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High-resolution Intravascular MRI-guided Perivascular Ultrasound Ablation

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Abstract

Purpose: To develop and test in animal studies *ex vivo* and *in vivo*, an intravascular (IV) MRI-guided high-intensity focused ultrasound (HIFU) ablation method for targeting perivascular pathology with minimal injury to the vessel wall.

Methods: IV-MRI antennas were combined with 2–4mm diameter water-cooled IV-ultrasound ablation catheters for IV-MRI on a 3T clinical MRI scanner. A software interface was developed for monitoring thermal dose with real-time MRI thermometry, and an MRI-guided ablation protocol developed by repeat testing on muscle and liver tissue *ex vivo*. MRI thermal dose was measured as cumulative equivalent minutes at 43°C (CEM₄₃). The IV-MRI IV-HIFU protocol was then tested by targeting perivascular ablations from the inferior *vena cava* of two pigs *in vivo*. Thermal dose and lesions were compared by gross and histological examination.

Results: *Ex-vivo* experiments yielded a 6-minute ablation protocol with the IV-ultrasound catheter coolant at 3–4°C, a 30ml/min flow rate, and 7W ablation power. In 8 experiments, 5–10mm thick thermal lesions of area 0.5–2cm² were produced that spared 1–2mm margins of tissue abutting the catheters. The radial depths, areas and preserved margins of ablation lesions measured from gross histology were highly correlated ($r = 0.79$) with those measured from the CEM₄₃=340 necrosis threshold determined by MRI thermometry. The *psoas* muscle was successfully targeted in the two live pigs, with the resulting ablations controlled under IV-MRI guidance.

Conclusion: IV MRI-guided, IV-HIFU has potential as a precision treatment option that could preserve critical blood vessel wall during ablation of non-resectable perivascular tumors or other pathologies.

Keywords

intravascular MRI (IVMRI); high intensity focused ultrasound (HIFU); MR-guided ultrasound ablation; liver and pancreatic cancer; vessel involvement

Introduction

The degree of involvement with adjacent blood vessels is often critical in determining whether a malignancy is surgically resectable. Pancreatic cancer, which has an incidence of 54,000 new cases and 43,000 deaths in the USA per year, is an example(1–4). Cancers with extensive tumor-vessel involvement and/or heterogeneous vessel contours around critical vessels like the superior mesenteric artery, are considered non-resectable and have very poor survival rates that are 3–10 times worse than those that are surgically resectable(1,5). Hepatocellular cancer, with 42,000 new cases and 32,000 deaths annually is another example. It has a high incidence of recurrence post-resection (~20%, ~50% and ~75% within 1, 3 and 5 years post-surgery respectively). In both examples, the need to preserve high-value tissue while carefully removing tumor at the margins are critical considerations(6,7). For these and other pathologies, new methods of precision-guided therapy delivery could have a critical impact on reducing their terrible toll and improving patient outcomes.

Two common types of palliative or potentially curative treatments undergoing clinical trials are percutaneous ablation and extracorporeal high-intensity focused ultrasound (HIFU)(8–10). Currently, percutaneous ablations include thermal ablation methods such as radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation and cryoablation; and non-thermal ablation such as irreversible electroporation (IRE) and photodynamic therapy. These are nearly all performed percutaneously in the abdomen, and are prone to complications, such as vascular damage, bowel perforation, fistulae, needle tract metastasis and organ dysfunction(5,11,12). Extracorporeal HIFU is a non-invasive alternative to percutaneous techniques which employs an array of external transducers that focus ultrasound energy on a target lesion, under the guidance of noninvasive magnetic resonance imaging (MRI). Yet significant challenges remain with HIFU due to the requirement of an ultrasound-transparent window between the HIFU transducers and the lesion; the complexity of tracking the precise motion of the treatment point under MRI; the obstruction or deflection of the incoming ultrasound fan-beam by air or bone; and the need to avoid injury to vital organs and vessels that lie in or near the beam's pathway(13–15).

Nevertheless, MRI is arguably an ideal modality for guiding intervention because of its lack of ionizing radiation and its multi-functionality(16). It offers angiographic-, perfusion-, diffusion-, soft-tissue relaxometry-, pathology- and therapy-sensitive contrast, as well as quantitative thermometry for titrating thermal therapies such as those using HIFU, for example(17–19). Intravascular (IV) MRI employing small internal detectors configured as catheters or guidewires, can provide higher resolution (<100µm) and signal-to-noise ratio (SNR) than regular MRI in clinical scanners(20,21). They potentially offer a precise, minimally-invasive, diagnostic(22,23) and interventional imaging modality, at least within a

range of a few centimeters from the probe. RFA employing a single IV-MRI probe for image guidance, energy delivery and thermometry for monitoring dose, has been demonstrated in tissue specimens and *in vivo* in a clinical 3 Tesla (T) MRI scanner(24). However, the RFA lesions produced this way are limited primarily to the point of contact of the MRI-sensitive portion of the catheter with the tissue, causing injury to the vessel wall in IV applications.

