Published in final edited form as:

Eur Radiol. 2017 February ; 27(2): 732–740. doi:10.1007/s00330-016-4376-5.

Magnetic Resonance-Guided Focused Ultrasound Treatment of Extra-Abdominal Desmoid Tumors: A Retrospective Multicenter Study

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Abstract

Objectives—To assess the feasibility, safety and preliminary efficacy of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of extra-abdominal desmoid tumours.

Methods—Fifteen patients with desmoid fibromatosis (6 males, 9 females, age range 7–66 years) were treated with MRgFUS, with 7 patients requiring multiple treatments (25 total treatments).

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Statement of Human Rights

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For retrospective studies, formal consent is not required.

Changes in viable and total tumour volumes were measured after treatment. Efficacy was evaluated using an exact one-sided Wilcoxon test to determine if the median reduction in viable tumour measured immediately after initial treatment exceeded a threshold of 50% of the targeted volume. Median decrease after treatment of at least two points in numerical rating scale (NRS) worst and average pain scores was tested with an exact one-sided Wilcoxon test. Adverse events were recorded.

Results—After initial MRgFUS treatment, median viable targeted tumour volume decreased 63%, significantly beyond our efficacy threshold ($P=0.0013$). Median viable total tumour volume decreased [105mL (IQR=217mL) to 54mL (IQR=92mL)] and pain improved (worst scores: 7.5 ± 1.9 vs. 2.7 ± 2.6 , $P=0.027$; average scores: 6 ± 2.3 vs. 1.3 ± 2 , $P=0.021$). Skin burn was the most common complication.

Conclusions—MRgFUS significantly and durably reduced viable tumour volume and pain in this series of 15 patients with extra-abdominal desmoid fibromatosis.

Keywords

MR-guided focused ultrasound; MRgFUS; desmoid fibromatosis; high intensity focused ultrasound (HIFU); thermal ablation

Introduction

Extra-abdominal desmoid fibromatosis is a locally aggressive, infiltrative monoclonal proliferation of myofibroblasts, associated with mutations in the β -catenin pathway¹. The incidence of desmoid tumours is 2-4 per million per year, yielding about 950 new cases in the United States every year². Desmoids may occur in children and adults, and have a peak incidence in the third decade. Although the aetiology of these tumours is not established, the sporadic extra-abdominal tumours are associated with prior surgery or trauma, and also with pregnancy³. Standard management methods seek to achieve durable local control of tumour while minimizing morbidity. Generally utilized approaches to management include observation to identify tumours that are symptomatic or growing, since some tumours spontaneously regress⁴; operative resection, typically trying to achieve negative margins; radiation therapy, targeting positive surgical margins or palliating unresectable tumours; and systemic chemotherapy⁵. Localized treatment with percutaneous cryoablation or ultrasound-guided high intensity focused ultrasound (HIFU) has been described^{3,6,7}.

Surgery either alone or in combination with radiation or chemotherapy may result in tumour control, but the morbidity and complications associated with treatment can have significant and lasting adverse effects on limb function and quality of life⁸⁻¹⁰. Surgery, even with negative margins, can have recurrence rates as high as 50%. Wide resection, which can reduce this rate, is not always possible without significant morbidity given the location and infiltrative nature of these tumours⁵. Radiation, either alone or in combination with surgery, results in local tumour control in 72-76% of adults, but appears to be less effective in children¹¹. Morbidity resulting from radiation occurs in up to 30% and includes pain and reduced range of motion, pathologic fractures, and secondary malignancies, a particular concern in this young patient population^{11,12}.

MR guided focused ultrasound (MRgFUS) is a minimally invasive method for thermal ablation of targeted tissue. MRgFUS is approved by the Food and Drug Administration for the treatment of symptomatic uterine fibroids¹³ and painful osseous metastases¹⁴, and is in investigational use for the treatment of primary cancers in the breast¹⁵, prostate gland¹⁶, and brain¹⁷. This technology uses directional ultrasound waves that achieve a narrow focus within the targeted tissue. The focused ultrasound energy heats the tissue, with subsequent tissue ablation achieved only at the focus, sparing surrounding healthy tissue. MR imaging is used to define the target and surrounding critical anatomic structures and assess treatment effects, including the volume of non-perfused tissue after ablation. The purpose of this study was to assess the feasibility, safety and preliminary efficacy of MR-guided focused ultrasound for the treatment of extra-abdominal desmoid tumours.

