High intensity focused ultrasonic ablation of sacral chordoma is feasible: a series of 4 cases and details of a national clinical trial.

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Abstract

High intensity focused ultrasound describes the use of high intensity focused ultrasound (HIFU) to ablate tumours without requiring an incision or other invasive procedure. This technique has been trialled on a range of tumours including uterine fibroids, prostate, liver and renal cancer. We describe our experience of using HIFU to ablate sacral chordoma in 4 patients with advanced tumours. Patients were treated under general anaesthetic or sedation using an ultrasound-guided HIFU device. HIFU therapy was associated with a reduction in tumour volume over time in 3 patients for whom follow up scans were available. Tumour necrosis was reliably demonstrated in 2 of the 3 patients. We have established a national trial to assess if HIFU may improve long term outcome from sacral chordoma, details are given.

Introduction

High intensity focused ultrasound (HIFU) describes the use of high energy ultrasonic waves to induce coagulative necrosis at the focal point of the beam leaving surrounding and overlying tissues intact: the treatment delivered is extracorporeal and non-invasive [1]. Target tissue response to HIFU can be monitored in real time using B-mode ultrasound (Ultrasound-guided HIFU)[2] or MRI (MRI-guided HIFU)[3], allowing treatment parameters to be adjusted to maintain treatment efficacy. HIFU has been successfully used in the treatment of uterine fibroids and as adjuvant treatment in prostate cancer [4-7]. It has been trialled on various other solid tumour types including renal, liver, bone, and pancreatic lesions [8]. Applications under trial or development in neurosurgery include treatment of movement disorders [9], thermal ablation of tumours [10], and stroke thrombolysis [11 12].

Chordoma is a rare form of tumour that arises from remnants of the notochord. Histologically chordoma is a low grade malignant tumour [13]. Sacral chordoma is rare, with less than 1 case per million people per year [14]. Sacral chordoma can present at any age typically with progressive sacral and lower limb pain, reduced mobility, bladder or bowel dysfunction, or as a pelvic mass. Symptoms typically are slowly progressive therefore there is often a delay between symptom onset and presentation to medical services as symptoms are often vague or non-specific in the early stages of the disease. Surgical resection (sacrectomy or pelvic exentration) and adjuvant radiotherapy are the mainstays of treatment [15-17]. However curative resection is often not feasible at time of presentation owing to tumour relationships to essential pelvic structures, and chordoma is relatively radio-resistant owing to its slow mitotic rate. Curative resection when feasible often requires sacrifice of bladder and bowel function resulting in the formation of colostomy and urostomy, and resection imperils lower limb function. Radiotherapy has the limitation that patients may not exceed their lifetime dose, preventing repeated cycles of radiotherapy should a tumour regrow after treatment. Thus current treatment options have many drawbacks which necessitate the search for improved treatments for chordoma.

Given these challenges in the treatment of sacral chordoma, we describe our experience of treating sacral chordoma with HIFU in 4 patients.

Materials & Methods

Ethical approval

HIFU trial treatment was approved by the Oxfordshire Clinical Research Ethics Committee and conformed to GCP guidelines. Patient 1 was treated under the auspices of a clinical trial: Extra-corporeal high intensity focused ultrasound for primary sacrococcygeal bone tumours: phase iib trial of clinical efficacy, approved by South East Scotland Research Ethics Committee 02, ref 12/SS/0144, ISCRTN 91527768.

Patient selection

Patients were referred to a single-centre multidisciplinary team consisting of urologists, a neurosurgeon and HIFU specialist. All patients were over 18yrs old. Patients had histologically confirmed sacral chordoma either by image-guided biopsy or from previously resected surgical samples. Potential suitability for HIFU treatment was determined from clinical data from referrers and MRI pelvis. Subjects with significant loco-regional metastases, poor performance status (>1) or high anaesthetic risk (ASA>2) were not offered treatment. Previous surgical resection or radiotherapy to the tumour did not contraindicate HIFU treatment, provided this had taken place more than 12 months before HIFU treatment and subjects had recovered sufficiently. From 13 referrals, 4 were deemed suitable for treatment. The remaining 9 were not suitable for treatment: 4 referrals came from outside the UK without funding, 2 UK referrals had significant metastatic disease. 3 others did not pursue treatment. Treated patient characteristics are summarised in table I.

Table I

Informed consent

All patients were required to give written informed consent for treatment. Specific risks of the HIFU procedure specified to patients included skin burns, failure to benefit from treatment, nerve injury to nerves supplying legs, bladder, bowel and sexual organs resulting in leg weakness, incontinence and sexual dysfunction, and a small theoretical risk of bowel perforation.