Like performing IV RFA, HIFU ablations can also be delivered via small ultrasound transducers(25,26). Unlike extracorporeal HIFU methods, a local IV-HIFU approach could avoid much of the difficulty with finding suitable acoustic windows. It could potentially enable the delivery of therapy from inside a nearby blood vessel to a perivascular target, without damaging the intervening vessel wall(27,28). While IV-HIFU's sister technology, IV ultrasound imaging (IVUS), could be used to guide IV-HIFU ablations, IVUS currently requires X-ray guidance for deployment and does not provide reliable thermometry. Without precision guidance and thermometry, it would be unable to precisely ablate a margin of tumor around a major vessel while safely preserving the vessel wall itself.

Here we present a novel IV-MRI loopless antenna detector combined with a water-cooled IV-HIFU ablation catheter that provides precision MRI-guided targeting, monitoring and thermal titration of perivascular ablation. In *ex vivo* experiments employing single and double-transducer IV-MRI catheter prototypes, we demonstrate the ablation of extra-vascular tissue targets while preserving a margin of the intervening vessel wall. IV experiments on healthy animals are used to develop a viable IV-MRI guided IV-HIFU ablation protocol and translate the technology *in vivo*. The ultimate goal is to provide a minimally-invasive, IV-accessed ablation technology that could provide precision localization and perivascular ablation to render an inaccessible or non-resectable cancer with vascular involvement, resectable.

Methods

Devices

All MRI studies were performed on a *Philips Achieva* (Koninklijke Philips N.V., Amsterdam, Netherlands) 3T scanner with an in-room image monitor for interventional studies, used previously(20–24). MRI-HIFU ablation catheters were comprised of a loopless IV-MRI antenna formed from an 0.8 mm outer diameter (OD), 0.88m long, biocompatible nitinol coaxial cable with a 42 mm whip tuned to resonate at 128 MHz in a lossy medium (0.35% saline). The antenna was deployed as a receiver coil which was turned-off during excitation via a positive-intrinsic-negative (PIN)-diode in its matching circuit(20). Operated alone, the antenna was tested *in vitro* and *in vivo* on this system, wherein heating on the wire and cable was kept within ~1°C during MRI(20,21). Maximum heating and MRI sensitivity occurred at the cable-whip junction.

The antenna was incorporated into intravascular HIFU ablation catheters fabricated with three different geometries affording single- or dual-beam ablation patterns with properties summarized in Table 1 (Fig. 1c, d, e). The antenna's cable-whip junction was aligned in the axial plane orthogonal to the catheter's long axis through the center of the HIFU transducer(s) to provide maximum MRI sensitivity in the ablation plane. The transducer(s)

in each catheter were encapsulated in a non-conducting biocompatible polymer jacket. The jacket was water-cooled at a 20–50ml/min flow-rate via a computer-controlled *Acoustic MedSystems Inc.* (Savoy, Illinois, USA) *TheraVision* pump with an off-the-shelf closed-loop water chiller, located in the MRI console room. The coolant protected the transducers from overheating and also cooled the IV-MRI antenna as well as the tissue immediately adjacent to the jacket. The IV-MRI antenna was externally affixed to HIFU catheters #1 and #2 (Fig. 1a) via paper tape to facilitate interchange of probes during development and testing. The heating profile and focus size of catheter #1 is included as *Supporting Information* (Fig. S2). Catheters #2 and #3 have diverging radiation profiles (Table 1). HIFU catheter #3 was fabricated with a 1.45mm OD central lumen to accommodate a guidewire through which the loopless antenna was inserted for IV-MRI (Fig. 1b).

During ablation, the transducers were driven by a 4-channel 6–14 W RF amplifier also controlled by the *TheraVision* unit. A schematic of the combined HIFU/MRI catheters and their connections is included as *Supporting Information* (Fig. S1). The RF coupling between the IV-MRI antenna and each HIFU catheter #1–3 was documented with S-parameter measurements of the power transfer (S21).

Thermometry

MRI thermometry was performed using the proton resonant frequency shift (PRFS) method and fast field-echo (FFE) imaging sequences. In initial experiments, FFE magnitude and phase images for each scan were transferred in real-time to a local computer equipped with modified *Sonallevé™* (*Profound Medical Corp.*, Mississauga, ON, Canada) software for temperature display(29). The product *Sonallevé* software operates with a transducer array embedded in a patient table not used here. Thus the software's focus-planning component was modified to enable selection of the catheter location relative to anatomical MRI scans(29) and the array-based adjustments eliminated. Subsequently, a dedicated *MATLAB* (*The MathWorks, Inc.*, Natick, MA, USA) IV-MR ultrasound ablation software interface (Fig. 1f) was developed for real-time temperature mapping and measuring thermal dose. This software incorporates drift corrections and accommodates the non-uniform sensitivity profile of the IV-MRI antenna. It runs on a laptop connected to the MRI system's console computer via an ethernet cable (Fig. 1f; inset), through which data are transferred via *MATLAB MatMRI*(30) software based on an 'eXTernal Control' (XTC) protocol(31).