Materials and Methods

Patients or their legally authorized representative provided written informed consent before treatment. Treatment was performed after approval by review board or ethics committee per individual hospital regulations; the review board at each institution approved this retrospective review of patient data. The study was compliant with the Health Insurance Portability and Accountability Act.

Patient Population

Eligibility for study entry included pathologically proven desmoid fibromatosis and patient review by a multidisciplinary committee including an orthopaedic oncologist and a medical oncologist specializing in the care of soft tissue tumours of the extremities. The decision to treat with MRgFUS was based on 1) the risk of significant comorbidities from planned surgical resection, or recurrence after surgery, with unacceptable co-morbidities expected from re-resection, 2) progression after chemotherapy and/or radiation, or unacceptable comorbidities from chemotherapy, or 3) patient refusal of surgery, chemotherapy, or radiation. MR imaging selection was based on acoustic accessibility of the tumour, such that at least 50% of the tumour volume could be targeted. Limitations to treatment accessibility include proximity to nerves, bones, vasculature, skin, tendons, and scars. Patients with contraindications to MR imaging and anaesthesia were excluded.

Procedure Details

Treatments were performed under general anaesthesia (n=8), regional anaesthesia (n=5), a combination of general and regional anaesthesia (n=7), or a combination of local anaesthesia and conscious sedation (n=5). The choice of anaesthesia was based on the practice patterns of each institution, as well as the location of the tumour and the expected length of the procedure. Procedures were performed by physicians with 2-5 years of experience with MR guided focused ultrasound interventions (initials removed to blind manuscript). An ExAblate 2000 MR guided focused ultrasound system with an in-table 1 MHz transducer (InSightec, Tirat-Carmel, Israel) was used with a 3T MR system (Discovery 750w; GE Medical Systems, Milwaukee, WI); the treatment of desmoid fibromatosis is an off-label use of this technology. The patient was positioned such that the tumour was aligned with the transducer, with acoustic coupling through a wet gel pad or a bag filled with degassed water. The

tumour was localized using multiplanar proton-density (FSE, 4.7s repetition time, 27ms echo time, 3mm slice thickness, 18-26cm field of view, 320×224 matrix, 139kHz bandwidth) and T2 weighted (FSE, 4.7s repetition time, 107ms echo time, 3mm slice thickness, 18-34cm field of view, 320×224 matrix, 122kHz bandwidth) MR imaging. Images were manually segmented to delineate the tumour contour and skin surface. Adjacent nerves were demarcated so that the system would plan treatment without energy passing through these areas. The initial treatment plan produced by the ExAblate software was manually modified before and during treatment in order to minimize heating on the skin and near structures such as nerves and vessels. Sonication number, size and energy were adjusted based on the temperature-energy response of the tumour. Heating was monitored in real time using proton resonant frequency shift MR thermometry (2D FGRE, 25.2ms repetition time, 12.4ms echo time, 30 degree flip angle, 5mm slice thickness, 28cm field of view, 256×128 matrix, 3.5s update rate, 1°C temperature resolution). Immediately after treatment, post-contrast images (LAVA, 3D SPGR, 8.6ms repetition time, 2.1ms echo time, 1.5mm slice thickness, 26-34cm field of view, 260×224 matrix) of the non-perfused volume of tumour were used to evaluate for treatment effect. Patients were typically discharged home on the day of treatment (n=22 of 25 treatments). The other 3 patients were observed overnight in the hospital and then discharged; these patients had a skin burn, venous thrombosis, and biochemical evidence of pancreatitis, respectively.

