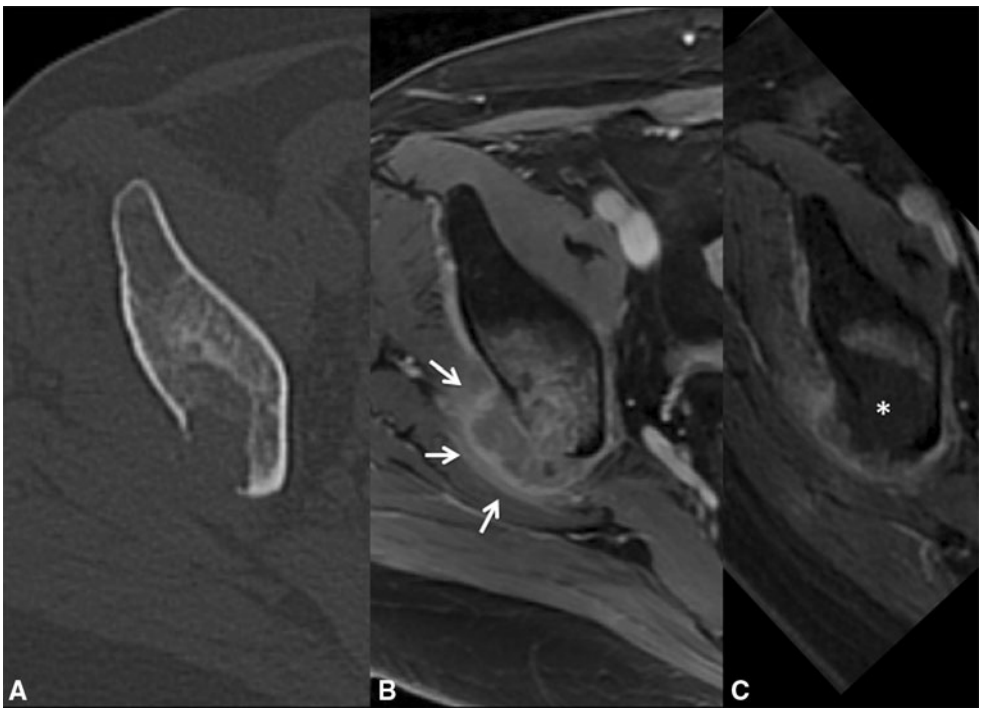

Fig. 6 A 56-year-old woman with lung cancer and single right hip bone metastasis. **A** Axial CT image showing lytic lesion located at the right iliac bone with evidence of cortical erosion. **B** Gadolinium-enhanced T1-weighted axial image showing secondary bone lesion with highly vascular pathological extending into periskeletal compartment (*white arrows*). **C** Postcontrast, posttreatment axial T1-weighted image shows a wide area of coagulative necrosis within the entire extension of the metastatic lesion (*asterisk*) with peripheral inner reaction but without residual local tumor, consistent with total ablation. This was achievable thanks to the fenestration of the anterior cortex that allowed complete penetration of high-intensity US energy; the final result was a combination of bone transmitted energy and direct energy deposition (similar to regular soft tissue ablation under MRgFUS, such as breast or fibroid treatment)

