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CASE REPORT

Carbon-ion radiotherapy of spinal osteosarcoma with long-term follow

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Abstract
Purpose Primary spinal osteosarcoma is quite rare, and the 5-year survival rate is very low. Because of its rarity, successful treatment experience with spinal osteosarcoma is limited. The purpose of this study is to report the effect of therapy of primary osteosarcoma of spine by carbon-ion radiotherapy (CIRT) and long-term follow.
Methods A 70-year-old with primary spinal osteosarcoma who received CIRT underwent combined anterior artificial vertebral body replacement and posterior lumbar fusion (L1–L5) 3 years later.
Results According to the surgical resection of tumoral lesion, pathological results showed that the intertrabecular space previously filled with tumor cells on the initial biopsy sample now contained necrotic tissue without tumor cells. This means that primary osteosarcoma of the spine was completely eliminated and achieved local control with CIRT, with a 7-year follow-up after the initial treatment.
Conclusions Carbon ion beam treatment is an effective local treatment for patients with spinal osteosarcoma for whom surgical resection is not a feasible option, especially for elderly patients. However, more patients need to be evaluated over a longer term to assess the curative effect of CIRT.

Keywords Carbon-ion radiotherapy · Osteosarcoma · Spine · Long-term follow

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Introduction

Osteosarcoma is one of the most common primary malignant tumors of the bone, arising most frequently in the extremities and very rarely in the spine [1–4]. It is a high-grade malignant tumor with a poor prognosis. Spinal osteosarcoma has a high rate of recurrence, metastasis and mortality, with a three-year survival rate for unresectable osteosarcoma of less than 10 % [5–7].

Because the incidence of spinal osteosarcoma is so rare, treatment experience with these tumors is very limited, and only one study has evaluated the treatment and outcome of elderly patients [8]. Although various treatment methods have been advocated for osteosarcoma, including surgical resection, radiotherapy and chemotherapy for local control [9–11], due to the anatomic constraints, surgical resection for spinal sarcoma does not achieve a wide margin of excision. Furthermore, critical structures that are contiguous or nearby, such as the spinal cord or thoracic abdominal organs, may restrict the dose of radiation that can be used for treatment. And chemotherapy is difficult to control osteosarcoma very well without effective targeted surgery or radiotherapy.

With new developments in technology, a number of studies [12, 13] have examined carbon-ion radiotherapy (CIRT) as a safe and effective modality for the management of spinal osteosarcoma. CIRT may be an effective alternative to surgery, especially for elderly patients. Unfortunately, there is little information on the long-term follow-up of spinal osteosarcoma after CIRT which makes evaluating its long-term prognosis difficult.

We present a case that achieved complete remission of spinal osteosarcoma after treatment with CIRT. This is the first report that primary osteosarcoma of the spine was completely disappeared and achieved local disease control with CIRT, with a 7-year follow-up after the initial treatment.

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Case presentation

A 70-year-old Japanese woman was referred to our department with osteosarcoma of the third lumbar vertebra (L3). She initially presented with left leg pain and low back pain that was treated conservatively for about 1 month, but symptoms worsened. MRI showed a tumor-like lesion at L3, and CT showed a compression fracture and pathological bone destruction (Fig. 1). CT-guided open biopsy provided a definitive diagnosis of spinal osteosarcoma at L3. Histopathologically, the tumor had bone formation and intertrabecular fibrosis with atypical, spindle-shaped tumor cells that were diagnosed as osteosarcoma (Fig. 4a).