Data Analysis

Total treatment time, the number of sonications and the energy per sonication were recorded. Total tumour volumes were measured before and after treatment, and non-perfused volumes were determined after ablation. On the day of treatment, prior to the first MRgFUS ablation, the tumour was assumed to be completely perfused, based on the pre-treatment MRI. Tumour volumes were calculated by manually contouring the total tumour area on each imaging slice. A threshold method was used to identify non-perfused volume using TeraRecon Aquarius iNtuition software, which reports total and non-perfused volumes. For patients with painful tumours, defined as a score of at least 4 out of 10 on the Numerical Rating Scale (NRS), the worst and average daily NRS pain scores were recorded before and at least 3 months after treatment. Durable clinical benefit of the MRgFUS treatments was defined as reduction in tumour size of $>50\%$ since the most recent treatment, and reduction in worst and average pain scores of at least two points, both maintained for a period of at least 6 months after treatment. Treatment-related adverse events were recorded, including the need for additional intervention to address the adverse event, and long-term consequences. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0¹⁸.

Clinical and imaging assessments were performed within 3 months of the first treatment, and continued thereafter. If tumour regrew and/or tumour-related pain recurred, patients were considered for retreatment of the desmoid tumour with MRgFUS; statistical analysis was based on the results of the initial treatment. Changes in viable targeted tumour volumes before and after initial MRgFUS treatment were tested using a 50% threshold for efficacy (i.e. enhancing volume post-treatment $<50\%$ of targeted volume pre-treatment) with an exact one-sided Wilcoxon test of the median percent reduction against a null hypothesis of 50% or

less reduction. Median decrease of at least two points between baseline and follow-up NRS pain scores was tested using an exact one-sided Wilcoxon test. Differences were considered statistically significant at a $P < 0.05$.

Results

From March 2011 to January 2015, fifteen patients (median age 24 years, range 7–66 years) diagnosed with pathologically proven extra-abdominal desmoid fibromatosis were treated with MR guided focused ultrasound (25 total treatments). Nine women (median age 25 years, 15–55 years) and six men (median age 16 years, 7–66 years) were treated. The technical treatment parameters are listed in Table 1. Patient and tumour characteristics and response to treatment are listed in Table 2. Seven patients had not been treated prior to MRgFUS ablation. Treatment examples are shown in Figure 1 and in Supplemental Digital Content 1 – 4.

Median total tumour volumes before initial treatment were 105mL (interquartile range (IQR)=217mL, range 4–1010mL). Fourteen of 16 cases targeted the entire tumour. The other two targeted 39% (patient #2) and 69% (patient #9) of the tumour volume, because the tumours had encased the tibial nerve or the Achilles tendon, respectively. Overall, immediately after the initial MRgFUS treatment, median reduction of 63% (95% CI: 49–74%) of the viable targeted tumour volume and median reduction of 58% (95% CI: 46–71%) of the viable total tumour volume were observed, both significantly beyond our efficacy threshold ($P=0.0013$ and $P=0.032$, respectively). The median reduction of viable tumour volume also surpassed our efficacy threshold when assessed separately in patients who had not had any treatment prior to MRgFUS or in patients who had been previously treated with surgery, radiation, and/or chemotherapy. The median time between receiving radiation and MRgFUS was 2.9 years (range 2.6–12 years); all patients previously treated with radiation had tumours that continued to grow. Median viable tumour volumes declined to 54mL (IQR=92mL, range 1–420mL) immediately after initial MRgFUS treatment and to 7mL (IQR=40mL, range 0–228mL) at most recent follow up. Median total tumour volumes also stabilized or declined in all patients after treatment, measuring 42mL (IQR=162mL, range 0–432mL) at most recent follow up, although this included patients who required several MRgFUS treatments, as well as one patient who was also treated with cryoablation and two patients who started chemotherapy (Figure 2). Excluding the 3 patients who received cryoablation or chemotherapy after the initial MRgFUS treatment, the median viable volume at most recent follow up was 9mL (IQR=26mL, range 0–228mL) and the median total tumour volume at most recent follow up was 27mL (IQR=97mL, range 0–432mL). Follow-up averaged 17.5 months (range 4–38 months), and patients averaged 1.7 treatments (range 1–4). Repeat treatments were performed to treat residual viable tumour in 7 patients.