Treatment

Treatment took place at the Churchill hospital, Oxford. Patients received gadolinium contrast-enhanced (CE) magnetic resonance imaging (MRI), baseline blood tests and symptom review prior to HIFU therapy. MRI was not repeated if the referring hospital had performed an adequate scan within 3 months of HIFU treatment. Prior to each treatment patients were kept nil by mouth for 6 hours and underwent bowel preparation using phosphate enema. Urinary catheterisation was performed to permit control over bladder content during the procedure.

HIFU treatment was performed using an extracorporeal HIFU device (Model JC and JC200 Focused Ultrasound Tumor Therapeutic Systems, Haifu Medical, Chongqing, China). The Model-JC HIFU System was used in cases 3 & 4 and has been described previously [18]. Briefly, the device has a 12 cm diameter, single element, piezo-ceramic transducer fronted by acoustic lenses of varying focal lengths, driven at either 0.8 or 0.95 MHz. An AU3 US imaging device (Esaote, Genoa, Italy) is mounted coaxially with the high-energy transducer allowing treatment to be guided in real time. Patients 1 & 2 were treated with the JC200 model. The Model JC200 HIFU system varies from the Model JC in that it has an integrated transducer consisting of a B-mode ultrasound imaging probe at the centre of the treatment transducer, such that the focus of the treatment tranducer is co-axially

aligned with the imaging probe. Similar single-element piezo-ceramic transducers of 0.8-0.95 MHz with similar focal lengths were used in these cases.

Treatment was performed under General anaesthesia in patients 2-4. Sedation was used in patient 1 to allow the patient to give verbal feedback during treatment to reduce the risk of iatrogenic sciatic nerve injury, whilst maintaining patient comfort. Patients were positioned over the treatment head of the device (transducer), in a water bath filled with degassed water cooled to 15^{o}C, using slings to maintain the correct position. Skin overlying the entry point of the focused ultrasound was first degassed using a suction device. At each session the tumour was imaged using diagnostic ultrasound devices and correlated to pre-treatment pelvic MRI. Ultrasonic imaging was used to define a treatment plan i.e. to define a target volume within the tumour to direct treatment towards. Treatment proceeded by isolating a test area and ramping up acoustic power from 100W until ultrasonic grey scale changes were observed. At this intensity, successive ablations were then delivered to the planned area. Treatment was performed in single shot, rather than moving beam mode, such that by lying exposures side-by-side rows could be used to form slices. Multiple slices were used to cover a confluent volume. Greyscale response to treatment was monitored throughout with B-mode diagnostic ultrasound and acoustic power was adjusted as necessary to achieve ablation. Treatment parameters are summarised in table II. Patients were then recovered from anaesthesia/sedation if used. Skin was checked for thermal injury by clinical examination immediately following the end of treatment. Patients were transferred to the ward for overnight recuperation with deep vein thrombosis (DVT) prophylaxis and early mobilisation. Typically patients were discharged the following day.

Table II

Treatment effect

Pre and post HIFU scans were assessed by 2 senior radiologists independently. The radiologists were blinded to the date of the treatment, the planned treatment target and to the parameters of

treatment. The radiologists measured the size of the target tumour on each scan in three orthogonal axes. The volume was then estimated using the ellipsoid volume approximation [19]. Necrosis was estimated where possible by analysing imaging features including T2 signal change and contrast uptake characteristics. However it was not possible to systematically analyse for necrosis as subject 4 had no long term follow up scans (he was resident outside the UK and unable to attend follow up) and in patient 3's case, the tumour returned a high T2 signal with little contrast enhancement in some images pre and post treatment therefore it was not possible to detect necrosis consistently.

Results

Effect of HIFU on tumour volume

Table III, Figure 1

The effect of HIFU on tumour volume was assessed in 3 of the 4 patients (Table III & Figure 1). Patient 4 was not a UK resident and owing to poor mobility was unable to attend follow up in the UK. In patients 1 and 2, HIFU was associated with a decrease in tumour volume at 6 months post treatment (1; 16%, 2; 58-60% reduction). The original scans were not available for patient 3 after the first and second treatments, only reports which did not record tumour dimensions. Reports at the time indicated a stable reduction of tumour volume with reduced contrast uptake between 0 and 5 months post treatment. Patient 3 had a skin nodule associated with the chordoma removed surgically 5 months after the first HIFU treatments (this portion was too superficial to treat with HIFU). It was noted intraoperatively by the operating surgeon that the deep portions of the tumour that had been targeted by HIFU treatment were necrotic, whilst the untreated superficial portions remained viable, these were removed surgically. Patient 3 underwent further HIFU treatment 7 months after the first treatments owing to increased contrast uptake in the previously necrotic portion of the tumour, although overall size had not changed. After the third HIFU treatment serial scans beginning approximately 1 month after the

second treatment were associated with a 27-50% reduction in tumour volume (see table III). Patient 3 did suffer a late regrowth of tumour approximately 18 months after the fourth treatment, follow up scans were not available after the 5th treatment.

