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Carbon ion radiotherapy for recurrent calf myxoid liposarcoma: a case report

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Abstract

Liposarcoma (LPS) is the most common soft tissue sarcoma. Myxoid LPS (MLPS) is the second most common subtype of LPS and accounts for 25% to 50% of all LPSs. Like most other soft tissue sarcomas, the mainstay of treatment for LPS is inevitably surgery. Multidisciplinary approaches, including surgery, chemotherapy, and radiotherapy, have been successful in the treatment of LPS during the last three decades. Even so, recurrence of LPS remains challenging. Carbon ion beams produce increased energy deposition at the end of their range to form a Bragg peak while minimizing irradiation damage to surrounding tissues, which facilitates more precise dosage and localization than that achieved with photon beams. Furthermore, carbon ion beams have high relative biologic effectiveness. We herein describe a patient who developed recurrent MLPS in the right calf after two surgeries and underwent carbon ion radiotherapy (CIRT), achieving complete disappearance of the tumor. The patient developed Grade I radiation dermatitis 30 days after CIRT, but no other acute toxicities were observed. The tumor had completely disappeared by 120 days after CIRT, and the patient remained disease-free for 27 months after CIRT. The CARE guidelines were followed in the reporting of this case.

Keywords

Carbon ion radiotherapy, liposarcoma, recurrence, case report, myxoid liposarcoma, surgical resection

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Introduction

Liposarcoma (LPS) is the most common soft tissue sarcoma.[1] Five histological subtypes of LPS have been identified: well-differentiated, myxoid, round cell, dedifferentiated, and pleomorphic variants. Most cases of myxoid LPS (MLPS) occur in the lower limbs, such as the thighs, and in the retroperitoneum.[2] MLPS is the second most common subtype of LPS and accounts for 25% to 50% of all LPSs.[3] Like most other soft tissue sarcomas, the mainstay of treatment for LPS is inevitably surgery. Multidisciplinary approaches, including surgery, chemotherapy, and radiotherapy, have been successful in the treatment LPS during the last three decades. Even so, recurrence of LPS remains challenging. Carbon ion beams produce increased energy deposition at the end of their range to form a Bragg peak while minimizing irradiation damage to surrounding tissues, facilitating more precise dosage and localization than that achieved with photon beams. Furthermore, carbon ion beams are independent of the cell cycle and have high relative biologic effectiveness (RBE) and a low oxygen enhancement ratio. This type of radiation also leads to double-strand breaks in DNA molecules, resulting in lethal damage to tumor cells. These properties are thus advantageous for treating radiation-insensitive tumors.[4] We herein present a case of recurrent MLPS in the right calf. The patient underwent CIRT, achieving complete disappearance of the tumor and remaining disease-free for 27 months after CIRT. This case has been reported in compliance with the CARE guidelines.[5]

Case presentation

A 55-year-old woman was referred to our institution to undergo CIRT for treatment of a right calf MLPS. She had no significant family history. Six years earlier, she had undergone surgery at another hospital with a chief complaint of a painless mass in her right calf. Postoperative pathologic examination showed a right calf MLPS of $9.6 \times 4.0 \times 5.0\,cm^3$ with an R0 margin. Hematoxylin and eosin staining showed a mixture of uniform oval non-lipogenic cells and small signet ring lipoblasts in a prominent myxoid stroma, and immunohistochemistry revealed S100 (−) and Ki-67 (2%–5% +). After surgery, the patient declined further treatment and underwent regular follow-up. Sixteen months later, follow-up magnetic resonance imaging (MRI) showed multiple nodules in the right calf muscle space that were considered to represent local recurrence. After further examination and multidisciplinary consultation, the patient underwent a second surgical excision of the tumor. The postoperative pathologic findings suggested an R0 margin and were consistent with the findings of the primary tumor in the first surgery. Postoperative adjuvant radiotherapy was performed 1 month after the operation (first course: target dose of 50.4 Gy in 28 fractions (1.8 Gy/fraction per day); second boost: target dose of 10 Gy in 5 fractions (2 Gy/fraction per day)). She underwent regular follow-up, and positron emission tomography/computed tomography 31 months after the postoperative adjuvant radiotherapy showed local recurrence of the tumor within the X-ray-irradiated field (Figure 1(a) and (b)). T1- and T2-weighted MRI showed a 4.2- × 2.0-cm focus of high signal intensity in the middle space of the right tibia and fibula (Figure 1(c) and (d)). The clinical diagnosis was recurrence of the right calf LPS, rpT2bN0M0G3, stage IIA (UICC 8th edition), and the patient's Eastern Cooperative Oncology Group physical status score was 1. The patient agreed to undergo CIRT using passive broad-beam methods. For our center's carbon ion complex, the mixed beam