Six patients reported significant pain prior to treatment as a result of their tumour. In these patients, the worst daily NRS pain score declined from 7.5 ± 1.9 to 2.7 ± 2.6 ($P=0.027$, $n=6$) and the average daily NRS pain score declined from 6 ± 2.3 to 1.3 ± 2 ($P=0.021$, $n=5$). These improved pain scores were recorded at a median of 8 months after treatment (range 4–17

months). All patients stopped scheduled medications for pain control within two weeks of treatment.

Durable clinical benefit was observed in 7 of 9 patients (#3, 4, 7, 12, 13, 14, 15). These 7 patients had a median reduction in viable tumour volume of 98% (IQR=20%), with an average follow up of 16 months since the most recent treatment (range 6-38 months). Patients #2 and 8 had 44% and 46% reduction in viable tumour volume 6 and 8 months after MRgFUS, respectively, below the defined efficacy threshold. Patients #1, 6 and 10 were not included in this assessment because there was less than 6 months follow up since the last treatment, and patients #5, 9 and 11 were not included because they received other therapies after MRgFUS (Table 2).

Treatment related adverse events, which included skin burns (n=8), nerve injury (n=3), and off-target heating (n=3), occurred in 10 of 15 patients and in 10 of 25 treatments. In patients who experienced 2nd degree skin burns, the tumour reached within an average of 4mm from the skin (n=6, range 0–5mm), and/or the blisters occurred along scars from prior surgery or biopsy (n=2). Four of the six cases of burns occurred at an interface between skin and air at the far field of the ultrasound beam. One of these patients, who developed blisters along the margin of a scar from prior resection of the desmoid, required oral antibiotics to treat a clinically suspected super-infection as the blisters healed (CTCAE grade 2); the others healed without intervention (CTCAE grade 1). Three patients had signs of nerve injury after treatment (CTCAE grade 2-3). In one patient, who had a tumour that encased the peroneal nerve and had evidence of nerve damage before treatment, foot drop worsened after treatment. The patient was counselled that treatment would be directed through the nerve, as this provided the best acoustic window for targeting the largest volume of tumour. The patient already used an ankle-foot orthotic prior to treatment, so the additional nerve injury had minimal impact on quality of life. MRgFUS ablation allowed the patient to discontinue chemotherapy, which was causing significant co-morbidities. In the other two patients, the tumour also encased the common peroneal nerve, which could not be visualized throughout its course. Although treatment was both planned to avoid the visualized portion of the nerve and performed to avoid heating the expected position of the nerve during treatment, foot drop was present after treatment. One patient temporarily required an ankle-foot orthotic, but both of these patients had full return of function at 8 months and 24 months, respectively. Off-target heating resulted in venous thrombosis of a peri-tumoral vessel, which resolved with anticoagulation (CTCAE grade 2); focal transient hypoperfusion of gluteal muscle due to heating in the near-field (CTCAE grade 1); and biochemical and imaging evidence of acute pancreatitis (CTCAE grade 2), likely due to repeated low-level heating from the far-field of the ultrasound beam. The latter two patients were asymptomatic and the findings resolved without further intervention.

Discussion

Desmoid tumours are locally infiltrative and may cause pain and dysfunction. Standard therapies including surgical resection, radiation and systemic chemotherapy suffer from inadequate efficacy and excessive side effects for treatment of a relatively benign disease¹⁰. This study demonstrates that MRgFUS treatment of desmoids is feasible and that this

