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Case Report

Role of diffusion-weighted imaging in monitoring treatment response following high-intensity focused ultrasound ablation of recurrent sacral chordoma

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ABSTRACT

Chordoma is the most common malignant tumor of the sacrum and is associated with significant neurologic morbidity. Local recurrence is very common, and the long-term prognosis is poor. High-intensity focused ultrasound (HIFU) is a noninvasive and nonionising ablative therapy that has been successful in treating other tumor types and is being evaluated as a new therapy for sacral chordoma. Contrast-enhanced magnetic resonance imaging is typically used to evaluate tumor perfusion following HIFU; however, its utility is limited in poorly perfused tumors. Diffusion-weighted imaging (DWI) provides tissue contrast based on differences in the diffusion of extracellular water without using gadolinium-based contrast agents. We present novel DWI findings following a planned partial HIFU ablation of a large sacral chordoma which had recurred after radiotherapy. Following HIFU, the treated tumor volume demonstrated loss of restriction on DWI correlating with photopenia on positron emission tomography. This suggests successful ablation and tumor necrosis. This novel finding may provide guidance for sequence selection when evaluating HIFU therapy for sacral chordoma and other tumor types for which contrast-enhanced magnetic resonance imaging may have limited utility.

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Background

Chordomas are low-grade malignant tumors characterized by slow, but locally invasive and aggressive growth [1]. Chordomas arise from notochordal remnants in the axial skeleton, and most commonly in the sacrum [2]. Sacral chordoma typically presents with pain and neurologic symptoms, such as motor, bladder, bowel, or sexual dysfunction. The symptoms are slowly progressive, and the tumor is typically large by the time of presentation.

While radical en-bloc surgical resection with wide margins is the treatment of choice for primary sacral chordoma [3], this is often not feasible due to the proximity of the tumor to essential structures. Even when feasible, there is high associated morbidity, for example, formation of colostomy and urostomy. Radiotherapy is used as an adjuvant or alternative to surgery, and recently particle beam therapy has shown promise [4,5]. Despite this, local recurrence is very common [6] and the long-term prognosis is poor [7]. Therefore, there is an ongoing search for improved treatments for sacral chordoma.

High-intensity focused ultrasound (HIFU) is a noninvasive and nonionising ablative therapy. HIFU delivers a large amount of acoustic energy to a small focal spot, causing instantaneous targeted tissue necrosis by both thermal and mechanical mechanisms [8]. HIFU has received Food and Drug Administration approval for the treatment of uterine fibroids, bone metastases, and prostate cancer [9] and is being trialled in several other tumor types [10].

HIFU has the potential to be a new therapy for sacral chordoma. Within the context of a phase II clinical trial, we have used HIFU to treat patients with sacral chordoma to date at our center [11]. In these cases, magnetic resonance imaging (MRI) demonstrated reduced contrast enhancement and reduced volume of the ablated tumor tissue in keeping with partial response to HIFU.

Gadolinium-based MRI contrast agents typically provide an effective means of assessing response. However, in certain tumor types, including previously irradiated recurrent sacral chordoma such as in our patient, contrast agents have limited value due to poor and heterogeneous baseline contrast enhancement. Moreover, gadolinium is associated with an extremely low, but serious, risk of allergic reaction, retention, and nephrogenic systemic fibrosis [12].

Diffusion-weighted imaging (DWI) provides tissue contrast based on local differences in the diffusion of water molecules within the extracellular space and does not require gadolinium. Diffusion characteristics are usually quantified using apparent diffusion coefficient (ADC) values. It has been shown in human and animal models of brain tumors that there is a positive correlation between ADC and necrosis [13], and a negative correlation between ADC and tumor cellularity [14].

In this case report, we describe novel DWI characteristics of sacral chordoma following HIFU, which have been correlated with functional metabolic assessment. We believe this will provide guidance for sequence selection when evaluating HIFU response in sacral chordoma and other poorly perfused tumor types.