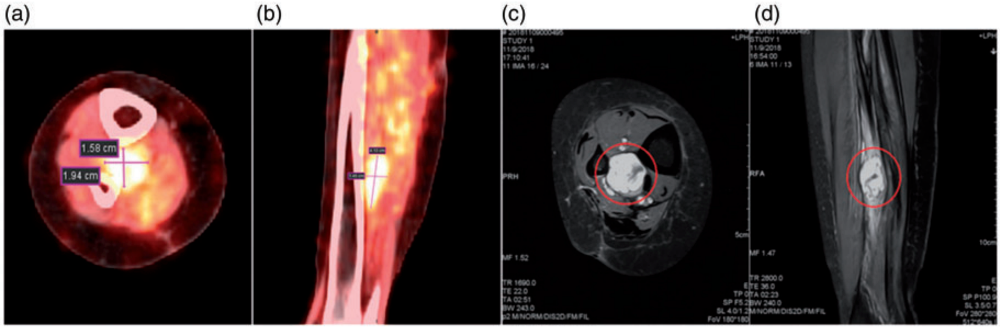

Figure 1. (a) Positron emission tomography/computed tomography axial imaging. Before treatment, a high standardized uptake value was observed. (b) Positron emission tomography/computed tomography sagittal imaging. A high signal focus was found on the T2-weighted image. (c) Axial and (d) sagittal magnetic resonance images.

model was developed to predict the RBE of the passively scattered carbon ion beams with tumor response as the relevant endpoint. Treatment planning was performed using the ciPlan system, version 1.0 (Institute of Modern Physics, Lanzhou, China). The gross tumor volume was delineated on the computed tomography images with reference to MRI and positron emission tomography using 2-deoxy-2-[18F]-fluoro-D-glucose. The clinical target volume included the gross tumor volume plus 10 mm to involve the tissues at risk of microscopic involvement. The planning target volume consisted of the clinical target volume plus 5 mm for positioning errors.

CIRT was delivered at a dose of 64 Gy (RBE) in 16 fractions over 28 days, once daily, five times per week (Monday to Friday) using two ports (a horizontal port and a vertical port) (Figure 2).

Evaluation of efficacy was performed according to the RECIST 1.1 criteria, and CTCAE v5.0 was used to evaluate adverse events. The Radiation Therapy Oncology Group (RTOG) acute radiation injury classification criteria were used to evaluate radiation damage. Following treatment, the treated tumor shrank noticeably, and no additional treatment was administered. The patient developed radiation dermatitis as a grade 1 adverse event, mild erythema, and dry desquamation (Figure 3). No grade $\geq$2 RTOG acute effects were observed, and the tumor shank and finally disappeared (Table 1, Figure 4, and Figure 5). As of February 2020 (27 months after CIRT), the patient was still alive and disease-free.

The patient was very satisfied with the outcome of CIRT; she was able to walk freely with only slight muscle weakness of the right leg. At 27 months after CIRT, MRI and X-ray examinations showed no tumor recurrence. No other severe reactions were observed.

Discussion

LPS is the second most common subtype of soft tissue sarcoma, comprising approximately 20% of soft tissue sarcomas. LPS has a higher incidence in men in their fifth decade of life. Proposed etiologies of tumor development include genetic contributions, metabolic imbalances, and trauma. LPS is most frequently found in the extremities, with a greater incidence in the lower extremities, particularly the thigh.[6] The most common histological subtype of LPS