technique may be used to control the growth of symptomatic desmoid tumours of the extremities, with decrease in both total and viable tumour volumes. In our fifteen patients there was a 63% median reduction in viable volume of the targeted tumours immediately after the initial MRgFUS treatment; this surpassed our target for efficacy, which was ablation of at least 50% of the tumour. Tumour reduction after MRgFUS occurred in tumours that were growing despite prior surgery, chemotherapy or radiation. Tumour-related pain also improved after MRgFUS, with a 64% decline in maximum pain scores. We did not observe a cumulative toxicity limit to surrounding normal structures, allowing re-treatment as necessary to ablate residual or recurrent tumour. In our experience, treatment with MRgFUS did not appear to accelerate the growth of the tumour, which was a theoretical concern given the possibility that trauma or surgery may lead to tumour progression¹⁹. MRgFUS treatment was feasible after surgery or chemoradiation, and was also combined successfully with other treatment modalities, such as chemotherapy and cryoablation, to treat remaining tumour. Encouragingly, MRgFUS was able to provide durable disease control even when used alone; in 9 patients treated only with MRgFUS since their initial MRgFUS treatment, and with at least 6 months follow up since their most recent treatment, 7 had a median of 98% reduction in viable tumour volume.

MRgFUS-related morbidity was mild relative to that observed using current treatment modalities. The most common complication, skin burn, was grade 1-2 in severity (CTCAE version 4), and is related to proximity of the tumour to the skin, and to the presence of surgical scars in the treatment path. As our experience has grown, we have developed methods to protect the skin in the near- and far-field and the incidence of such skin burns has decreased. The most severe complication, nerve injury, was grade 3, but resolved in the two patients in whom nerve injury was inadvertent. Note that in other cases where nerves were visible and located along the deep or superficial margin of the tumour, MRgFUS treatment was accomplished without nerve injury by directing sonications away from the nerve. Surgical resection often involves removal of large segments of healthy tissue surrounding the tumour, and can result in scarring, prolonged recovery, infection and neurovascular injury, all of which can lead to significant patient morbidity and dysfunction²⁰. Radiation therapy, while useful in controlling desmoid tumours, results in complications in more than 20% of patients; these include soft tissue necrosis, fracture, oedema, fibrosis, vascular complications requiring limb amputation, neuropathy, limb shortening, osteoarthritis, and secondary malignancy^{1,12,21,22}. Deciding between these options should be made on a case-by-case basis, with involvement of a multidisciplinary team of physicians to advise on treatment alternatives, and with shared decision-making by the patient.

Given that desmoids are not malignant tumours, our usual treatment approach has been to control tumour growth while minimizing side effects. In cases where the tumour is sufficiently separated from nerves and skin, MRgFUS can be used to eradicate the tumour, as was achieved in five of our patients, with two more patients having more than 90% of their tumour ablated. Other ablative techniques have been reported for the treatment of desmoids. This includes a report using percutaneous cryoablation for local control or palliation of inoperable tumours in 5 patients, with complete ablation reported in two cases⁶. These cases required placement of between 2–6 probes under CT and ultrasound guidance, as well as hydrodissection to protect adjacent critical structures. Ultrasound-

guided HIFU has been reported in 10 patients with desmoid tumours, with ablation of 78-100% of the tumour⁷. Our study, in which the total tumour volume has decreased by 52% and the viable volume has decreased by 80%, compares favourably with that study, in which all tumours were smaller by at least 50% at a mean of 30 months after treatment. Compared to cryoablation, MR guided focused ultrasound is non-invasive, which is an advantage for a procedure that may need to be repeated to achieve tumour control. Compared to both of these other approaches, combining focused ultrasound with MR imaging guidance provides several advantages, including the ability to localize the tumour margins precisely relative to the surrounding skin, muscle, bone, vessels and nerves, as well as to monitor response to therapy in real-time²³.

This study was limited by the sample size and the length of follow up in some patients. Patients had also undergone variable treatments prior to MRgFUS ablation, which may have influenced adverse events observed during treatment, as patients with prior surgical scars were more difficult to position for treatment and were at greater risk for skin burns. Three patients also received additional intervention after MRgFUS; although this did not impact our assessment of the efficacy of MRgFUS treatment, which was based on changes in tumour viability measured immediately after the initial MRgFUS treatment, it did impact the measurement of tumour volumes after the subsequent intervention. These three patients were not included in our assessment of clinical durability.