Phase-difference images were computed from dynamically-acquired FFE phase images and converted to temperature maps with a resonant frequency shift coefficient $\alpha = -0.0094 \text{ ppm}/^\circ\text{C}$. The temperature of unablated tissue measured with a remote fiber-optic temperature probe (*Neoptix Canada LP, Qualitrol Company LLC*, Fairport, NY, USA) was assumed as baseline. The *MATLAB* software automatically detected the catheter location from the IV-MRI antenna's non-uniform sensitivity profile, and selected regions 5cm from the transducer to serve as constant-temperature reference points on the thermal maps. These were used to provide a first-order temperature drift correction. During ablation, pre-ablation cooling, and post-ablation cool-down periods, the operating parameters (ablation time, flow rate, power level) of the *TheraVision* system were manually adjusted to achieve the desired heating and cooling based on the real-time thermometry monitor.

Post-ablation, thermal dose maps—measured in cumulative equivalent minutes at 43°C ('CEM₄₃')—were derived by temporally integrating the dynamic real-time temperature maps(32,33) after de-noising and co-registering them with anatomical images. A CEM₄₃ of 340 has been assumed as a threshold for producing necrosis(24,34,35), so the MRI-based lesion-dose-threshold CEM₄₃=340 contours were calculated, smoothed to generate continuous loops, and overlaid on co-registered photographs of lesions. The areas of the continuous CEM₄₃=340 loops were measured as a potential IV-MRI proxy for lesion size.

A flowchart of the treatment/monitoring protocol is provided as *Supporting Information* (Fig. S3).

Ex vivo studies

Bench-top and in-scanner *ex vivo* studies of tissue specimens were used to characterize system performance. The efficacy of the probe cooling and ablation sub-systems were first evaluated in bench-top ablation experiments on chicken breast muscle. The chicken was immersed in saline at 37°C, and an IV-HIFU catheter inserted. Coolant flow, temperature, IV-HIFU power level and duration were adjusted to determine a range of suitable operating parameters for in-scanner studies. After bench-top ablation, the tissue was sectioned axially at the ultrasound transducer location, and thermal lesions photographed.

In-scanner studies were performed on chicken breast tissue as above, and with IV-MRI/HIFU catheters inserted in the blood vessels of fresh porcine liver specimens. Each catheter-bearing specimen was immersed in a 10L box of saline at 37°C, which in turn was enclosed in a 1cm-thick rigid polyurethane thermal insulating jacket. With the *TheraVision* ablation controller in the scanner console room, the coolant circulation tubing was connected to the catheter via a wall-port on the cable penetration panel penetrating the scanner's RF screen-room. High-resolution anatomical imaging was performed before and after ablation using balanced FFE (bFFE; repetition time, TR=6.2ms; echo time, TE=2.4ms; flip angle, FA=20°; resolution=300µm; slice thickness, SL=4mm; field of view, FOV=150mm); spin-lattice relaxation time, T₁-weighted FFE (T1FFE; TR/TE=15/3.9ms; FA=7°; resolution=300µm; SL=4mm; FOV=150mm); and three-dimensional (3D) fat-suppressed, T₁-weighted high-resolution isotropic volume examination (THRIVE; TR/TE=23/11ms; FA=12°; resolution=300×300µm; SL=4mm; FOV=150mm) sequences.

After locating the transducer and ablation target by sagittal and coronal IV-MRI, an imaging plane was placed perpendicular to the HIFU transducer. Coolant was circulated and MRI thermometry commenced with real-time thermal monitoring (Fig. 1f) using FFE Cartesian (TR/TE=100/25ms; FA=25°; echo-planar imaging, EPI factor=11; resolution =300µm; SL=6mm; FOV=150mm; acquisition time =6.0s) or radial (TR/TE=25/12ms; FA=14°; angle density=50%; resolution=300µm; FOV=150mm; acquisition time=6.2s) sequences. HIFU ablation was typically initiated after 5min of pre-cooling and continued for a period of about 6min. Ablations were repeated with the IV-MRI HIFU probe in different locations, cooling, power levels and specimens, to determine the relationship between thermal dose measured by MRI thermometry, and lesion size; and to characterize the ablation unit's settings and MRI thermometry signature that avoided tissue damage immediately adjacent to the probe.

Post-ablation, samples were sectioned at the ablation plane and photographed. To differentiate lesion from normal-appearing tissue, principal component analysis (PCA) was performed on approximately equal numbers of pixels from normal tissue (crimson) and lesions (pallid) in each photograph based on the International Commission on Illumination uniform color space ('1976 CIELAB')(36). Color space values for each pixel were projected to the first principal component to generate scalar maps representing the appearance of pixels from normal tissue (lower values) and thermal lesions (higher values). The maps were normalized to a 'CIELAB₁₀₀₀' scale of 0 to 1000, with a threshold of CIELAB₁₀₀₀=500 chosen to contour lesion areas using an active snake-contour object-detection algorithm(37). Vessel walls were then traced manually on the photographs. Portions of the same lesions that extended to different dissections were co-registered based on their positions relative to the vessel wall to determine maximum lesion depths. Anatomical MRI scans were reconstructed at the thermometry plane by interpolation, co-registered with the CEM₄₃=340 dose contour, and annotated with the catheter and vessel wall locations. The images were scaled and co-registered with the contoured photos for comparison.