Clinical presentation

All patients enrolled on the clinical trial at Churchill Hospital, Oxford, received a patient information leaflet and careful counselling as to available treatment options prior to giving written, informed consent [15].

A 48-year-old man, with no past medical history of note, presented with a large mass arising from the lower sacrum and coccyx, which was histologically confirmed as sacral chordoma.

Surgical resection was not performed given the close relationship of the tumor mass to essential pelvic structures. The patient opted for carbon ion radiotherapy (CIRT). A radioprotective silicon spacer was inserted between the tumor and the rectal wall. He initially received CIRT at a total dose of 70.4 Gy.

A year later, MRI showed satellite nodules within the right gluteal subcutaneous fat. He received further CIRT at a total dose of 57.6 Gy to this region.

Unfortunately, 4 years after his initial presentation, MRI showed that the tumor mass was progressive. He commenced imatinib therapy. He was then referred to our center for consideration of HIFU treatment within a clinical trial.

The patient was assessed by a multidisciplinary team consisting of a neurosurgeon, a radiologist, and a HIFU specialist. Contrast-enhanced MRI with DWI sequences was performed for procedure planning. Given the radiotherapy-related skin change and tethering on the right buttock, it was decided to undertake HIFU treatment with palliative intent on the left side only to reduce the risk of any further skin damage.

The patient had HIFU treatment under sedation using an extracorporeal HIFU device (Model JC200 Focused Ultrasound Tumor Therapeutic Systems, Haifu Medical, Chongqing, China). A $7 \times 6 \times 6$ cm volume on the left side of the sacral chordoma was successfully ablated under ultrasound-guidance. There were no complications. Given the success of the initial procedure, the patient had a second attempted HIFU procedure to the right side of the tumor; however, the procedure was abandoned due to pain when treating over the area of radiotherapy-related skin change.

Response to treatment was evaluated with MRI 1 month after the first HIFU ablation. Tumor volume was determined by an experienced radiologist measuring the maximum linear dimension in 3 planes and applying the ellipsoid formula (product of the 3 measurements $\times 0.52$) [16]. Following HIFU to the left side of the tumor, there was a 15% reduction in total tumor volume. There was no clear change in contrast enhancement; however, this was poor and heterogeneous at baseline. DWI showed restricted diffusion within the untreated right side of the tumor, which is typical for chordoma [17]. In contrast, the treated left side showed low signal on b1000 images and high ADC values. This indicates reduced diffusion restriction in the treated tumor volume (see Fig. 1).

Eleven months post-HIFU, the patient underwent 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) imaging for the characterization of new soft tissue lesions in the lumbar spine and lung. PET/CT showed mild FDG avidity within the untreated right side of the sacral chordoma, which is expected for this tumor type [18–21]. However, the treated left side was markedly

