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Review

High-intensity focused ultrasound: Noninvasive treatment for local unresectable recurrence of osteosarcoma

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ABSTRACT

Objective: Local unresectable recurrence of osteosarcoma is one of the most challenging tumors to treat. High-intensity focused ultrasound (HIFU) is a new, noninvasive technique with potential to ablate and inactivate tumors. Treatment of solid tumors with HIFU has been reported. In this study, we assessed safety and efficacy of HIFU in treating local unresectable recurrence of osteosarcoma.

Methods: We performed a retrospective analysis of 27 patients who had local unresectable recurrence of osteosarcoma from 2006 to 2010. Changes of biochemical markers and pain rating, response rate, disease control rate, local disease progression-free survival, progression-free survival (PFS) and overall survival (OS) were used to evaluate efficacy of HIFU treatment.

Results: HIFU resulted in a significant change in alkaline phosphatase and lactic acid dehydrogenase and a remarkably relief in pain rating, without severe side effects. According to MRI examination 4–6 weeks after HIFU treatment, 2 (7.4%) patients had complete response (CR), 12 (44.4%) had partial response (PR), 9 (33.3%) had stable disease (SD) and 4 (14.8%) had progression disease (PD). The response rate was 51.8% and the local disease control rate was 85.2%. The 1-, 2-, and 3-year local disease control rates were 59.2%, 40.7% and 33.1%, respectively. The median local disease progression-free time was 14 months, the median progression-free time was 13 months and the median over-all survival time was 21 months. Patients without pulmonary metastasis had a better local disease control rate at 1-,2-,3-year and a longer local disease progression-free time, progression-free time, over-all survival time than patients with pulmonary metastasis.

Conclusion: HIFU is a safe and noninvasive treatment for local unresectable recurrence of osteosarcoma, with good local control and without severe complications.

Contents

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Introduction

Osteosarcoma is the most common malignant primary bone tumor in childhood [1], with an age-standardized incidence of approximately 5 per million per year [2]. Cure rate of osteosarcoma has significantly improved in the last 25 years by combining surgery with aggressive multi-agent chemotherapy. Despite the improvement in combined treatments, approximately one-third of the patients with localized disease at present will relapse and local recurrence occurs in 4–10% of patients following effective treatment [3]. Although the reported rate of local recurrence is lower than that of distant metastasis, once developed, it suggests a poorer outcome than metastasis alone [4–7]. This is not surprising as the majority of osteosarcoma patients with local recurrence have previously received multi-agent chemotherapy and might have developed drug resistance in their recurrent disease [8]. Somehow, for those patients without metastases, previous study suggest a 41% chance of still being alive at five years after the incidence of local recurrence [8], which suggested a promising future for this subgroup and a necessity for local control treatment.

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, tumor resection often damages nerves and muscles and causes severe functional impairment. Chemotherapy is another mainstay of treatment for osteosarcoma. But it is impossible to control osteosarcoma without effective local treatment, which is similar to the controversy relating to the routine use of chemotherapy in patients who develop metastases and which is as yet unresolved [5]. Meanwhile, osteosarcoma is often radio-resistant, few reports described effective local control using radiotherapy for osteosarcoma. Thus, local unresectable recurrence of osteosarcoma is one of the most challenging tumors to treat. Development of novel techniques for local treatment in osteosarcoma patients with local unresectable recurrence is highly desired.

High-intensity focused ultrasound (HIFU) ablation is a noninvasive modality for the treatment of localized tumors and has been shown to demolish tumor vasculature, as well as to result in coagulative necrosis of tumor cells. An ultrasound beam can be focused as it passes through tissue. This enables the use of an ultrasound generated by an extracorporeal focusing US transducer to induce thermal ablation of a tumor at a depth through the intact skin. Under the guidance of real-time ultrasonographic imaging, the motion of a therapeutic transducer can facilitate ablation of a three-dimensional target [9,10]. This technique has been used to treat patients with various kinds of malignancies, including prostate, liver, breast, kidney, pancreas, bone metastasis, glioblastoma and soft tissue sarcoma [11–18]. A previous study has proven the efficacy of HIFU as a safe and feasible method in initial treatment of primary osteosarcoma [18–20]. Taking all the above into account, we wonder that HIFU ablation might be a noninvasive treatment preferred for local unresectable recurrence of osteosarcoma.

The purpose of this study was to evaluate the efficacy of HIFU in the treatment of osteosarcoma patients with local unresectable recurrence.

Materials and methods

Patient eligibility

From January 2006 to May 2010, 27 osteosarcoma patients (20 male, 7 female; median age, 19 years; age range, 11–56 years) with local unresectable recurrences were enrolled in this respective study. Ethical approval for the study was provided by the independent ethics committee, Sixth people's Hospital, Shanghai Jiao-Tong University. Informed and written consents were obtained from all patients or their advisers according to ethics committee guidelines.

Patients were selected based on the following criteria: (a) Recurrence of osteosarcoma diagnosed by core biopsy; (b) Local recurrence without involvement of nerves or vessels; or with main vessels and nerve tracts intact/displaced from compression by tumor; (c) Refused to undergo surgery or not a candidate for surgery. (d) Progression of local recurrence by RECIST 1.1 standard after underwent multi-agent chemotherapy including ADM(doxorubicin), DDP (cisplatin), IFO (ifosfamide)and MTX (methotrexate) and no other standard forms of treatment remained; Exclusion criteria for the study included patients with local recurrences which extensively involved skin and/or subcutaneous tissue; and patients with excessively scarred, radiation damaged, severe skin lesions. Patients with pulmonary metastasis often accept resection or stereotactic radiosurgery to cure their metastatic lesion. Considering that HIFU has proven to be a safe treatment for osteosarcoma in previous study [18–20], it is reasonable to believe that HIFU treatment would not interrupt other treatment so that pulmonary metastasis was not considered to be an exclusion criterion.

Each patient met with three orthopedists (at least 10 years clinical experience) before deciding to undergo high-intensity focused ultrasound rather than or in addition to other treatments. Radiologic examinations included computed tomography (CT), magnetic resonance (MR) imaging, and bone scintigraphy. Chest CT was performed to define lung metastases.

The sites of primary osteosarcoma of 27 patients were: six at proximal femur, eleven at pelvis, six at scapula, three at proximal humerus and one at distal femur. Seven recurred in bone and the other twenty in surrounding soft tissue. Among ten patients with primary tumor site at extremity, eight patients had limb salvage surgery while the other two had amputation. Only 4 of the 27