The gap, L_g (mm), comprised of non-ablated tissue lying between each lesion and the vessel wall, was measured as the average distance between the endo-luminal wall and the closest segment of lesion contour in the marked photographs. The longest radial distance, L_r (mm), between the lesion's distal-most and proximal-most points relative to the endo-luminal vessel wall, and the ablation area, L_a (mm²), were also measured from the dissections. L_g , L_r , and L_a were compared with the gap (mm) between the vessel wall and the CEM₄₃=340 contour; the longest radial length of the CEM₄₃=340 lesion contour; and the CEM₄₃ 340 contour area measured by IV-MRI thermometry, respectively. Overlap between the CEM₄₃ 340 lesion areas and those from photos were quantified via the Jaccard index, equal to the fraction of the area of the intersection divided by the total area of the two together.

The post-ablation image processing and data analysis were implemented in *MATLAB* and applied identically in 8 (non-selected) consecutive liver ablation experiments performed with catheter #1.

In vivo studies

To test the IV-MRI guided HIFU ablation catheter *in vivo* where blood flow, perfusion, and physiological motion are potentially confounding, ablation experiments were performed in two live pigs under general anesthesia with approval of our Institutional Animal Care and Use Committee. *Psoas* muscle and colon near the inferior *vena cava* (IVC) were selected as ablation targets. Real-time IV-MRI thermometry with the loopless antenna was used to guide, target and titrate thermal dose.

In each anesthetized pig, the right common femoral vein was accessed with a micropuncture kit and sequential fascial dilators. A 16 French (Fr) 30cm *Cook Medical* (Bloomington, Indiana, USA) sheath was placed and HIFU catheter #3 advanced into the IVC over a 0.035" guidewire in the central lumen of the catheter, under X-ray fluoroscopy. The position of the distal tip of the catheter was confirmed by fluoroscopy and cone-beam X-ray computed tomography. The 0.035" guidewire was replaced by the IV-MRI antenna. The left femoral artery was accessed via a 5Fr sheath and a fiber-optic temperature probe placed in the sheath

to monitor body temperature far from the ablation site, for determining absolute temperature via the PRFS method. Pigs were heparinized prior to catheterization.

After catheterization, each animal was transferred to the MRI scanner, and the catheters were located by three orthogonal (transverse, sagittal and coronal) T₁-weighted FFE IV-MRI projections (TR/TE=9.4/4.6ms; FA=15°; FOV=300×300×400 mm³; resolution=1.5 mm; scan time=10s). Positioning was confirmed by spin-spin relaxation time (T₂) weighted turbo spin-echo imaging (T2wTSE; TR/TE=4s/95ms; FA=90°; FOV=200 mm; resolution=0.7mm, SL=5mm) using a pair of *Flex-M* (Koninklijke Philips N.V., Amsterdam, Netherlands) surface coils placed above and below the abdomen at the catheter's approximate location; and by high-resolution sagittal and coronal T₁ FFE images acquired with the IV-MRI antenna using the same protocols as in *ex vivo* studies. The high-resolution transverse images were acquired to provide precise anatomical registration for thermometry for locating the ablation target and avoiding vessel injury. Device advancement and retraction was performed by an operator in the scanner room in communication with the scanner operator.

Pre-cooling was commenced followed by high-resolution real-time MRI thermometry (Fig #1: radial acquisition, TR/TE=25/7.7ms, FA=14°, angle density=100%, resolution=0.5mm, FOV=150×150×6mm³, acquisition time=7.5s; Fig #2: Cartesian acquisition, TR/TE=168/17ms, FA=30°, EPI factor=11, resolution=0.5mm, FOV=150×150×6mm³, time of acquisition=6.0s) employing the loopless antenna as a receiver and the MATLAB software interface for temperature monitoring (Fig. 1f). Based on evidence of heating by MRI thermometry, torque was applied to the ultrasound catheter to rotate the HIFU beam to the intended target. With HIFU power titrated based on IV-MRI thermometry, sufficient heat was deposited in the target to form a lesion, as guided by the results of the *ex vivo* studies. The transducer was powered off and the catheter was withdrawn 1–2 cm along the blood vessel. MRI and ablation procedures were then repeated to create separate or contiguous thermal lesions.

Animals were humanely euthanized, post-ablation. The IVC through which the catheters were routed, the colon wall, adjoining *psoas* muscle and other tissue surrounding the ablation sites were harvested and assessed for lesion formation and comparison with the thermal dose measured by MRI thermometry. Dissected tissues were fixed and processed for histology with hematoxylin and eosin (H&E) and Masson's trichrome (MT) staining which was reviewed by a pathologist (KG). Movat staining was also used to highlight vessel wall in some *in vivo* and *ex vivo* studies.