In conclusion, our experience indicates that MR guided focused ultrasound may safely and effectively treat extra-abdominal desmoid tumours. This non-invasive procedure can be used to eradicate viable tumour, or to provide durable control of tumour growth through repeated treatments. Compared to traditional treatment modalities, MR guided focused ultrasound may have advantages including no cumulative dose limit, and relatively mild side effects, while preserving the ability to be used as an adjunct to other treatment methods. Given the promising outcomes seen in our study, further clinical trials are needed to confirm the safety of MR-guided focused ultrasound for the treatment of soft tissue tumours and to assess more definitively the rate of durable disease control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors are grateful to Dr. Sheri Spunt for her comments on the manuscript.

The scientific guarantor of this publication is Pejman Ghanouni. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. This study has received funding by NIH P01 CA159992. One of the authors has significant statistical expertise. Institutional Review Board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Some study subjects have been previously reported in Avedian et al. (2016) Is MR-guided High-intensity Focused Ultrasound a Feasible Treatment Modality for Desmoid Tumors? Clin Orthop Relat Res. 474(3): 697-704.

Methodology: retrospective, observational, multicenter study.

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Key Points

Retrospective four-centre study shows MRgFUS safely and effectively treats extra-abdominal desmoid tumours.

This non-invasive procedure can eradicate viable tumour in some cases. Alternatively, MRgFUS can provide durable control of tumour growth through repeated treatments.

Compared to surgery or radiation, MRgFUS has relatively mild side effects.

Figure 1.

MR guided focused ultrasound treatment of an enlarging, painful desmoid tumour located in the posterior right ankle of a 66 year old man. He refused surgery, radiation and chemotherapy. In A, a sagittal post-contrast T1 weighted 2D FSPGR fat saturated image obtained 2 weeks before initial treatment shows an enhancing mass (white arrow) located between the Achilles tendon (+) and the flexor hallucis longus tendon (*). In B, an axial MR thermometry magnitude image acquired during sonication shows a representative sonication (green rectangle) and beam path (blue hourglass). The location of the tibial nerve and posterior tibial vessels has been demarcated (purple line); the system does not allow the beam path to cross this contour. The orange crosshair represents the location where temperature is being examined; this crosshair can be adjusted during sonication. Temperature is displayed in real-time during treatment (inset, red curve represents single hottest pixel, and green curve represents average of a 3×3 pixel area around the crosshair). In C, an axial post-contrast T1 weighted 3D SPGR image with fat suppression acquired immediately after treatment reveals the ablated area of the tumour (white arrow). Out of 42mL total tumour volume, 26mL (62%) no longer enhanced after ablation. The red arrow points to preserved enhancement between the posterior tibial vessels, which remain patent, and the flexor hallucis longus tendon (*). This area was not treated in order to avoid damaging the tibial nerve. In D, a sagittal post-contrast T1 weighted 2D FSPGR fat saturated image obtained 20 months after initial treatment and 11 months after a second treatment shows residual tumour, which is necrotic centrally, with peripheral enhancement. Total tumour volume declined to 29mL (31% decline) and the perfused viable volume was 17mL (60% decline). The patient's tumour-related pain resolved after MRgFUS treatment. Please see Supplemental Digital Content for additional images of this and other treatments.

Figure 2.

Decline in tumour volumes after ablation. Total (A) and viable (B) tumour volumes are plotted relative to time. The vertical dashed line in each graph indicates the initial treatment, and black arrows indicate subsequent MRgFUS treatments. In A, after MRgFUS treatment, the total tumour volume stabilized or declined for varying amounts of time; when tumour regrowth was seen, another treatment was performed. In B, the red curves or data points show the enhancing tumour volume prior to treatment, and the blue lines are enhancing volumes after treatment. Figure 1 demonstrates results from patient #4. In patients #5 and