HIFU induced necrosis

Table IV, Figure 2

Tumour necrosis was observed post HIFU by both radiologists in patient 1 and 2 (Table IV & Figure 2). The estimated volume of necrosis in patient 1 after 6 months (having underwent two HIFU treatment sessions in that time) was 30% (Radiologist 1) to 80% (Radiologist 2), and in patient 2 30% (Radiologist 1) to 70% (Radiologist 2). Necrosis was observed surgically and reported radiologically after the first two treatments in patient 3 (30%), although only radiologist 2 reported necrosis: radiologist 1 commented that low contrast uptake and high T2 signal prevented assessment of necrosis.

Side effects

The 4 subjects completed 10 sessions of HIFU therapy in total. The most common side effect of treatment was some discomfort at the site of treatment requiring overnight analgesia post treatment. This was mild in terms of severity and settled with analgesia (Common toxicity criteria, CTC grade 2). One subject (patient 3) suffered some mild skin toxicity at the treatment site on their 2nd treatment, experiencing a small superficial blister that did not require further treatment (CTC grade 2)

Subject 2's treatment was terminated early owing to tumour tissue oedema at the target site. Post treatment, patient 2 complained of increased numbness over buttock, right leg and perineum the morning after treatment. Patient 2 failed trial without catheter therefore had to persist with intermittent self-catheterisation (ISC) on discharge. At 6 months post treatment,

patient 2 still had to perform ISC despite evidence of reduction in tumour size on 6 month MRI scan. Subject 3 after the fourth treatment experienced transient bladder dysfunction requiring catheterisation returning to normal bladder habit within 1 month of treatment. Subject 3 also experienced increase of pre-treatment leg weakness (CTC grade 3) after treatment that improved within 1 month of treatment to independent walking. Subject 4 experienced a drop in haemoglobin between pre and post HIFU treatment from 8.0 to 6.3 that was felt to be dilutional from anaesthesia, but underwent transfusion of 2 units of blood. Subject 1 experienced some leg discomfort during her 3rd treatment therefore the treatment was terminated early. This was not associated with post-treatment symptom change.

Discussion

HIFU has been trialled on a range of solid tumour types in the abdomen and pelvis including renal, liver and prostate amongst others [8]. Our group has shown that in renal cell and liver tumours treated with HIFU, areas of ablation demonstrated on MRI imaging agree with histological findings at surgery [20]. The advantages HIFU has over several of the other modalities is that ablation can be achieved non-invasively and without the use of ionising radiation, thus may be used for as many repeat treatments as the patient requires or can tolerate. Coagulative necrosis is achieved even in mitotically inactive tumours as treatment efficacy does not depend on target tissue mitotic rate, as radiotherapy depends upon. A further advantage is that ablation of tissue can be monitored in real time, by monitoring B-mode changes on an ultrasound-guided system, thus allowing the efficacy of treatment to be monitored and adjusted as necessary during treatment.

Our experience in this case series was that HIFU can result in successful ablation of chordoma tissue *in vivo* resulting in radiologically evident tumour necrosis in some cases and reduction in tumour

volume. HIFU is associated with risks, namely bladder/bowel dysfunction, sciatic nerve injury, but these risks should be judged against the alternative treatment of debulking surgery which may include pelvic exentration. We propose that nerve injury risk can be reduced by performing treatment under sedation rather than general anaesthesia, due to verbal patient feedback, and by limiting treatment in regions near significant nervous structures. The 2 subjects that experienced post treatment nervous dysfunction (subject 2 and subject 3 on 4th treatment) were performed under general anaesthesia.

The main limitations we encountered was that the locally advanced nature of the tumours prevented achieving ablation of the whole tumour volume. We propose that full ablation would be achievable on less advanced tumours. Tumour proximity to the rectum and nervous structures such as the sciatic nerve can prevent safe ablation of the entire tumour in advanced tumours. HIFU has been associated with bowel perforation if applied inadvertently to the bowel which is also a limiting factor of the technique in treatment of other abdominal or pelvic tumours [21]. Also, although necrosis and a reduction in tumour volume could be reliably and safely achieved, at the current time we cannot discern if HIFU can improve outcome of chordoma. Regrowth of tumour between treatments was an issue, for example in patient 3. Further clinical data and follow-up is required in this regard.