Results

Ex vivo studies

The S21 parameters for the IV-MRI antenna combined with each of the three catheters from 0.1MHz to 150MHz were –70dB to –25dB. Bench testing in chicken, indicated that key factors improving the preservation of tissue immediately adjacent to the IV-HIFU catheter were: reducing the temperature of the coolant; and increasing the flow to the catheter. Other factors were: the thermal energy delivered by the ablation transducers, as monitored by MRI

thermometry; and transducer geometry. A coolant temperature of 3–4°C at the pump output and 10–13°C where it entered the catheter, a flow of ~30 ml/min and a HIFU power ~7 W for ~6 min were found to produce thermal lesions of up to 2 cm² while preserving a 1–2 mm margin of tissue abutting the catheter. Parallel to the catheter, maximum lesion extent corresponded to the transducer length (Table 1).

Exemplary results from chicken are shown in Fig. 2, where an inner margin of pink preserved tissue at the catheter location is surrounded by a pallid ablation lesion (Fig.2a). On MRI, the IV-MRI/HIFU catheter is easily located via the bright sensitivity of the antenna (Fig.2b,c). During pre-ablation cooling, real-time temperature maps reconstructed from dynamic MRI phase images show local temperature decreases 10°C (Fig. 2d). During ablation, increases of 70°C are evident 3–5 mm away from the catheter (Fig.2e), with no evidence of heating adjacent to the IV MRI probe itself. The MRI thermometry-based CEM₄₃=340 contour co-registered onto a photograph of the section (Fig. 2f), showed fair consistency with the CIELAB₁₀₀₀=500 lesion (magenta and white contours; Jaccard index=0.62).

Fig.3 illustrates an IV MRI-guided HIFU ablation accessed from a blood vessel in a porcine liver using catheter #1. Dynamic MRI thermometry shows the evolution of the temperature rise 5–10mm away from the vessel wall (Fig.3d–f). Fig. 4(a) shows a dissection through the ablation plane. Fig. 4(b) is the corresponding CIELAB₁₀₀₀ map of the dissection used for segmenting the lesion. Fig. 4(c) shows an annotated anatomical MRI reconstructed at the thermometry plane, delineating the CEM₄₃=340 contour. Fig. 4(d) shows the dissection annotated with the CEM₄₃=340 contour, co-registered with the CIELAB₁₀₀₀=500 contour. The estimates (depth, area, and gap to vessel) of lesion area enclosed by the CEM₄₃=340 contours and the lesion areas measured from all the samples sections are plotted in Fig.5 and are highly correlated ($r>0.79$; $p<0.02$). The ablations spared the intervening vessel wall by >0.5mm in 6 of 8 experiments (Fig.5c), with one failure due to parting of the tape affixing the IV-MRI antenna to the HIFU catheter. Jaccard indices for the 8 experiments are all >0.51 (Fig.5d).

Incorporating the IV-MRI antenna into a lumen—as in HIFU catheter #3 (Fig.1b)—improved the visibility of the catheter components in porcine liver (Fig.6a). The transducer elements do not interfere with the performance of the IV-MRI antenna, suggesting negligible coupling. The inclusion of two transducer elements provided simultaneous and/or sequential thermal beams that heated in opposite directions (Fig.6b–e). Movat-stained histology shows preservation of a non-ablated tissue margin between the vessel wall and lesion (Fig.6g).

In vivo studies

Sagittal T2wTSE images confirmed the location of the IV-MRI/HIFU ablation catheter #3 in a porcine IVC *in vivo* via its hyperintense signal (white arrow, Fig.7c). With three orthogonal image projections, the catheter was easily located within a minute. A high resolution, axial MRI acquired from the IV antenna in the catheter lumen is shown in (Fig. 7d). Thermometry for several ablations in the *psaos* muscle and colon are shown in Fig. 8(a–e). Initially, power was applied to the HIFU transducer to determine the ablation path. Within 7–15s it was evident that the HIFU beam was not facing the *psaos* muscle target.

This was maintained for 70s to produce the thermal map in Fig. 8(c). The catheter was then rotated towards the target (Fig. 8d). In addition, to the *psaos* muscle, power was applied to the transducer on the opposite side of the catheter to test whether it could access and ablate the colon (Fig. 8d,e). The HIFU power levels were ~11W for 6 min per transducer. The MRI times were 10s for a scout localization image; 5min for localization and high-resolution anatomical MRI; and 8–12min for thermometry scanning during and post-ablation for each treatment target.

Post-mortem sectioning revealed thermal lesions on the mucosa surface of the colon (Fig. 8f) and the *psaos* muscle where ablations were performed (Fig. 8g,h). We observed no evidence of a lesion at the site of the mis-directed beam. Histopathology confirmed skeletal muscle degeneration, edema and hemorrhage in H&E stained slides, consistent with thermal lesions.

