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Significance of HIFU in local unresectable recurrence of soft tissue sarcoma, a single-center, respective, case series in China

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ABSTRACT

Purpose: Multimodality treatment of soft tissue sarcoma(STS) by expert teams reportedly affords a tremendous improvement in outcome of patients. Despite advances, treatment of local unresectable recurrence remains difficult and is not standardized. We performed this retrospective study in order to assess the efficacy and safety of high-intensity focused ultrasound (HIFU) ablation in treating STS patients with local unresectable recurrence.
Methods: Thirty-six STS patients with local unresectable recurrence from January 2015 to December 2016 were recruited according to the inclusion criteria. Pain rating, response rate, disease control rate, local disease progression-free survival(LPFS), progression-free survival (PFS) and overall survival(OS) were used to evaluate efficacy of HIFU treatment.
Results: HIFU resulted in a significant relief in pain rating, without severe side effects. According to magnetic resonance imaging(MRI), three months after HIFU treatment, response rate was 47.3% and the local disease control rate was 80.6%. Twelve months post HIFU treatment, response rate was 38.9% and the local disease control rate was 55.6%. The median LPFS, PFS and OS time for 36 patients was 13 months, 10 months and 20 months respectively.
Conclusion: HIFU is a tolerated treatment modality with promising activity and safety in STS patients with local unresectable recurrence.

1. Introduction

Soft-tissue sarcomas (STS) collectively account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. In 2018, an estimated 13,040 people will be diagnosed with soft tissue sarcoma in the United States, with approximately 5150 deaths [1,2]. In patients with primary diagnosed STS, the therapy of choice involves limb-sparing surgical resection with clear margins, usually followed by radiation treatment to decrease local recurrence, with or without adjuvant chemotherapy [3]. Despite the improvement in combined treatments, approximately 12–28% patients with soft tissue sarcoma relapsed with local recurrence [4–8], and, once developed, local recurrence usually suggests a poorer outcome, with a 2-year survival rate ranging from 50% to 70% [9,10], especially for local unresectable recurrence. A retrospective study involving 753 intermediate to high-grade STS patients pointed out that local recurrence of STS was significantly associated with increased morbidity, and was the single most significant factor associated with decreased overall survival, in part reflecting greater biological tumor aggressiveness [11].

Despite improvements, treatment for local recurrence remains quite challenging today [1,9,12,13]. Surgery has been the mainstay therapy for local recurrence. However, resection is sometimes difficult because of the location and extension of the tumor. Even when it is possible, the attainment of negative surgical margins may require extensive surgery and could result in a loss of extremity function. Additionally, in cases of recurrence with large tumor size or location adjacent to critical anatomic structures, the surgical approach to attaining negative margins in locally recurrent disease is associated with considerable morbidity [14]. Radiation therapy combined with surgical resection have replaced extensive surgical procedures in order to preserve functionality while

Abbreviations: STS, Soft tissue sarcoma; HIFU, high-intensity focused ultrasound; LPFS, Local disease progression-free survival; PFS, progression-free survival; OS, Overall survival; US, ultrasound; ECOG PS, Eastern Cooperative Oncology Group performance status; CT, Computed tomography; MRI, Magnetic resonance imaging; VAS, Visual analogue scale/score; PNET, Primitive neurotodermal tumour; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progression disease

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maintaining adequate local control [15]. However, the possibility to achieve satisfying control by external beam radiation therapy can be limited in local unresectable recurrence of STS, especially in STS patients with radiation-resistant subtype or a previously radiation treatment history. Available evidence, although underpowered, suggests that doxorubicin/ifosfamide-based postoperative chemotherapy would improve outcome in selected patients at high risk of recurrence [16]. Somehow, in STS patients with chemo-resistant subtype, once developed local unresectable recurrence, chemotherapy might have minimal impact on survival of patients. Thus, development of novel techniques for local control in STS patients with local unresectable recurrence is highly desired.

High-intensity focused ultrasound (HIFU) is based on the fact that ultrasound (US) beams can be focused and transmitted through solid tissues within the body, resulting in some effects that can destroy and coagulate in-depth tissue through thermal effects and cavitation. HIFU coagulates target lesions through intake skin without surgical exposure or insertion of instruments. HIFU techniques for solid tumors treatment [17,18] have been reported as noninvasive and conforming with real-time monitoring, including bone tumors [19,20] and synovial sarcoma [20]. On the basis of these favorable results, we conducted the present retrospective study to evaluate the safety and efficacy of HIFU therapy in STS patients with local unresectable recurrence.