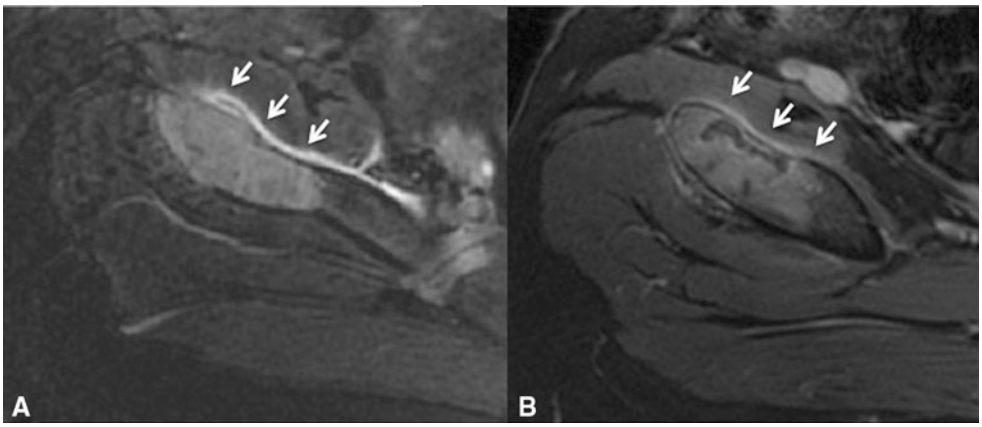

Fig. 7 A 38-year-old woman with breast cancer and right iliac metastasis. Pain score of 10 (maximum scale) before treatment and at 0 at 3 months' follow-up. Treatment was carried out exclusively for pain palliation because the anterior cortex had small fenestrations, although those were multiple but not large enough for trying a tumor control. Axial gadolinium-enhanced T1-weighted image (**A**) before and (**B**) after treatment. Necrosis in pain palliation treatment is limited to the cortical and immediate pericortical compartment for periosteal neurolysis. In this specific case, however, a limited amount of focused US energy went through the whole lesion and faced the opposite cortex, where it created partial necrosis of the inner cortex tumor

78 % of patients analysis of posttreatment biopsy samples revealed no evidence of residual cancer; 5- and 7-year freedom from biochemical recurrence rates (according to the Phoenix criteria) were 83–75 % for low-risk patients, 72–63 % for intermediate-risk patients, and 68–62 % for high-risk patients. A study by Blana et al. [38] presented an 8-year experience among 140 patients, with a 5-year disease-free survival rate of 66 %. All these studies were conducted

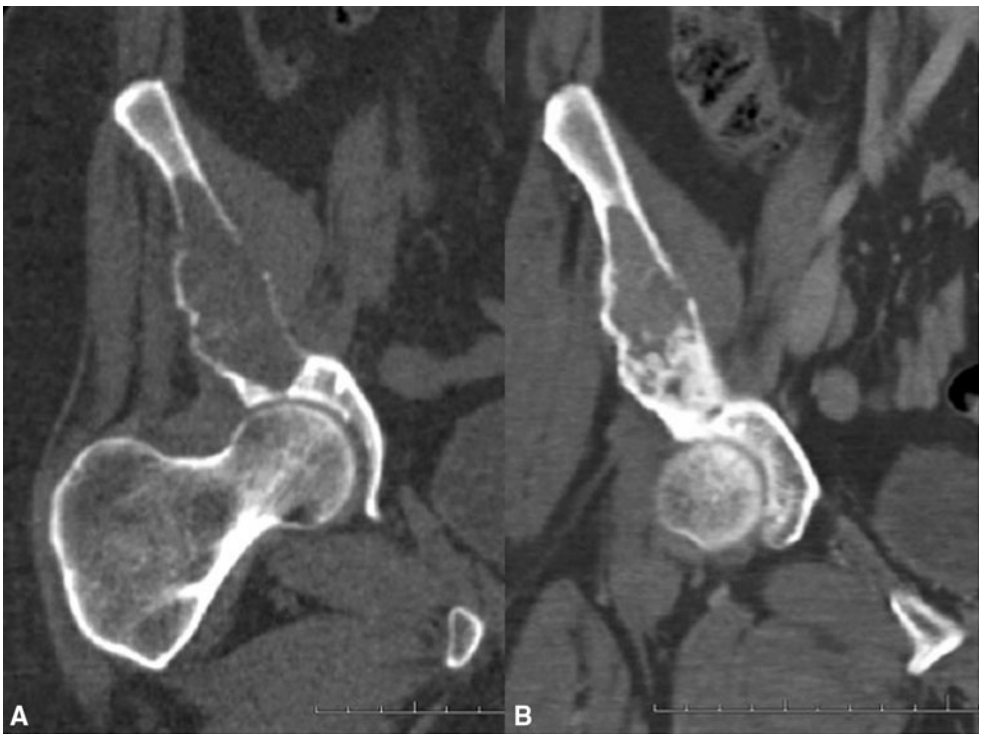

Fig. 8 Same patient as in Fig. 7, bone rearrangement followed at MRgFUS pain palliation treatment; coronal CT images performed (**A**) before and (**B**) at 3 months' follow-up revealed an increase of bone density with restoration of the cortical border as sign of de novo mineralization