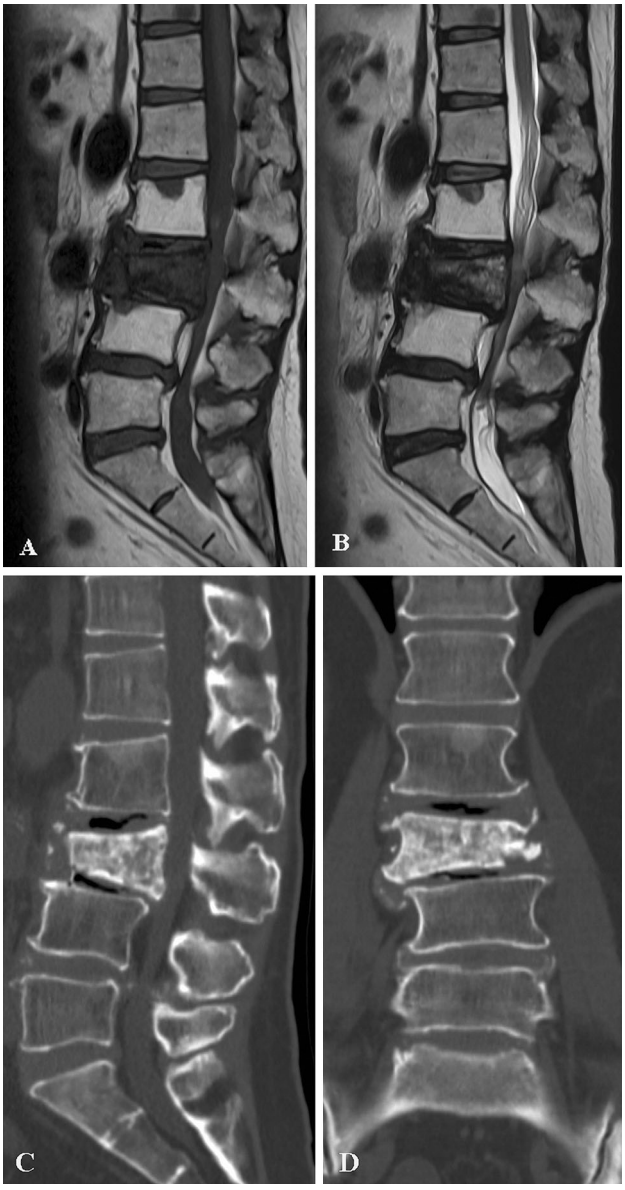

Fig. 1 Sagittal **a** T_1-weighted and **b** T_2-weighted MRI images showing low signal intensity at L3. **c**, **d** CT showing a compression fracture and bone lysis at L3 at presentation in 2007

The Karnofsky performance status (KPS) scale [14] and Zubrod Scale [15] were used to evaluate the patient's health statue. The KPS scale was 40 (the scale from 0 to 100) and Zubrod Scale was Grade 3. Based on the scoring, the patient could not tolerate high-dose chemotherapy or aggressive en bloc resection surgery. After discussing all her options, the patient consented to CIRT for her L3 osteosarcoma. The CIRT relieved her low back pain, but 3 years later; this patient began feeling numbness in both lower extremities and dysbasia due to lumbar spinal stenosis from a tumor-like, hyperplastic compression fracture. During this period, the tumor-like lesion was found in her liver S6 region through the ultrasound liver, CT abdomen and MRI abdomen, while PET-CT and tumor marker showed negative result of liver region. Because the patient worried the further spread of the liver tumor, invasive examination (biopsy) was refused. Unfortunately, the initial liver tumor was increasing from 15 to 135 mm and developed to multiple lesions without specific treatment in the next 5 years follow-up. Therefore, the patient was highly suspected liver metastases clinically. In the latest 1 year follow-up, lung lesion was found through CT scanning. Pulmonary metastasis was also highly suspicious clinically. Considering her condition, the patient first received only a wide range laminectomy at L3 to relieve her symptoms. After 6 months, a plain lumbar radiograph showed further destruction and a compression fracture in L3 (Fig. 2) secondary to bone lysis from the tumor. She finally underwent combined anterior artificial vertebral body replacement and posterior lumbar fusion (L1–L5). Near-normal function has been restored to her both legs and the patient has no low back pain. During the operation, the remaining tumoral lesion was totally resected (Fig. 3), assessed and re-diagnosed as degeneration of osseous tissue and osteonecrosis. Pathological results showed that the intertrabecular space previously filled with tumor cells on the initial biopsy sample now contained necrotic tissue without tumor cells (Fig. 4b). The osteosarcoma treated with CIRT was completely eliminated, and over 7 years of follow-up, there has been no evidence of local recurrence of spinal osteosarcoma. The patient can do some house work herself and walk by walker-assisted and lives in hospice care center.