2. Materials and methods

2.1. Patient eligibility

From January 2015 to December 2016, 36 STS patients with local unresectable recurrences were treated in our institution and their data were collected and analyzed. Ethical approval for the study was provided by the independent ethics committee, Sixth people's Hospital, Shanghai JiaoTong University. Informed and written consents were obtained from all patients or their advisers according to ethics committee guidelines.

Inclusion and exclusion criteria were followed as listed below. Inclusion criteria: (a) Recurrence of STS confirmed histologically; (b) Patients with adequate hepatic/renal/bone marrow function, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; (c)Refused to undergo surgery or not a candidate for surgery; (d) Progression of local recurrence by RECIST 1.1 standard after two cycles of chemotherapy with doxorubicin and ifosfamide; (e) Tumor not involving the neurovascular bundles. Exclusion criteria: (a) Targeted tumor located in the vertebral column; (b)local recurrences which extensively involved skin and/or subcutaneous tissue and patients with excessively scarred, radiation damaged, severe skin lesions; (c) Patients with distant metastasis since systemic treatment might affect evaluation of local recurrence.

Each patient met with three orthopedists (at least 10 years clinical experience) before deciding to undergo high-intensity focused ultrasound rather than other antitumor treatments. Radiologic examinations including computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy were performed to define margin of local recurrence and existence of metastasis.

2.2. Procedures for HIFU treatment

HIFU was performed using HIFUINT-9000 system (Shanghai A&S Sci-Tec Co., Ltd, Shanghai, China), which is a US-guided device [21]. Firstly, tumor location, size, and the morphological characteristics are identified by CT or MRI; in the meantime, the influence of tumor on adjacent organs and blood vessels is also evaluated. Next, the detecting head of this system will complete the relocalization of the therapy area. Finally, the ablation energy focus is controlled to move sequentially along the three dimensional axis until the target lesion is totally covered. The main HIFU parameters of treatment in this study were the following: intensity, 5–10 kW/cm^2; therapy depth, 2–15 cm; practice-focused sphere, $3 \times 3 \times 8\ mm^3$; unit transmit time (t1): intermission time (t2) = 1:2; and HIFU times at each lesion, 8–10 times. All of the parameters can be varied depending on the depth of the tumor.

2.3. Response to treatment and adverse effects

The primary outcome of this single-center, respective study was local disease progression-free survival(LPFS) and VAS(visual analogue scale/score) change of patients. The secondary end points were 3- and 12-month local tumor response rate, progression-free survival(PFS) and overall survival(OS). LPFS was defined as an interval from the start of HIFU to relapse of local recurrence. Progression-free survival (PFS) was defined as an interval from the start of HIFU to progression of the disease or death from any cause. Overall survival was defined as the period from the HIFU treatment to the last follow-up or death. Imaging examinations were performed to evaluate the therapeutic effectiveness of HIFU. Before HIFU and 3 months after HIFU, all patients underwent contrast-enhanced magnetic resonance imaging (MRI) evaluate the change of local tumor size. Then a routine CT scan or MRI was conducted every three months to evaluate the efficacy. The response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). VAS pain scores were also recorded and assessed before HIFU ablation, and at 1 and 3 months post-HIFU treatment. AEs were recorded, and the severity was graded in accordance with the Common Terminology Criteria for Adverse Events, version 4.25.

2.4. Statistical analyses

Survival analysis of patients was conducted by the Kaplan–Meier method. To obtain more detailed descriptions of the survival, stratified analyses by the characteristics of cases were also performed. Comparisons of VAS scores were carried out using a two-tailed Student's *t*-test (MS Excel). All the data analyses were performed by Stata 19.0 software (Stata Corp LP, College Station, TX, USA). A P-value < 0.05 indicated statistical significance.

