Clinical and Translational Radiation Oncology 2 (2017) 41–45

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

# Sequential histological findings and clinical response after carbon ion radiotherapy for unresectable sarcoma

Katsuhiro Hayashi [a,*], Norio Yamamoto [a], Toshiharu Shirai [a], Akihiko Takeuchi [a], Hiroaki Kimura [a], Shinji Miwa [a], Takashi Higuchi [a], Kensaku Abe [a], Yuta Taniguchi [a], Hisaki Aiba [a], Hiroki Kiyohara [b], Reiko Imai [c], Hiroko Ikeda [d], Hiroyuki Tsuchiya [a]

[a] Department of Orthopaedics, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan
[b] Department of Radiation Oncology, Gunma University Graduate School of Medicine, Gunma, Japan
[c] Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
[d] Department of Pathology, Kanazawa University Hospital, Kanazawa, Japan

ARTICLE INFO

*Article history:*
Received 18 November 2016
Revised 9 January 2017
Accepted 9 January 2017
Available online 6 February 2017

*Keywords:*
Carbon ion radiotherapy
Histology
Sarcoma

ABSTRACT

*Background and purpose:* The efficacy of carbon ion radiotherapy (CIRT) for bone and soft tissue sarcoma has been reported recently. Although histological assessment after CIRT requires skilled interpretation, little information is presently available. In this study, we report sequential histological findings after treatment with CIRT, and evaluate the association between these findings and clinical response.
*Material and methods:* Seven patients with unresectable sarcoma underwent needle biopsy 12 times at an average of 14.3 months after CIRT and were included in this study.
*Results:* One patient underwent two biopsies after CIRT for chordoma. Although a few suspected residual chordoma cells were observed at 19 and 30 months after CIRT, the tumor continued to shrink at 75 months. Immunohistochemical analysis of post-CIRT specimens revealed CK AE1/3, EMA, and S100 expression, as in the pre-CIRT specimen. In total, viable tumor cells were found in 9 of 12 specimens; however, only 2 patients showed recurrent masses on radiological examination. The other 5 patients had stable disease.
*Conclusions:* Viable tumor cells after CIRT did not always cause recurrence. This may be due to observation of dying cells or radiation-induced deformed cells. Histological evaluation after CIRT should be done carefully.


## Introduction

Standard treatment for bone and soft tissue sarcoma includes surgery and chemotherapy. Neoadjuvant chemotherapy is well established, especially in bone sarcoma, for reducing tumor size, which contributes to limb-sparing surgery. As for osteosarcoma, which represents a primary bone malignancy, the 5-year survival rate was 60–70% using a multimodal treatment approach consisting of neoadjuvant systemic chemotherapy followed by local surgical therapy, and then, adjuvant chemotherapy [1]. Neoadjuvant radiotherapy is also utilized, especially for soft tissue sarcoma patients, which contributes to minimized surgical margin and reduction of local recurrence rate [2]. There are several different methods of neoadjuvant therapy for bone and soft tissue sarcoma to obtain better local tumor control: systemic chemotherapy, radiotherapy, isolated limb perfusion, hyperthermia, or the combination of them [3]. Bone and soft tissue sarcomas may occur in sites throughout the body, and the treatment strategies differ depending on tumor location. For tumors in the extremities, amputation might be an option as curative local management, particularly for tumors that are too large to excise while ensuring preservation of neurovascular bundles. Conventional irradiation is generally less effective for bone and soft tissue malignancies, with the exception of small round-cell sarcomas [4]. In contrast, for tumors located deep in the body, such as in the pelvis or spine, surgical options are severely limited. Obtaining a sufficient surgical margin is critical during sarcoma surgery and wide excision, so resection of normal tissues around the tumor is required to ensure local control. However, due to anatomical difficulties, wide margins are rarely obtained in pelvic and spinal surgeries, resulting

* Corresponding author at: Department of Orthopaedic Surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa 920-8641, Japan. Fax: +81 762344261.
*E-mail address:* khayashi830@gmail.com (K. Hayashi).

http://dx.doi.org/10.1016/j.ctro.2017.01.002

**Table 1**
Clinical characteristics of 7 patients who underwent biopsy after CIRT. *Abbreviations:* Y, years; F, female; C, The National Institute of Radiological Sciences in Chiba; G, Gumma University; CIRT, carbon ion radiotherapy; M, months.