In a second pig study, ablations were performed at three locations approximately 1cm apart during a ‘pullback’ to create a contiguous ablation lesion during simultaneous thermal monitoring. At each location, an anatomical reference image was acquired for thermometry, followed by continuous thermometry (Fig. 9b–d). As in Fig. 8(c), the HIFU beam in the first location (Fig.9b) was mis-oriented too far clockwise relative to the target and the catheter was rotated slightly for the second and third ablations (Fig.9c,d).

Post-mortem dissection revealed evidence for three thermal lesions on the *psaos* muscle at the ablation locations beneath the IVC. The first lesion was rotated relative to the others (Fig.9e, white arrow). The second and third lesions (yellow and cyan arrows) were contiguous. The thermal lesions were confirmed by the histopathologic evidence of skeletal muscle degeneration, edema and hemorrhage. The IVC segments dissected post-ablation showed no gross lesions visually, but vessel wall hemorrhage was noted in some histological slides. Whether hemorrhage was caused by mechanical abrasion from the catheter or thermal injury was unclear.

Discussion

This is the first report on IV MRI-guided transvascular HIFU ablation. The technology combines IV-MRI’s advantages of high-resolution, multi-functionality and a unique thermal mapping capability(24), with access to extra-vascular ablation targets afforded by IV-HIFU. It thus presents an ablation therapy option for situations where conventional extra-corporeal MRI-guided HIFU may not be possible due to acoustic opacity, or the presence of critical tissue or vessels in the path of the external beam. The results demonstrate that IV-MRI guided HIFU ablation can be reliably performed right up to the edge and within a millimeter of, the intervening vessel wall without thermal injury (Figs. 2,4,5). Surprisingly perhaps, the performance of the IV-MRI antenna was little impaired by the presence of the HIFU transducers and cooling system. Although we used X-ray fluoroscopy to guide initial catheter placement, a fully MRI-guided interventional procedure is the ultimate goal, and high-speed ‘MRI endoscopy’ is currently under development as a possible MRI-based catheterization modality(38–40). Meanwhile, the present *in vivo* studies demonstrate a viable protocol for locating the ablation catheter relative to the anatomy; manipulating the

ablation transducers to direct them at an ablation target; and titrating the delivery of thermal therapy. As such, the technology seems promising for treating tumors that are currently surgically inaccessible, or that are non-resectable due to perivascular involvement.

IV-MRI probes of the same design used here have been tested *in vitro* and *in vivo* at 1.5T and 3T, and were shown to be safe from RF heating when used alone(20,21). Here, the probes were turned off during transmit, but their use in conjunction with a HIFU catheter could introduce new coupling mechanisms and risk of heating. However, the high isolation indicated by the S21 measurement; the lack of MRI artifacts other than the absence of signal from components that lack mobile protons (Figs. 2,3,6a); and the preservation of tissue immediately adjacent to the catheter (Fig. 5), suggest that electromagnetic coupling, if extant, is minimal. Moreover, the IV-MRI probe benefits from the HIFU transducer's cooling system and non-conducting polymer sheath, especially in catheter #3 used *in vivo*. Here, the whip junction—which is expected to heat the most(20)—is completely enclosed by it, so if it does heat during MRI, the water cools it. While loopless IV-MRI antennas were used here because of their small size, loop antennas could also be deployed if the isolation from the HIFU transducer is similarly maintained. Incorporating them into the HIFU transducer space instead of the lumen would allow an OD of ~2mm, and a discoidal-shaped FOV suitable for transmit/receive MRI endoscopy(21).

The highly-localized sensitivity of the IV-MRI antenna (Fig.7c) enables localization of the transducer in a few projections that could be incorporated into an automated pre-scan localization routine(39) and followed by user-prescribed high-resolution imaging and thermometry. Although not used here, the localized sensitivity profile of each projection may also provide a means of motion-correction(40). Like conventional thermometry, high resolution IV-MRI thermometry is subject to drift in the reference phase during procedures(41–44). Acquiring a reference phase image prior to commencing each ablation, limits the potential drift period to the duration of each ablation. Moreover, for highly localized IV-HIFU ablation targets, monitoring temperature remote from the ablation site, which presumably remains at body temperature (Figs. 8,9), provides a measure of drift for correcting temperature.

Of the three HIFU transducer designs tested, the flat (catheter #1) and cylindrical segment or 'sector' (catheter #3) transducers penetrated deeper than the transducer with the 360° radial pattern (catheter #2), if only because the latter had a higher driving frequency (Table 1) and hence a higher attenuation in tissue(45). Nevertheless, the catheter #2 transducer preserved a ring of tissue and was more efficient at ablating a circular lesion for creating an ablation margin around the vessel, for example (Fig.2a). Gluing or mechanically attaching the HIFU and IV-MRI antenna would certainly provide more robust mounting options than the taping used for catheter #1 and #2 implicated in the failure noted for Fig. 5(c). Including the lumen in catheter #3 (Fig.1b) provided easier device exchange without risking detachment. It also facilitated multi-modality image guidance—X-ray fluoroscopy and MRI—with less metal artifacts in the images (Fig.6a). More precise control and tailoring of the thermal ablation beam could be achieved in future by adding more individually-powered transducer elements.