3. Results

3.1. Patient characteristics

In total, 36 patients were enrolled in this study, including 25 males and 11 females, with a median age of 40 years (range: 8–67 years). The median time to develop local recurrence was 12.46 months from the date of first surgery (range: 4–25months). The median VAS prior to HIFU was 6 (range: 0–9), while 83.3% of the cases had a VAS ≥ 4. Explicitly, the tumors pathological subtypes included lipoblastoma in 8 patients, undifferentiated pleomorphic sarcoma in 7, leimyosarcoma in 3, fibrosarcoma in 6, chondrosarcoma in 4, synovial sarcoma in 3, aggressive fibromatosis in 2, and alveolar rhabdomyosarcoma, clear cell sarcoma, PNET(primitive neurotodermal tumour) in 1 respectively. The mean of maximum diameter of tumor before HIFU treatment was 11.31 cm (range 8–17 cm). The sites of local recurrences of 36 patients were: 21 at lower limbs, 12 at pelvis and 3 at upper limbs. The median follow-up for patients until January 2019 was 20.5 months (range: 7–34 months). Besides, at last follow-up, patients who were still alive all have a follow-up time more than 2 years.

3.2. Safety of HIFU treatment

A total 196 sessions of HIFU was given while 24 patients underwent 5 sessions, 4 patients underwent 3 sessions, and the other 8 patients underwent 8 sessions. A low-grade fever was observed in 12 patients (37.7–38.2° celsius) after HIFU treatment and disappeared within 3 days. Regional body temperatures remained unchanged. Mental status

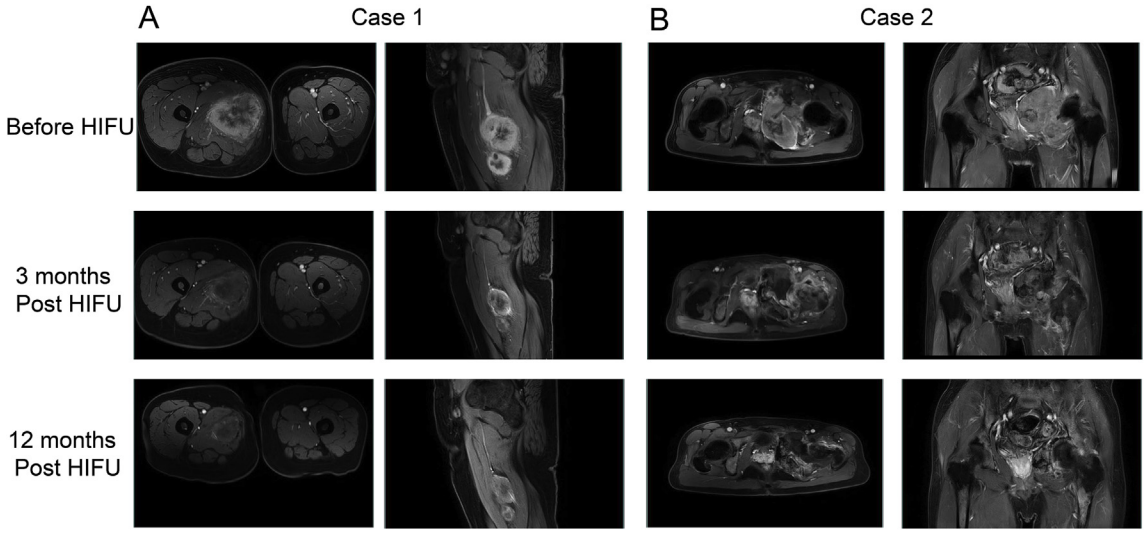

Fig. 1. Two typical cases of HIFU treatment efficacy. A: 36-year-old man with local recurrence of chondrosarcoma in the upper left thigh. B. 51-year-old man with local recurrence of undifferentiated pleomorphic sarcoma in the left pelvis.

and appetite remained normal throughout HIFU treatment. 21 patients exhibited venous skin engorgement before HIFU treatment. After treatment, 9 patients no longer exhibited these symptoms, 10 patients improved, and 2 patients had no obvious change. Within one week, swelling in therapy areas disappeared.

Twenty-one patients had first-degree burns while underwent HIFU treatment. The discomfortable symptom faded without intervention within two weeks. No scars observed one month after treatment in all patients. For patients with recurrent tumor in limbs, three lacked feeling in the affected limb during HIFU treatment, but the symptoms were alleviated within one week after treatment.

3.3. Efficacy and survival

According to MRI or CT examination 3 months after HIFU treatment (Fig. 1), the response rate for patients was: no CR(complete response), 17 (47.3%) had PR(partial response), 12 (33.3%) had SD(stable disease), and 7 (19.4%) had PD(progression disease). The response rate (CR + PR) was 47.3% and the local disease control rate (CR + PR + SD) was 80.6%. 12 months after HIFU treatment, the response rate for patients was: no CR, 14 (38.9%) had PR, 6 (16.7%) had SD, and 16 (44.4%) had PD. The response rate(CR + PR) was 38.9% and the local disease control rate(CR + PR + SD) was 55.6%.