| Case | Age (Y) | Gender | Diagnosis | Location | Chemotherapy | CIRT institute | Timing of histologic analysis after CIRT (M) | Histological comments | Viable tumor cells (histology) | Recurrence (radiology) | Follow-up (M) | Local control period (M) | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 76 | F | Chordoma | Sacrum | | C | 19 | A few residual chordoma cells | Yes | | 75 | 75 | Alive |
| | | | | | | | 30 | A few residual chordoma cells | Yes | | | | |
| 2 | 14 | F | Osteosarcoma | Sacrum | Yes | C | 6 | A few viable cells | Yes | | 20 | 19 | Died of lung metastasis |
| | | | | | | | 12 | Almost necrotic tissue | | | | | |
| | | | | | | | 15 | Viable osteosarcoma cells | Yes | Yes | | | |
| 3 | 47 | F | Osteosarcoma | Ilium | Yes | C | 22 | No tumor cells | | | 24 | 24 | Alive |
| 4 | 27 | F | Osteosarcoma | Sacrum | Yes | C | 3 | Fibrosis with viable osteosarcoma cells | Yes | | | | |
| | | | | | | | 9 | A few spindle cells | | | 57 | 57 | Died of lung metastasis |
| | | | | | | | 20 | A few viable cells | Yes | | | | |
| 5 | 40 | F | Extraskeletal myxoid chondrosarcoma | Ilium | | C | 6 | Same as pre-radiation biopsy | Yes | | 36 | 36 | Alive |
| 6 | 76 | F | Chordoma | Sacrum | | G | 27 | Same as pre-radiation biopsy | Yes | | 20 | 20 | Alive |
| 7 | 44 | F | Synovial sarcoma | Thoracic spine | Yes | G | 3 | Recurrent synovial sarcoma | Yes | Yes | 18 | 3 | Alive |
| Average | 46.3 | | | | | | 14.3 | | 75% | 22% | 35.7 | 33.4 | |

in higher local recurrence rates and lower survival rates [5]. Thus, for tumors located deep in the body for which curative surgical removal is difficult, few treatment options, except for palliative irradiation for local control, are available.

The efficacy of carbon ion radiotherapy (CIRT) for bone and soft tissue sarcoma has been recently reported. CIRT has higher biological efficacy than X-ray irradiation. It causes cell death by inducing DNA double-strand breaks. The dose distribution exhibits a steep fall-off after the Bragg peak, so precise dose localization can be achieved. Carbon ions, which deposit high linear energy transfer (LET) radiation within the Bragg peak, differ from X-rays and protons, which deposit low LET radiation. Owing to the fundamental physical difference, CIRT could present different therapeutic results compared with conventional irradiation or proton beam therapy [6].

Matsunobu et al. reported that CIRT resulted in a local control rate of 62% in patients with unresectable osteosarcoma, and relatively small tumors were associated with a 5-year overall survival rate of 46% and a 5-year local control rate of 88% [7]. Serizawa et al. reported local control rates at 2 and 5 years for unresectable retroperitoneal sarcomas of 77% and 69%, respectively, without any complications in the gastrointestinal tract [8]. These results are encouraging for patients with unresectable sarcoma who do not have any options for long-term prevention of local tumor progression. Due to these good responses, insurance providers in Japan started covering CIRT for bone and soft tissue sarcoma in 2016. However, because CIRT is a newer treatment, several issues need to be resolved in the near future to optimize its use. For example, which follow-up assessments, such as radiological assessments and histological analysis, should be conducted after CIRT remains unclear. Diagnosis of local recurrence in patients with malignant tumors treated by CIRT remains difficult. Options for evaluating post-radiation recurrence include computed tomography (CT), MRI, and fludeoxyglucose-positron emission tomography (FDG-PET). Yanagawa et al. recommended a combination of FDG-PET and enhanced MRI for detection of local recurrence in patients with sarcomas who undergo CIRT; however, none of the parameters obtained during the assessments performed before and 3 months after CIRT accurately predicted the development of local recurrence [9]. Radiological tumor findings usually do not change immediately after CIRT. Moreover, some cases experience tumor enlargement, despite CIRT being sufficiently effective. More experience with post-CIRT follow-up is required and more accurate tools are needed to determine whether tumors have been killed or remain alive. Rock et al. mentioned the utility of magnetic resonance spectroscopy imaging to detect recurrence after irradiation [10]. Interpretation of histological findings after CIRT also remains unclear and controversial. Only a few studies about post-CIRT histology have been reported. Matsumoto et al. performed spondylectomy after CIRT for chordoma of the mobile spine. These investigators reported 2 patients with histological evidence of viable tumor cells in excised specimens [11]. However, we are uncertain whether these viable cells had the same characteristics as the tumor cells observed before CIRT, and it is important to understand how the viable cells behave if they remain in the body. In this study, we report sequential histological findings after treatment with CIRT obtained through repeat biopsy, and evaluate the association between these findings and clinical response.

## Material and methods

Between 2008 and 2015, 20 patients were diagnosed with unresectable sarcoma at the Kanazawa University Hospital, and CIRT was selected as local therapy and performed at the National