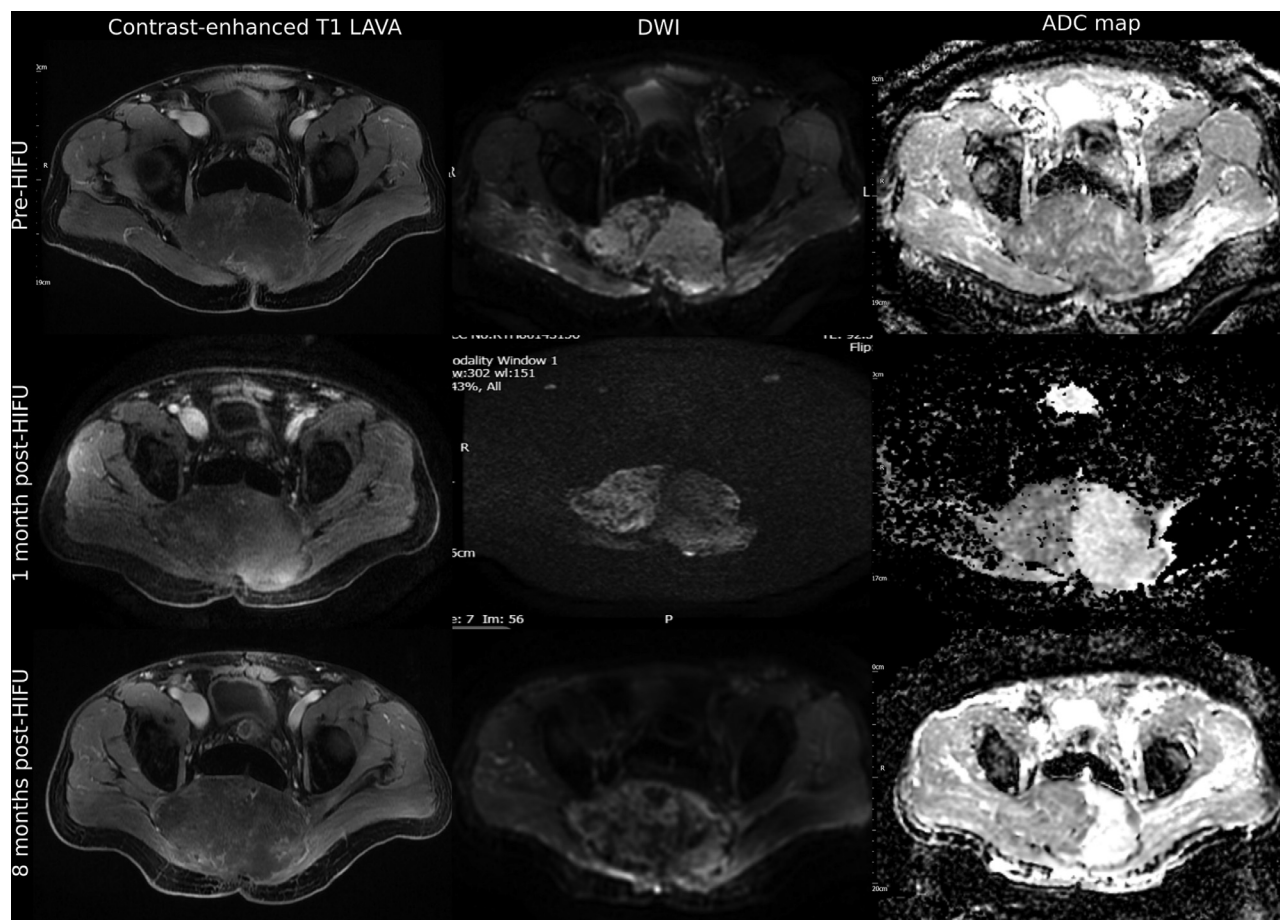


Fig. 1 – MRI prior to HIFU treatment (top row) and at 1 month (middle row) and 8 months (bottom row) after HIFU treatment. Left column: axial T1-weighted fat-suppressed fast-spoiled gradient echo (LAVA) sequence, venous phase imaging. Middle and right columns: axial DWI and ADC map at $b = 800$ (top row), $b = 1000$ (middle row), $b = 700$ (bottom row). ADC values are significantly higher on the HIFU-treated left side of the chordoma than the untreated right side, indicating a reduction in diffusion restriction.

photopenic, in keeping with tumor necrosis and supporting the previous DWI findings (see Fig. 2). Unfortunately, despite successful local tumor ablation, the new soft tissue lesions in the lumbar spine and lung are thought to represent chordoma metastases.

Discussion

The MRI appearances of chordoma have been described previously [2,22]. Sacral chordoma is typically a lobulated mass arising from the sacrum. On T1-weighted images, chordomas are iso- or hypointense relative to muscle, with areas of high signal corresponding to hemorrhagic and mucinous material. On T2-weighted images, chordomas are very hyperintense, reflecting the high water content of the notochordal-origin nucleus pulposus tissue. Chordomas show a modest degree of heterogeneous contrast enhancement. DWI characteristics have been described in skull-base chordomas [17]; they show low ADC values indicating abnormal diffusion restriction. This

may be because their mucinous stroma impedes the free motion of extracellular water.