#11, planned partial treatments were combined into single volumes for representation. In patient #3 tumour volumes declined with chemotherapy, but he did not tolerate the side effects. Prior to MRgFUS, chemotherapy was discontinued, and MRgFUS alone was subsequently used to control tumour growth. Asterisks indicate initiation of additional treatment modalities after MRgFUS. Patient #5 had cryoablation of residual viable tumour. Approximately 67% of the tumour was treated with MRgFUS, but portions close to the skin and the anterior abdominal wall and stomach were deemed safer to treat with cryoablation after hydrodissection. In patient #9, the inferior portion of the tumour encased the Achilles tendon, and the patient opted not to ablate near the tendon; chemotherapy was initiated 3 months after MRgFUS to treat residual, untreated tumour. Patient #11 had residual tumour treated with sorafenib beginning 8 months after MRgFUS. Patient #13 had two separate tumours treated. Note that post-contrast imaging was not obtained in patient #14 immediately after treatment.

Table 1

Technical Treatment Parameters

	Mean $\pm$ SD ^I	Range
Treatment time	3.5 $\pm$ 1.6 hours	0.8 – 8 hours
Number of sonications per treatment	90 $\pm$ 47	17 – 235
Sonication energies	1482 $\pm$ 562 J	419 – 2867 J
Average peak temperature per sonication	58 $\pm$ 5°C	50 – 68°C

^ISD = standard deviation

Treatment Results

Table 2

Patient number	Age at first treatment	Location of tumor	Prior treatment	Total tumor volume on treatment day (mL)	Initial treatment		Most recent total tumor volume (mL)	Most recent viable tumor volume (mL)	Change in viable tumor volume / volume	Months of total follow up	Number of treatments
					Targeted volume (mL)	Non-perfused volume (mL)					
1	14	Buttock	Surgery, chemotherapy	98	98	73	5	4	−96%	23	4
2 ²	16	Popliteal fossa	Chemotherapy, imatinib	142	55	52	196	79	−44%	27	2
3	17	Lateral knee	Surgery, radiation, chemotherapy	157	157	75	98	27	−83%	15	2
4	66	Posterior ankle	None	42	42	26	29	17	−60%	20	2
5 ³	28	Abdominal wall	None	1010	1010	676	248	0	−100%	12	2
6	24	Lateral shoulder	None	40	40	29	27	15	−63%	10	2
7	31	Anterior shoulder	None	8	8	7	0	0	−100%	9	1
8	26	Calf	Surgery, chemotherapy	323	323	202	280	175	−46%	8	1
9 ⁴	15	Calf	None	195	135	110	156	118	−39%	9	1
10	14	Palm	None	4	4	2.3	0.9	0.9	−78%	5	1
11 ⁵	16	Popliteal fossa	None	310	219	132	77	0	−100%	36	2
12	55	Posterior thigh	Chemotherapy	31	31	22	0.3	0	−100%	28	1
13a	48	Abdominal wall #1	Radiation	30	30	13	0	0	−100%	38	1
13b	48	Abdominal wall #2	Radiation	105	105	51	9.7	9	−91%	24	1
14	41	Calf	Surgery, chemotherapy, radiation	120	120	ND ⁶	54	5	−96%	12	1
15	7	Thigh	Surgery, radiation and chemotherapy	772	772	352	432	228	−70%	6	1

¹ Change in viable tumor volume = (Total tumor volume on treatment day – most recent viable tumor volume) / total tumor volume on treatment day

² Patient #2 had a partial treatment planned to avoid the tibial nerve, which was encased by the medial portion of the tumor.

³ Patient #5 had two treatments within one week of each other, because of the large volume of the tumor. The results of these treatments have been combined above. Viable tumor remaining after MRgFUS was treated with cryoablation, due to the need for hydrodissection of the remaining tumor from the skin and anterior abdominal wall.

⁴ Patient #9 had a partial treatment planned to avoid the Achilles tendon, with subsequent initiation of chemotherapy to control remaining viable tumor.

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Patient #11 had a planned partial “test” treatment of a small inferior portion of the tumor, followed by subsequent treatment of the superior portion of the tumor. The results of these treatments have been combined above. Eight months after the second treatment, the patient began treatment with sorafenib for 20 months.

ND = not done. Patient #14 did not have post-contrast imaging performed immediately after treatment.