Discussion

Spinal osteosarcoma is a rare disease with a poor prognosis. Approximately 3 % of primary osteosarcoma arise in the spine [1–4], and most occur in people at an older age. Furthermore, the prognosis is worse for osteosarcoma of the spine than of the extremities [1, 2, 9], and long-term survival for spinal osteosarcoma is poor. Barwick et al. [1]

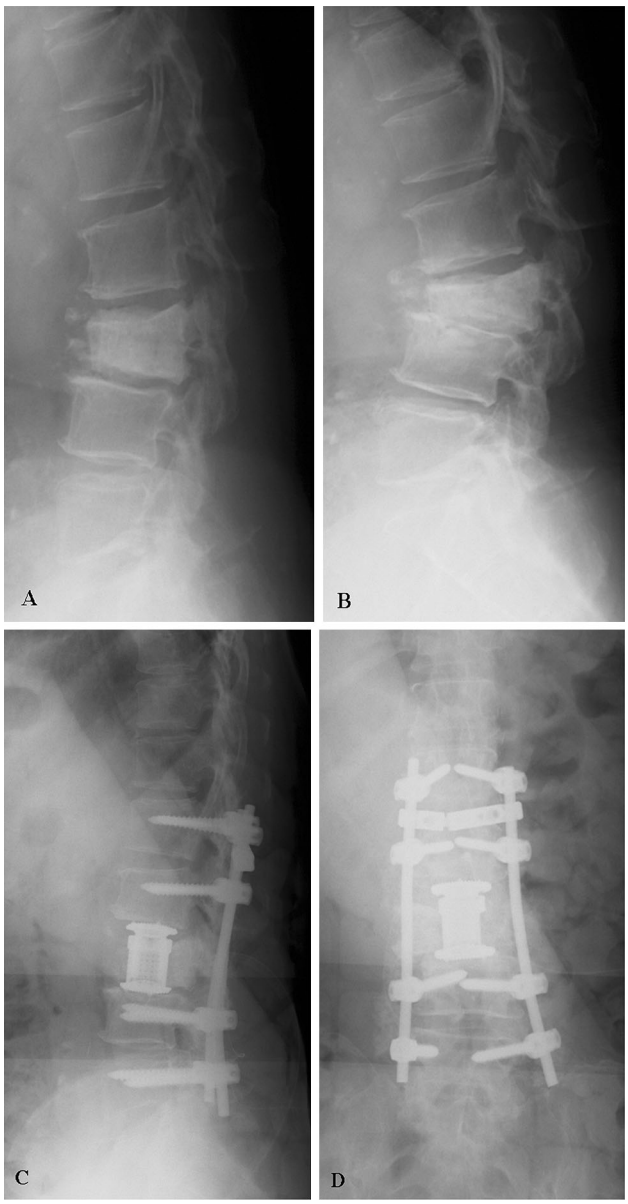

Fig. 2 **a** Plain radiograph taken during the patient's first visit to the hospital. **b** Compression fracture after the CIRT. **c**, **d** Post-operative lateral and AP views

and Shives et al. [2] reported that the median survival for spinal osteosarcoma was 6 months in 10 patients and 10 months in 27 patients, respectively, which is similar to the natural history of this disease. More recently, Ozaki et al. [11] reported that only 36 % of patients lived more than 2 years in 22 spinal osteosarcoma cases who received chemotherapy including 5 patients who underwent wide or marginal surgery. Schoenfeld et al. [16] reported results for 26 patients in Massachusetts General Hospital who received advanced treatment including wide or marginal surgery in combination with radiotherapy and chemotherapy, but the median overall survival for all patients was only 29.5 months.