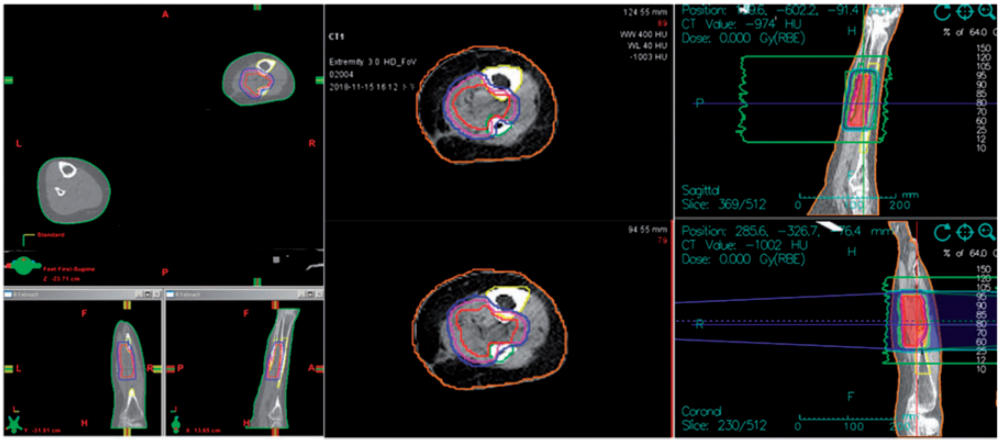

Figure 2. Target design and dose distribution.

Figure 3. Skin reactions at 30, 60, and 90 days after carbon ion radiotherapy.

Table 1. Evaluation of efficacy and maximum diameter of tumor.

		After CIRT				
Time	Before CIRT	Day 1	Day 30	Day 60	Day 90	Day 120
Diameter, mm	42	41	41	22	22	0
Efficacy	–	SD	SD	PR	PR	CR

CIRT, carbon ion radiotherapy; SD, stable disease; PR, partial response; CR, complete response.

is MLPS (56.2%), followed by well-differentiated LPS (also known as atypical LPS tumor) (21.9%), pleomorphic LPS (17.8%), dedifferentiated LPS (6.8%), and round cell LPS (4.1%).[1] The incidence of MLPS is high during the fourth and fifth decades of life, and there is no sex predilection.[2] LPS, like most other sarcomas, are radiation-resistant tumors, and conventional photon radiotherapy is ineffective.

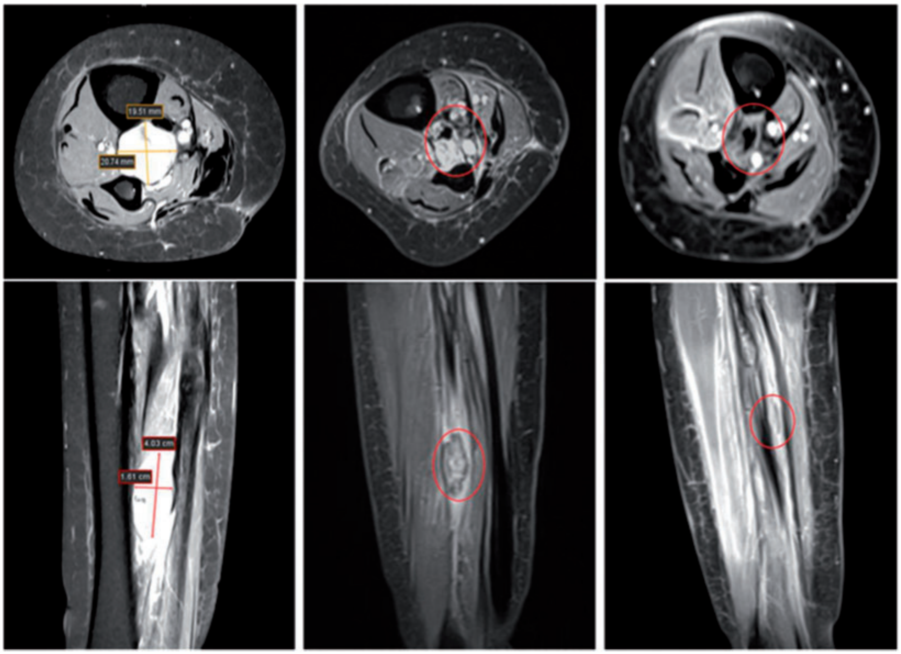

Figure 4. Comparison of imaging data before carbon ion radiotherapy, 60 days after carbon ion radiotherapy (partial response), and 120 days after carbon ion radiotherapy (complete response).