Improving the IV-HIFU/MRI catheter design to reduce its diameter and increase flexibility are important considerations for facilitating interventional procedures, especially if access to pathologies from smaller vessels is sought. While the evidence is inconclusive, we think that the overall size and flexibility of catheter #3 (4.3mm OD), was the likely cause of the occasional hemorrhage seen in the second *in vivo* study, given the absence of MRI thermometry and histological evidence for vessel wall heating at ablation sites where exposure was greatest (Figs. 5–8). Heating affects are potentially addressable by adjustments to the coolant temperature and/or flow, and catheter biocompatibility evaluated with sham procedures not involving MRI or HIFU. The development of an IV-MRI/HIFU needle may be another option for interstitial targets or where vessel size is limited.

That the temperature and flow of coolant to the probe affects the preservation of adjacent tissues suggests a dual role for it in cooling both catheter and the tissue immediately surrounding it. Although we set the *TheraVision* system's water-cooling heat exchanger in the console room at 3°C and used closed-cell polyurethane thermal insulation on the 5m long coolant hoses, the combined effect of the ~20°C room temperature and heating during ablation, resulted in a coolant temperature at the catheter head of an intermediate 10–13°C. The coolant temperature at the catheter could be reduced by establishing a reservoir inside the scan room or by increasing the flow-rate. However, the flow-rate is limited by catheter size, whose diameter is ultimately constrained by vessel size.

The acquisition of temporal MRI thermometry data enabled calculation of thermal dose in CEM₄₃ and the estimation of the shape and size of thermal lesions (Fig.4, Fig. 5a,b). As a threshold for producing thermal coagulation and lesions(34,35), we observed that the CEM₄₃=340 contour derived from MRI thermometry tended to overestimate the size of lesions identified by quantitative analysis of the sample dissections (Fig. 5). In some experiments (#1, #5 in Figs. 5a,b), significant areas of lesion appeared on different slices which may have contributed to underestimation in the individual dissections, as compared to thermometry. Some tissue loss and deformation of lesion areas is also inevitable during the preparation of dissections. The finite length of the HIFU transducer (~1cm) and limited depth of ablation parallel to the catheter's long axis are other mitigating factors.

In addition, CEM₄₃-based methods can overestimate thermal injury in a manner that depends in a complex way on the temporal temperature profile(35). Lesions manifesting significant color changes at gross examination are likely to correspond only to fully-coagulated cores and may not extend to the entire lesion area. Indeed, various studies have shown that the coagulation core continues to expand up to 2 weeks post-ablation, gradually establishing a rim that is evident on MRI and comprised of non-viable liquefying cells at histology(46–49). Both of these considerations would tend which would reduce CEM₄₃-based over-estimation of lesion size *in vivo*.

In conclusion, IV-MRI guided and IV-MRI titrated IV-HIFU has the potential for precision ablation of perivascular tumor and other pathological tissues, while preserving vessel wall. The technology potentially offers a new approach to treating localized disease including inaccessible tumors or pathologies involving critical blood vessels. It is possible that such a procedure could render a non-resectable tumor, resectable. As the current study

demonstrates feasibility of IV MRI-guided IV-HIFU, given the size of the current devices, further *in vivo* testing would require evaluation on a large animal tumor or disease model.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Combined intravascular (IV) MRI and ultrasound (HIFU) ablation catheters (a-e) and the software interface (f). In initial studies, the IV-MRI antenna was taped (not shown) to the HIFU transducer (a). Subsequent IV-HIFU catheters incorporate a lumen to take an X-ray guidewire or the MRI antenna (b). Catheter denoted #1, #2 and #3 from Table 1 are pictured in (c)-(e). A screen-shot of the MATLAB-based real-time thermal monitoring software interface installed on a personal computer (PC), is shown in (f). The monitor is connected to the scanner console computer via an ethernet cable. Inset (bottom right) shows an experiment with data transfer between the scanner console and the PC.

Figure 2.

Photo of a section of chicken breast tissue in the ablation plane following bench-testing with catheter #2 (a). A preserved tissue margin (pink) surrounds the probe location, inside the ablation lesion (white). The IV HIFU catheter ablation transducer (yellow arrows) and IV MRI loopless antenna whip junction (white arrows) are seen in orthogonal high-resolution IV MRI planes (b,c). Screen shots of online thermometry (scale in °C at right) during pre-ablation catheter cooling (d) and ablation (e) are shown. The catheter position is denoted by blue circles (yellow arrows). Part (f) is a photo annotated with contours of the 86% lethal thermal dose of $CEM_{43}=340$ as determined by MRI thermometry (magenta) and with a contour (white) enclosing the lesion (bleached).

Figure 3.