with whole gland ablation performed as the treatment protocol, which demonstrated excellent tumor control with complication rates (urinary or sexual dysfunction) comparable to traditional therapeutic strategies (surgery, radiotherapy). Ahmed et al. proposed a focal or multifocal HIFU approach to prostatic cancer, using US guidance with the aim to treat known disease and preserve existing function [39]. The study reported a lesser rate of complications but also a variable degree of oncological control. This can be explained by the fact that treatment planning was performed using MRI, while sonications were guided by US imaging. A basic precondition to focal therapy is the utilization of the same image modality for lesion identification and treatment planning; therefore, in our opinion, MRI guidance provides a better contribution to HIFU ablation because of its superior spatial and contrast resolution.

Prostate Cancer: Clinical Indications and Personal Experience

Wide experience obtained with US-guided HIFU suggests that this kind of focal therapy is emerging as an alternative to active surveillance for management of 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. There are, however, some relevant limits in treatment efficacy assessment, substantially related to the intrinsic technical nature of conventional US. Transrectal conventional US is able to identify index lesions as hyperechoic areas, but it is not able to provide real-time controls on ablative procedure or to define treatment effects with high spatial resolution. On the other hand, MRI provides a thermometric monitoring and a superior anatomic imaging with feasible multiparametric evaluation of prostatic neoplasm (including dynamic contrast-enhanced imaging, proton spectroscopy, and diffusion weighted imaging [DWI]). However, at present, the literature reports only animal tests [40] and occasional case descriptions of MRgFUS ablations of prostatic cancer in humans [41]. Its feasibility, safety, and efficacy remain under investigation.

In our department, 3 patients with biopsy-proven unifocal T2 prostate cancer underwent transrectal MRgFUS ablation; target lesions were identified with turbo spin echo T2-weighted sequences, dynamic contrast-enhanced T1-weighted sequences, and DWI sequences. MRgFUS treatment involves deposition of focused acoustic energy within the target lesion. Patients underwent peripheral block by spinal anesthesia, and a urinary catheter was positioned to ensure urine flow during the procedure. A transrectal MRgFUS transducer device was covered with a plastic balloon filled with cooled, degassed water to reduce

thermal dispersion at the rectal wall interface and to preserve mucosal and submucosal layers from collateral damage during prostate treatment. As in standard MRgFUS ablative protocol, low acoustic energy administration precisely defined the targeted lesion, and high-energy ablation was performed once focus targeting was confirmed. In all subjects MRgFUS ablation was performed without significant adverse events, and no pathological enhancement was demonstrated at perfusional posttreatment MRI (Fig. 9). All patients subsequently underwent radical retropubic prostatectomy. Pathologic specimens demonstrated extensive coagulative necrosis at the MRgFUS ablation site, surrounded by healthy tissue with inflammatory changes.