However, MLPS is an exceptionally radiosensitive soft tissue sarcoma subtype, and radiotherapy to 36 Gy has high radiological and pathological response rates in patients with MLPS.[7,8] CIRT can cause 70% of DNA molecules to sustain more than two double-strand breaks. Key sites are more vulnerable to damage and difficult to repair, leading to tumor cell death. Additionally, the carbon ion-mediated killing of tumor cells is independent of the cell cycle; thus, the higher RBE of carbon ions can result in better efficacy in necrotic and hypoxic tumor areas. CIRT for tumors provides high protection of normal tissues, high tolerance to radiotherapy, few toxic radiotherapy-related adverse effects, and strong radiobiological effects of carbon ions in the killing of tumor cells; moreover, CIRT exhibits improved killing effects in tumors resistant to photon radiotherapy (melanoma, osteosarcoma, chondrosarcoma, chordoma, and soft tissue sarcoma).[4] Mohamad et al.[9] reported the results of CIRT treatment for spinal sarcoma; the 5-year local control, overall survival, and progression-free rates were 79%, 52%, and 48%, respectively. These results are encouraging for patients with unresectable sarcomas who have no options for long-term prevention of local tumor progression.

Wuwei Heavy Ion Center is China's first carbon ion facility dedicated to medical use and was designed by the Institute of Modern Physics of the Chinese Academy of Sciences. Construction of the heavy ion accelerator complex in Wuwei was completed at the end of 2015. In November 2018, treatment of patients was initiated at the Wuwei Heavy Ion Center affiliated to Wuwei Cancer Hospital.

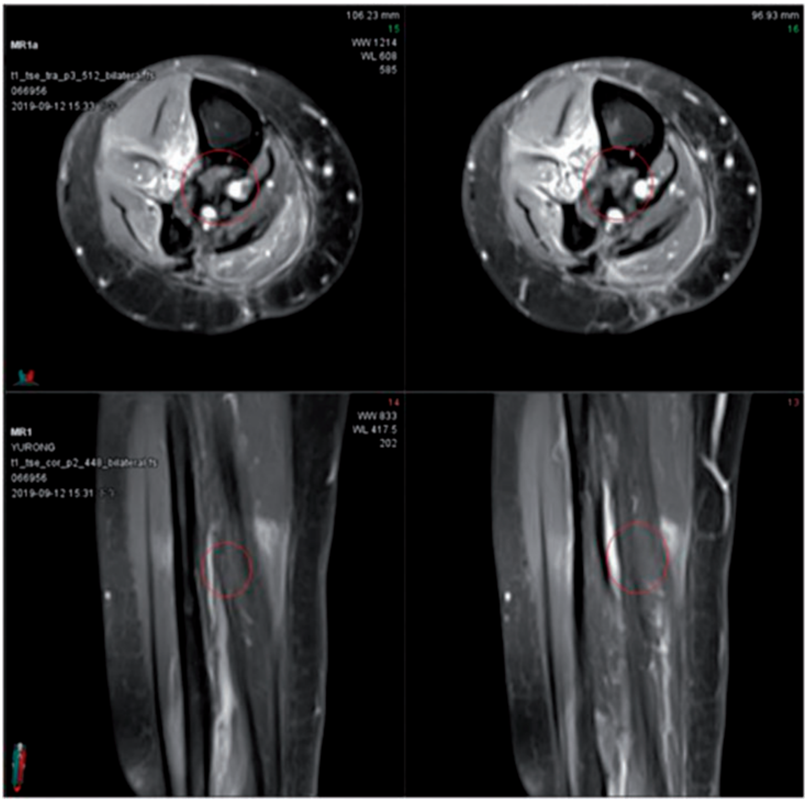

Figure 5. Gadolinium-enhanced magnetic resonance imaging 270 days after carbon ion radiotherapy showing that the lesion had completely disappeared.

CIRT is being found to be a favorable option for primary and recurrent sarcomas in increasingly more cases worldwide, especially in Japan. We have used China's first heavy ion accelerator complex to treat many kinds of solid tumors. For the MLPS in the present case, we achieved favorable effects with no severe grade $\geq$2 adverse events. At the time of this writing, 27 months after CIRT, the patient was still alive and disease-free. Longer-term follow-up of this patient will be continued.

MLPS is a relatively rare disease. The main treatment option for locally recurrent MLPS is surgical reresection; however, the recurrence rate after re-resection is also high. The present case and experience with similar cases in Japan indicate that CIRT can be a promising treatment option for MLPS.

Ethics

Written informed consent was obtained from the patient for publication of the present study. The study protocol was approved by the Medical Ethics Review Committee of Gansu Wuwei Cancer Hospital (approval number 2018-11).

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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