We have established a trial to attempt to answer the question can HIFU be used to ablate sacral bone tumours safely and effectively: Extra-corporeal high intensity focused ultrasound for primary sacrococcygeal bone tumours: phase iib trial of clinical efficacy, South East Scotland REC 02 ref 12/SS/0144, ISCRTN 91527768. The trial is open to recruitment in the UK with the aim of testing if HIFU treatment of sacral chordoma (or other primary intraosseous sacrococcygeal solid tumour) can improve outcome. The main inclusion criteria are:

- Subjects 18yrs and over who are able and willing to consent to treatment

- Histologically confirmed diagnosis of chordoma or other primary osseous tumour of the sacrococcygeal spine
- Previous surgical treatment and/or radiotherapy are permitted provided they were completed 12 months prior to HIFU treatment
- Clinically acceptable haematological, renal and liver blood tests within 14 days of treatment.
- American Society of Anesthesiologists (ASA) grade 2 or less
- World Health Organisation (WHO) performance status of 1 or less.

The main exclusion criteria are:

- Females who are pregnant, lactating or planning pregnancy during the course of the study
- Significant renal, hepatic, cardiovascular, respiratory or other illness that results in unacceptable anaesthetic or treatment risk

The primary end points of the trial are 5 year survival, pain experience and quality of life measures, and secondary end points include volume of tumour ablation, number and severity of adverse events.

Conclusions:

From our experience we propose that in technically feasible cases; HIFU may be an efficacious, and non-invasive treatment option to ablate sacral chordoma but further research is required to determine if this is associated with improved outcomes for patients.

For trial information, please contact martin.gillies@ouh.nhs.uk. Referrals should be addressed to Miss Stana Bojanic, Department of Neurosurgery, West Wing, John Radcliffe Hospital, Oxford, OX3 9DU. More details are available on the Cancer research UK website www.cancerresearchuk.org

and Society of British Neurological Surgeons website

www.sbns.org.uk/index.php/research/advertisement-for-clinical-trials/.

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Declaration of interest: FW serves as the director of the clinical department at Chongqing Haifu (HIFU) Technology Co. Ltd, manufacturer of the JC200 and JC devices and as director of the Tumour Therapeutic Centre, Chongqing University of Medical Science. The remaining authors declare no potential conflicts of interest.

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Figure legends

Table I: Patient characteristics

Table II: Treatment parameters and timings of treatments. Device (JC200 or JC), transducer head, focal length, average power in watts and exposure time.

Table III: Effect of HIFU on tumour volume. Table demonstrating changes in total tumour volume in cm3. Rx n: treatment number n, scan time: days from preceding treatment, negative number denotes a pre-treatment scan. Tumour volume: ellipsoid volume in cm3, R1: radiologist 1, R2: radiologist 2. % of pre-treatment volume calculated as current volume/pretreatment volume x

100% (in case 3 this was the first recorded volume after second treatment). N/A – not assessed because of lack of original scans.

Table IV: Relationship between estimated treatment volume and observed necrosis post treatment. Table demonstrates relationship of HIFU treatment volume to observed necrosis in tumour. Estimated treatment volume: ellipsoid volume targeted by HIFU specialist during treatment, approximated in patient 3. % necrosis calculated as volume of signal change/reduced contrast uptake compared to most recent pre-treatment scan.

Figure 1: Effect of HIFU on tumour volume. Graphic representation of volume changes over time. Volume normalised by pre-treatment volume, pre-treatment volume = 1.0. In the case of patient 3, volumes normalised to post-treatment number 2 volume. Arrows indicate time of HIFU treatment in relation to scans, number indicates number of days since 1st treatment, 0 indicates first treatment. Hollow circles: radiologist 1's estimate, filled squares: radiologist 2's estimate.

Figure 2: Demonstration of necrosis secondary to HIFU. Example of HIFU induced necrosis in patient 1. Water liver acquisition and volume acquisition (LAVA) post contrast MRI scan in 3 planes pre-treatment (upper images) and 2 months post-treatment (lower images). Signal change and loss of contrast uptake is observed posteriorly and inferiorly.

Author Contributions:

MJG, FW, TL, DC, FVG, & SB designed the current national trial, arranged funding, achieved ethical and local NHS permissions to conduct the trial, and organised publicity for the trial.

TL, FW, DC and SB organised ethics and funding prior to the current trial, selected patients, assessed patients pre-treatment, performed treatment and conducted follow up of treated patients (patients 2-4).

Patient selection was conducted by DC, SB and TL.

Pre and post-treatment patient care and assessment was done by PCL and MJG.

HIFU treatment was conducted by FW and PCL.

Radiological assessments were performed by DYC and FVG.

The manuscript and figures were composed by MJG, FVG and PCL

All authors read and approved the final submission draft of the manuscript.