The median LPFS, PFS and OS time for 36 patients was 13 months, 10 months and 20 months respectively(Fig. 2A–C). Additionally, among 27 patients who had disease progression, their first disease progression were: 16 patients had distant metastasis prior to secondary relapse of local recurrence, while 9 had distant metastasis after secondary relapse of local recurrence and two had distant metastasis plus secondary relapse of local disease simultaneously(Fig. 2D).

3.4. Pain relief

One-month post HIFU treatment, among 33 patients who suffered from pain, pain was relieved in 25 patients (75.8%). Complete remission of pain (0 pain score and no need for opioid analgesics) was observed in 9 patients (27.2%), a partial remission of pain (decrease in pain score by 2 or more) was observed in 16 patients (48.4%), and no improvement of pain was observed in 8 patients (24.2%). For VAS score, one month after treatment, pain was significantly alleviated, on a median rating was 2 (range: 0–5, $P < 0.01$). Pain relief was observed in 94.1% (16 of 17) of patients who had an objective tumor response and in 7 patients(58.3%, 7 of 12) who did not show an objective tumor response. This pain alleviation maintained stable three months after HIFU treatment, with a median rating was 3 (range: 0–6, $P < 0.01$, Fig. 2E).

4. Discussion

Treatment of local unresectable recurrence of STS remains difficult and is not standardized. Numerous predictors, such as patient age, presentation status, tumor size, tumor depth, histologic grade, surgical margins, and radiation, reportedly have a significant influence on the cause-specific hazard of local recurrence [22]. Recurrences after aggressive initial local treatment are likely to be more difficult to manage because of the prior treatments given such as radiotherapy and chemotherapy, and possibly also because recurrent tumor may possess some inherent characteristics that can explain its recurrence and make it more resistant to treatment [23]. This is the reason we set to determine whether options of local treatment as HIFU could improve outcome of STS patients suffered from local unresectable recurrence.

As a noninvasive treatment, HIFU does not require the insertion of an applicator into a target tissue, and an extracorporeal source can be used to treat large-volume tumors with real-time imaging guidance. As reported by numerous studies, it could be applied in patients with advanced pancreatic carcinoma safely and effectively [24]. Our retrospective investigation demonstrated that.

HIFU therapy was active and well tolerated as an ideal option in STS patients with local unresectable recurrence, with a response rate of 47.3% plus disease control rate of 80.6% 3 months post treatment, a response rate of 38.9% plus disease control rate of 55.6% 12 months post treatment, and a LPFS time of 13 months. Additionally, among 27 patients who had disease progression during follow-up, most of their progression (59.2%, 16 patients) first manifests as distant metastasis rather than local secondary relapse. Besides, there is a consensus that cancer-related pain can negatively affect patient survival by directly reducing the quality of life, impeding the administration of a full chemotherapy dose, and/or causing a decline in the patient's overall health [25]. Our study revealed that HIFU could give patients significant pain relief and reduced VAS pain scores in STS patients with local unresectable recurrence, indicating that HIFU could be a potential clinical approach in cancer pain control, one of the most feared consequences of cancer.

The main complications of HIFU therapy in malignant bone tumor included skin burns in the therapy area and local nerve injury. Other potential complications included fracture of the tumor-affected bone,