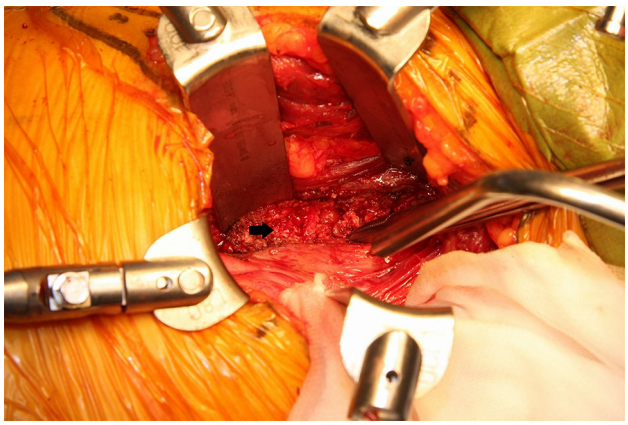

Fig. 3 Intraoperative photograph of the tumor (*black arrow*) at L3. The lesion was degenerative osseous tissue and osteonecrosis

Osteosarcoma is thought to be radioresistant [2, 17], and few reports have described effective local control using photon radiotherapy for osteosarcoma of the spine [11, 18]. CIRT has a better dose distribution to the tumor than other types of irradiation. Literature from the National Institute of Radiological Sciences, Chiba, Japan [12] and Heidelberg Ion Therapy Center, Germany [19] illustrate better local control rate with CIRT than with other radiation treatments at a lower physical dose (Gy). Because of these factors, CIRT can minimize damage to the surrounding normal tissues.

Carbon ions can achieve precise localization and sufficient dose in the target lesion in a shorter treatment time while avoiding damage to nearby organs and surrounding normal tissues [13, 20]. Carbon ion beams emit a low dose of radiation after penetrating the body, and they deliver their maximum dose at the end of their range, beyond which the dose drops sharply (the Bragg peak). Compared to photons, electrons and protons, Carbon ions produce a densely ionizing, i.e. high-LET (linear energy transfer) radiation that guarantees optimal dose distribution to the tumor. The LET is used to evaluate the biological effects of radiation because as the LET increases, the relative biological effect (RBE) also increases [21, 22]. Based on the above analysis, the physical and radiobiological advantages of CIRT make it the most balanced and optimal treatment choice for unresectable spinal osteosarcoma.

Along with these advantages, carbon ion beams also can feasibly reduce pulmonary metastasis of tumor cells. This is vital for treating unresectable osteosarcoma which is prone to lung metastasis. Ogata et al. [23] showed that treatment with carbon ions induced DNA damage in vivo, which can possibly inhibit lung metastasis by the tumor cells and reduce the number of lung metastases in a dose-dependent manner. Tamaki et al. [24] and Akino et al. [25] confirmed that finding. However, clinical findings of