Images of the IV MRI antenna (white arrow) and HIFU catheter #1 (yellow arrow) in a blood vessel of pig liver *ex vivo* in transverse (**a**) and co-axial planes (**b**; inset denotes the expanded region in **c**). MRI thermometry shows temperature maps (scale in °C at right) from the transverse slice in (a): before ablation (**d**); during ablation at maximum temperature (**e**); and immediately after the HIFU transducer is turned off (**f**).

Figure 4.

Co-registration of lethal thermal dose contours with lesions on tissues slices dissected after ablation experiments performed with catheter #1 located in pig liver blood vessels *ex vivo*. Tissue slices at the ablation location expose the pallid lesion area (white arrow) (a). The projected, normalized color mapping of the section differentiates the lesion from normal tissue (b, scale at right). The lesion area (white line) is identified by an active contour algorithm for object detection. The vessel wall is manually traced (blue line). The $CEM_{43\ 340}$ (magenta line) contour is calculated from MRI thermometry and co-registered on the anatomical MRI reference scan (c). The catheter (yellow circle) position and the enclosing vessel (green line) are identified manually on the reference scan. Landmarks

identified from MRI, MRI thermometry and the photo color map are co-registered on the original photo for comparison and correlation (**d**).

Figure 5.

Comparison of lesion sizes exceeding a thermal dose $CEM_{43} \geq 340$ as measured from MRI thermometry, with lesions measured from photos of the dissected ablation planes. The radial depth, L_r (a); area, L_a (b) of lesions; and the average gap between lesion and vessel wall, L_g (c), are correlated (correlation coefficient, $r > 0.79$; Pearson probability, $p < 0.02$; solid lines, least-squares regression line; the dashed line is the identity line). Numbers near the data points denote the experiment number (a-c). Part (d) shows the Jaccard index (area of intersection divided by the area of the united lesion areas) for each experiment.

Figure 6.

IV MRI of catheter #3 with thru-lumen design (from Fig.1b) in a porcine liver (a). IV MRI thermometry (scale, °C at right) shows pre-cooling (b); ablation in one direction (c); simultaneous ablation in two directions with both transducers turned-on (d) and after turning one transducer off (e; blue circle denotes catheter position). Part (f) is a photo of the dissected transverse section through the ablation showing lesion in both directions (white arrows; blue circle denotes the vessel hosting the catheter). Part (g) shows the Movat-stained histology indicating a margin of preserved tissue between the vessel wall and lesion (white arrow).

Figure 7.

Placing an IV MRI HIFU catheter #3 in a porcine IVC from the right femoral vein *in vivo* (a) confirmed by fluoroscopy (b). The left femoral artery is accessed by a 5 French sheath (a), for a fiber-optic temperature probe to monitor the body temperature for base line calibration of the PRFS method. Sagittal T2wTSE MRI (c; white arrow). High-resolution IV MRI (d; pink arrow denotes catheter; S1 is the targeted psoas muscle; S2 is the colon, a second target; S3, aorta; S4 is the IVC; S5 is the spine).

Figure 8.

Anatomical reference scan for an *in vivo* porcine study (a); and IV MRI thermometry frames (scale in °C at right) acquired pre-ablation (b); Initial mis-direction of the thermal beam was detected by thermometry (c) and redirected to the psoas muscle; during ablation of the psoas muscle (white arrow) and colon (yellow arrow; d); and immediately after turning the transducer power off (e). Blue circles denote the catheter location. Part (f) shows thermal lesions in the colon mucosa from multiple ablations (white arrows). Part (g) shows thermal lesions in psoas muscle (g, white arrows). Part (h) shows MT-stained histology of the lesion (black arrow).

Figure 9.

IV MRI thermometry of ablations performed at three locations (during pullback from head to feet direction) in the psoas muscle in a second *in vivo* porcine study using catheter #3. The anatomical MRI reference scan at the first location (**a**) shows the ablation target (red arrow). Part (**b-d**) shows the temperature rise (white, yellow and cyan arrows) during ablation (scale in °C at right) at three pullback locations. In (b) the thermal beam is slightly clockwise of the target so the device was rotated for the acquisitions in (c) and (d). Blue circles denote the catheter location. Part (e) shows the post-mortem photo of thermal lesions

in the psoas muscle. The first ablation lesion (e; white arrow) is skewed relative to the second and third lesions (e; yellow and cyan arrows) which extend to form a continuous lesion.

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Table 1

Specifications of intravascular ultrasound ablation catheters developed for this study.

Name	OD (mm)	Transducer shape	Number of channels	Ablation angle	Operating frequency (kHz)
Catheter 1	2.5	5.5mm Flat	1	60°	6260
Catheter 2	2.4	10.4mm Hoop	1	360°	7347
Catheter 3	4.3	10.0mm Sector	2	$\overset{\uparrow}{\downarrow}$ 90°/90°	$\overset{\uparrow}{\downarrow}$ 6473/6818

$\overset{\uparrow}{\downarrow}$ Values for channel 1 and channel 2, respectively.