Neurological Disease: Background and Clinical Indications

Rudimentary HIFU devices were tested for neurosurgical applications in the late 1940s and the 1950s, with brain tumors ablation attempted through craniotomy windows [7]. Although the procedure was potentially promising, it was significantly limited by the lack of adequate imaging guidance. MRgFUS now has the potential to overcome these limitations, providing a noninvasive and reproducible alternative to other therapeutic options in the field of brain oncology. Ram et al. performed MRgFUS ablation through bony windows in 3 patients with recurrent glioblastoma [42], observing immediate changes in contrast-enhanced T1, T2, and DWI scans in the treated regions with subsequent histological evidence of thermocoagulation. However, effective penetration of focalized HIFU beam through the intact skull still represents a challenge that must be undertaken, and a preliminary craniotomy completely depletes MRgFUS of its noninvasive feature; in particular, the most relevant technical efforts are directed toward preservation of sufficient beam energy for ablation brain tissue, with significant energy dispersion occurring when the HIFU beam crosses the bony cortex of the skull. At present the development of a dedicated brain ablation device is based on the combination of the 3 following technologies in a single unit: (1) thermal ablation with HIFU, (2) intraoperative guidance by MRI and real-time thermal monitoring, and (3) full hemispheric US phased arrays to correct cranial bone distortion and focus the beam deeply into the brain. Two commercially available MRI-guided HIFU surgery (MRgFUS) units are currently being marketed by Insightec (Haifa, Israel).

Another experimental study conducted by McDannold et al. [43] evaluated the clinical feasibility of this technique without creation of the bony window, using an hemispherical phased-array transducer. Three patients with glioblastoma were treated. The operators found it possible to focus the transcranial US beam into the brain and to visualize the tissue heating with MR temperature mapping; however, treatment was limited by the device power available at the time and did not seem to achieve proper thermal coagulation.

In addition to neoplastic indications, today there are now several modern applications of US in the field of neurological disease. The capability of occluding vessels could make focused US a therapeutic tool for the treatment of vascular malformation [44]. Furthermore, lesions can be induced using MRI targeting to treat movement disorders (Parkinson disease) or epilepsy; in the first clinical trial in 1960, the Fry brothers used US to ablate small tissue volumes to treat Parkinson disease [7].

Focused US can be used not only as a functional neurosurgical method, but also as a way to achieve targeted drug delivery through selective opening in the blood–brain

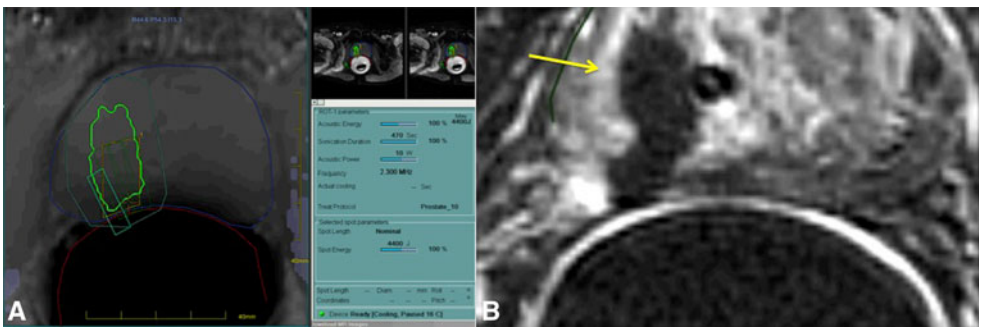

Fig. 9 A 68-year-old man with low-risk organ confined prostate cancer (prostate-specific antigen nadir, 8; Gleason score, 6 – 3 + 3) indicated to radical prostatectomy was included in a phase I trial for MRgFUS treatment before surgery. **A** At treatment time, prostate cancer was visible at 3 T MR images that were used for treatment planning. The system automatically generates a lesion-specific sonication program that spares normal prostate parenchyma for focal ablation. More importantly, the system spares the rectal wall, preventing local parietal damage through active intrarectal cooling and real-time temperature mapping at treatment. **B** Immediately after treatment, gadolinium-enhanced T1-weighted image was acquired for treatment efficacy and safety control. The ablated volume appears as a nonperfusing area (*yellow arrow*) with intact adjacent rectal wall. Surgery after MRgFUS treatment was carried out without treatment-related complications or operator difficulties

barrier and to introduce large molecular drugs into targeted brain regions [45, 46]. These large molecules can be used for chemotherapy or can act as functional neuropharmacological agents [47, 48].