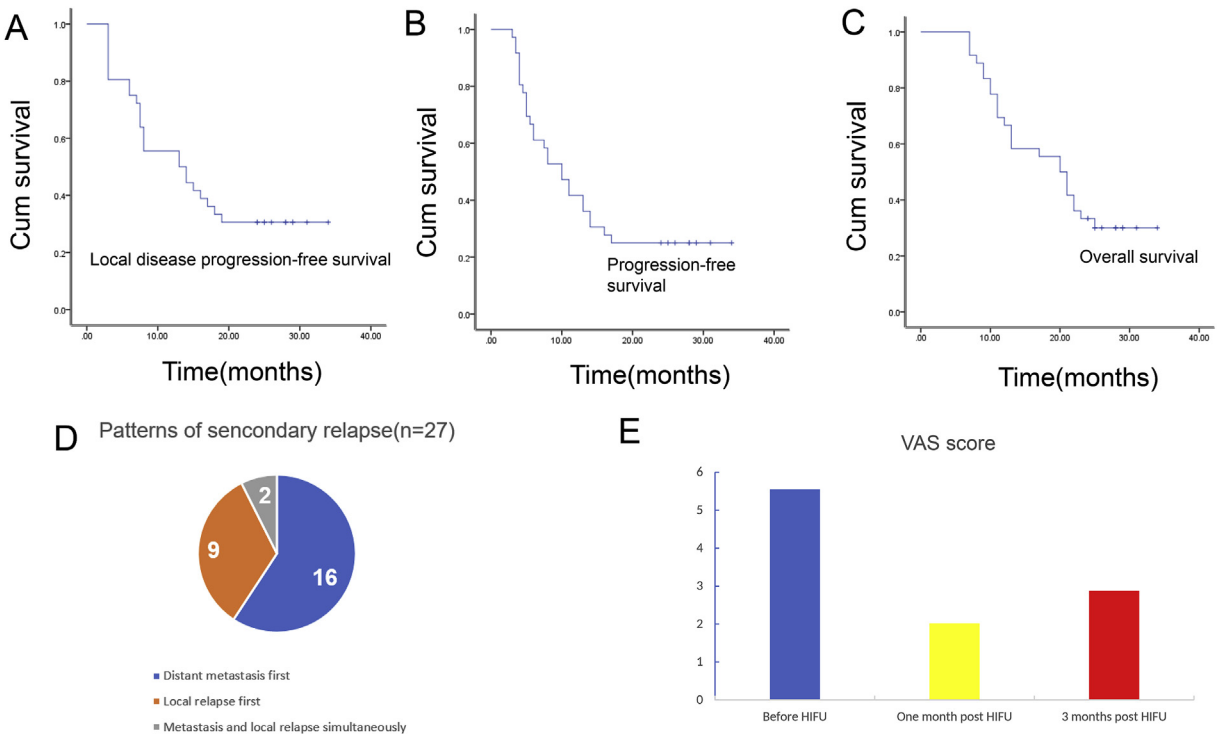

Fig. 2. Efficacy of HIFU treatment in STS patients: **A:** Local disease progression-free survival curve for 36 patients. **B:**Progression-free survival curve for 36 patients. **C:** Overall survival curve for 36 patients. **D**: Patterns of secondary relapse after HIFU treatment; **E:**Pain relief of HIFU on patients.

functional loss of nearby joints, and hemorrhagic infection of the tumor [26,27]. In our investigation, we took safety parameters as superficial burns/blisters, fractures associated with the treatment, pain after the procedure, neurovascular dysfunction post-treatment, and any local or systemic side effects into account. We observed all patients tolerated HIFU treatment well and no severe complications during treatment, which strongly suggest that HIFU is safe and efficacious modality for the treatment of STS local recurrence.

Although suggested as a category 2B recommendation due to limited and conflicting data regarding the potential benefits [15], sometimes chemotherapy might be the only systemic treatment for STS patients who are symptomatic with distant metastasis. Meanwhile, since STSs are frequently associated with angiogenesis and angiogenesis, inhibitors such as pazopanib has been prescribed in some cases of stage IV STS. Thus, we wonder that in STS patients with local unresectable recurrence, whether HIFU could achieve a better outcome in local lesion, while combined with other standard treatment, like second-line chemotherapy or target therapy? We noticed that among 36 patients, survival analysis revealed that LPFS(13 months) was longer than PFS (10 months), mainly due to most of disease progression first manifested as distant metastasis rather than local secondary relapse. Thus, we speculated this indicate the administration of systemic treatment after HIFU treatment, like second-line chemotherapy or target therapy, might further improve the outcome of STS patients with local unresectable recurrence? Indeed, it needs more evidence, especially data from large-scale prospective study to confirm.

There were several limitations in our investigation study. First, our results came from a single-center, non-blinded observation study, which would not provide the highest quality evidence of clinical practice. Second, our sample scale is relatively small(36 patients), and the follow-up period is not long enough. Therefore, top-level designed trials with a larger sample size are needed. Nevertheless, our investigation has provided a reliable clinical evidence for the new direction of HIFU treatment in STS patients with local unresectable recurrence due to its promising activity and safety.

5. Conclusion

HIFU is a tolerated treatment modality with promising activity and safety in STS patients with local unresectable recurrence.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.06.004.

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