Following HIFU ablation of sacral chordoma, our group has previously described low signal change and nonenhancement on T1-weighted fat-suppressed fast-spoiled gradient echo (LAVA) sequence [11]. In our patient, who had previously received radiotherapy, the tumor showed poor and heterogeneous contrast enhancement prior to HIFU treatment, hence contrast-enhanced MRI was of limited value in evaluating HIFU response.

DWI appearances following HIFU ablation of sacral chordoma have not been characterized before. We are the first to report a significant low signal change on DWI and increase in ADC values following HIFU, indicating reduced diffusion restriction after ablation.

Interestingly, a study of skull-base chordomas found that ADC values are higher after radiotherapy [17]. Similar DWI findings have been described in other benign and malignant tumors treated with HIFU. In patients with bone metastases [23], uterine fibroids [24] and primary hepatic carcinoma [25], ADC values are significantly higher after HIFU ablation. In an

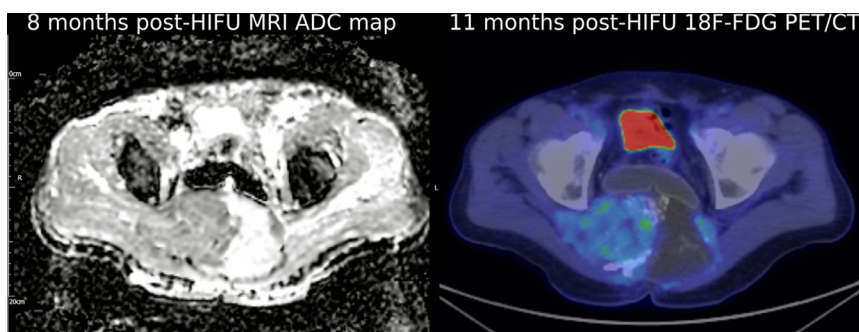


Fig. 2 – Axial ADC map 8 months after HIFU treatment (left) and axial fused 18F-FDG PET/CT 11 months after HIFU treatment (right). The HIFU-treated left side of the chordoma show excellent correlation with high ADC values and no 18F-FDG uptake, indicating tumor necrosis.

ex vivo animal study, a 20% increase in ADC following HIFU ablation correlated with macroscopic tissue damage [26]. This suggests that DWI is able to evaluate the nonperfused volume following HIFU ablation.

18F-FDG PET/CT is a mainstay of staging for many metabolically-active cancers. Typically sacral chordoma demonstrates heterogeneously increased 18F-FDG uptake [18–21]. In our study, the HIFU-treated tumor volume showed excellent volumetric correlation between high ADC values and complete lack of 18F-FDG uptake. This suggests the DWI appearances are likely to represent tumor necrosis after HIFU ablation.

Summary

A 48-year-old man with local recurrence of sacral chordoma after CIRT and imatinib therapy was referred to our center for HIFU ablation. He successfully underwent HIFU ablation with palliative intent to the left side of the tumor. The right side was not treated due to overlying postradiotherapy skin change. We report novel diffusion weighted imaging findings following HIFU ablation. The treated tumor volume demonstrated high ADC values, indicating a reduction in abnormal diffusion restriction. There was no FDG uptake within the treated tumor volume on PET/CT, suggesting the DWI appearances represent tumor necrosis following HIFU ablation.

Learning points

- HIFU is an established treatment for many benign and malignant tumors and is being trialed in patients with sacral chordoma.
- Gadolinium-based contrast enhanced MRI is typically used to assess the radiological response to HIFU ablation, but of limited value when assessing poorly perfused tumors. DWI provides contrast based on differences in the diffusion of water molecules and avoids the risks associated with contrast agents.

- Sacral chordoma typically demonstrates abnormal diffusion restriction. Following HIFU ablation, we report loss of diffusion restriction on DWI sequences together with a lack of FDG uptake on PET/CT. This is likely to represent necrosis of the ablated tumor volume.

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