Moreover, on the basis of clinical evidence in functional neurosurgery for neuropathic (or neurogenic) pain with radiofrequency stereotactic interventions in medial thalamus [49], in 2012 Jeanmonod et al. [50] performed transcranial MRgFUS in 11 patients with chronic therapy-resistant neuropathic pain, inducing a thermal ablations of 3–4 mm in the posterior part of the central lateral thalamic nucleus. Treated patients exhibited pain relief in subsequent clinical follow-up, from a preoperative mean visual analog scale pain score of 59.5/100 to a postoperative mean score of 34.3/100 at 3 months and 35.3/100 at 1 year.

Ablation of Abdominal Moving Organs Tumors: Background

US-guided HIFU is presently an emerging noninvasive technique for the ablation of solid tumors in abdominal organs in selected patients [51]. Hepatic, renal, and pancreatic treatment have been performed in large patient cohorts with good success rates [52–54]. In particular, the liver has been sonicated with a focused US beam in animal models, and in the past decades, the ablative technique has been widely optimized, with several literature reports of treatment of hepatocellular carcinoma with HIFU alone or in combination with transarterial chemoembolization [55], without significant adverse events or collateral damage to vulnerable structures such as intraparenchymal vessels or bile ducts. Other research groups [56, 57] have successfully performed US-guided treatments in patients with liver metastases, with complete response after ablation. On the other hand, treatment of pancreatic cancer has been performed on a small number of patients, mostly in subjects in whom other therapeutic options have been exhausted; occasional literature reports demonstrate a reduction in lesion size after treatment of between 20 and 70 %, pain relief after ablation, and increase in survival rate without significant complications [58]. Similar observations have been noted in patients with renal cancer, with complete

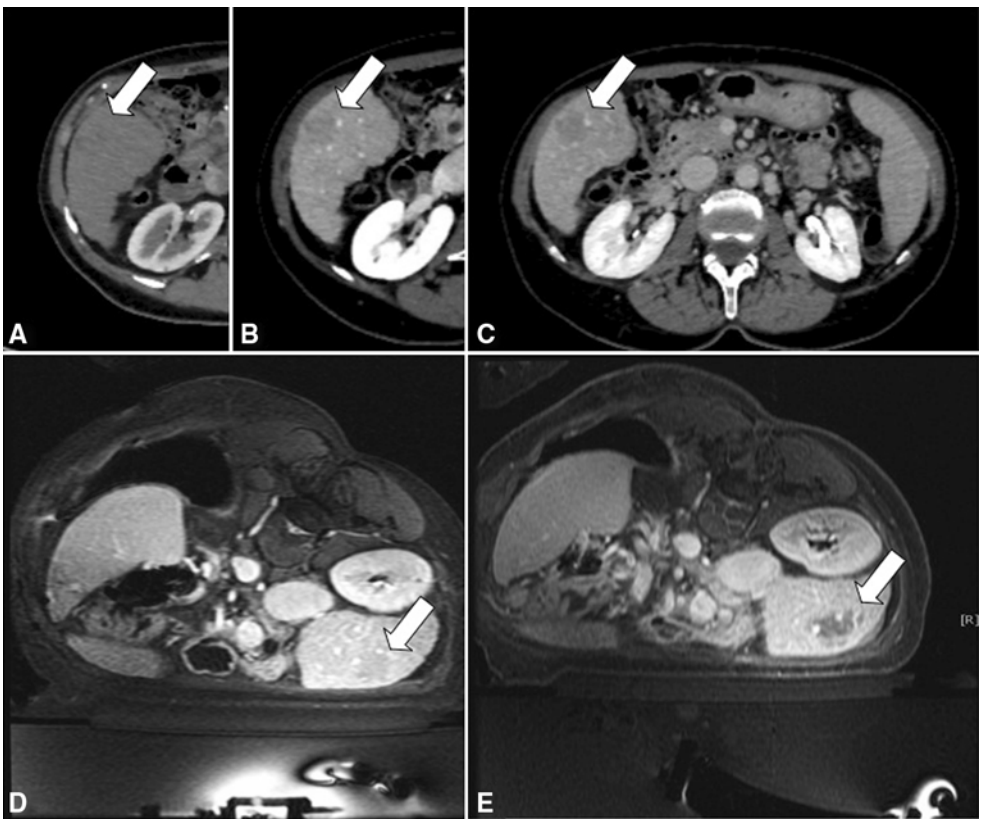

Fig. 10 A 68-year-old woman with hypovascular HCC on the VI hepatic segment, previously resected for a single nodule at the left lobe, refused another surgery. It was proposed that she undergo MRgFUS treatment of an acoustically accessible lesion. Contrast-enhanced axial CT image shows a hypovascular hepatocellular carcinoma (*white arrow*) in the VI segment during arterial (**A**), portal venous (**B**), and late venous phase (**C**). The treatment was performed under general anesthesia, with the patient positioned the right lateral decubitus in order to reduce liver movement and to achieve wider contact between the abdominal wall and the transducer surface. Pretreatment localization of the tumor with contrast-enhanced acquisition (**D**) and posttreatment visualization of the nonperfused area (**E**)

tumor ablation and reduction in hematuria without adverse effects [59].

Ablation of Abdominal Moving Organs Tumors: Clinical Indications and Personal Experience

The principal feasibility of HIFU ablation has been proved and extensively validated for parenchymal abdominal organs; MRI guidance application in this field should thus be considered a natural evolution of this modality. As a state of the art, there are only occasional literature reports of MRgFUS ablation performed the in abdominal organs, mostly on animal models of liver lesions, with clinical trials in humans still ongoing. This scenario is probably related to the fact that MRI visualization and tracking of abdominal organ movement is still under development, and real-time guidance is at present more easily achieved with US, pushing abdominal applications HIFU toward this later guidance system. More recently, real-time liver motion compensation has been developed and tested in healthy volunteers, potentially providing a chance for more accurate MRI guidance for liver ablation.

In our department, MRgFUS ablation has been successfully performed in 1 patient with unifocal hepatocellular carcinoma in the right liver lobe (segment VI). The patient refused surgery and was not eligible for other treatment options, including transarterial chemoembolization and RF ablation. The treatment was performed under general anesthesia, with the patient positioned lying on the right side to reduce liver movement and to achieve wider contact between the abdominal wall and the transducer surface. Because the lesion was predominantly hypovascular and could be adequately identified only on hepatobiliary excretion phase imaging, treatment effects were evaluated indirectly, mostly on the basis of the size and overlap of the necrosis area compared to the original lesion location (Fig. 10). Posttreatment follow-up laboratory analysis demonstrated a decrease of α-fetoprotein compared to baseline levels.

Two further patients with unresectable cancer of the pancreatic body have been also treated with MRgFUS as a last-line option to manage tumor growth and symptoms after failure of other clinical options, including alcoholization of the celiac plexus. In both cases, treatment was performed under general anesthesia with patients in the prone position. Treatment efficacy was evaluated with dynamic contrast-enhanced MRI, revealing an extensive decrease of contrast agent uptake from tumor tissue after MRgFUS ablation compared to baseline examination. Also, clinical evaluation of both subjects demonstrated significant reduction of symptom severity at 1–6 months as assessed by a visual analog scale.

Conclusions

High-intensity focused ultrasound has been proven to be an effective, noninvasive ablation technique for the treatment of both benign and malignant tumors, with a well-established clinical experience under conventional US guidance. Recent introduction of MRI guidance systems featuring real-time thermal mapping technology, as well as the development of advanced focused US transducers, can significantly improve the efficacy of this modality, mostly in consideration of new clinical applications, such as transcranial brain ablation or moving-organ ablation. Although the MRgFUS procedure has high initial costs, it provides rapid gains in quality of life and shortens the rehabilitation time after treatment compared to surgery. Moreover, MRgFUS has been demonstrated to reduce the length of hospitalization for treated subjects; it is feasible on an outpatient basis and requires no specific care on an inpatient basis. Severe complications are virtually absent.

Conflict of interest The authors declare that they have no conflict of interest.

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