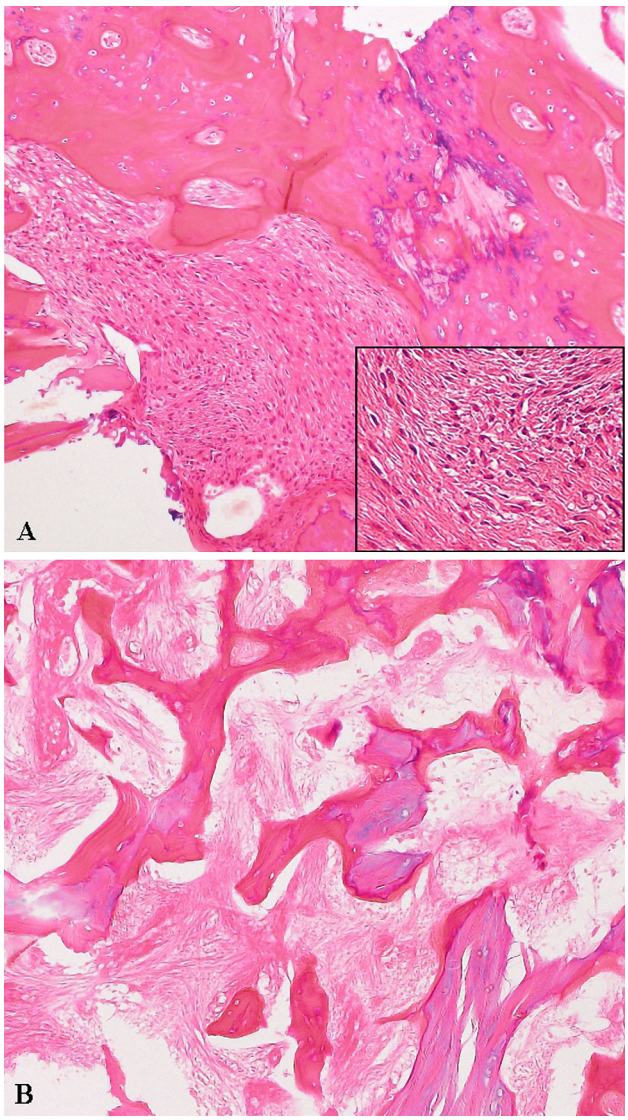

Fig. 4 Photomicrographs (hematoxylin and eosin stain). **a** Bone biopsy specimen showing bone formation and intertrabecular fibrosis with tumor cells (middle power ×40) (*inset*). Tumor cells are atypical, spindle-shaped cells diagnosed as osteosarcoma (high power ×400). **b** Resected specimen showing intertrabecular space replaced by necrotic tissue without tumor cells (low power ×40)

suppressed metastatic capabilities are not yet available, further studies are needed to confirm those findings. For this case, although the pulmonary metastasis was found clinically 6 years after initial treatment, it is difficult to judge whether CIRT has positive effect on inhibiting pulmonary metastasis in the early stage or not.

Clinical results of CIRT for unresectable spinal sarcoma are satisfactory for local control, overall survival and progression-free rates [12, 26]. Imai et al. reported rare case about cervical spine osteosarcoma achieved local control with CIRT successfully [27]. Our pathological findings also support the argument that CIRT is one of the best treatments for trunk osteosarcoma. We believe that this is the first report that primary osteosarcoma of the spine was completely disappeared by CIRT.

Carbon ion beam treatment is an effective local treatment for patients with spinal osteosarcoma for whom surgical resection is not a feasible option, especially for elderly patients. Although we need to evaluate more patients over a longer term to assess the curative effect of CIRT, this treatment is very promising.

Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest.

References

1. Barwick KW, Huvos AG, Smith J (1980) Primary osteogenic sarcoma of the vertebral column: a clinicopathologic correlation of ten patients. Cancer 46:595–604. doi:10.1002/1097-0142
2. Shives TC, Dahlin DC, Sim FH, Pritchard DJ, Earle JD (1986) Osteosarcoma of the spine. J Bone Joint Surg Am 68:660–668
3. Campanacci M, Cervellati G (1975) Osteosarcoma: a review of 345 cases. Ital J Orthop Traumatol 1:5–22
4. Tigani D, Pignatti G, Picci P, Savini R, Campanacci M (1988) Vertebral osteosarcoma. Ital J Orthop Traumatol 14:5–13
5. Grimer RJ, Carter SR, Tillman RM, Spooner D, Mangham DC, Kabukcuoglu Y (1999) Osteosarcoma of the pelvis. J Bone Joint Surg Br 81:796–802
6. Kawai A, Huvos AG, Meyers PA, Healey JH (1998) Osteosarcoma of the pelvis. Oncologic results of 40 patients. Clin Orthop Relat Res 348:196–207
7. Duffaud F, Digue L, Baciuchka-Palmaro M, Volot F, Perles-Daniel C, Garbe L, Favre R (2000) Osteosarcomas of flat bones in adolescents and adults. Cancer 88:324–332
8. Longhi A, Errani C, Gonzales-Arabio D, Ferrari C, Mercuri M (2008) Osteosarcoma in patients older than 65 years. J Clin Oncol 26:5368–5373. doi:10.1200/JCO.2007.14.9104
9. Bielack SS, Wulff B, Delling G, Gobel U, Kotz R, Ritter J, Winkler K (1995) Osteosarcoma of the trunk treated by multimodal therapy: experience of the Cooperative Osteosarcoma study group (COSS). Med Pediatr Oncol 24:6–12. doi:10.1002/mpo.2950240103
10. DeLaney TF, Park L, Goldberg SI, Hug EB, Liebsch NJ, Munzenrider JE, Suit HD (2005) Radiotherapy for local control of osteosarcoma. Int J Radiat Oncol Biol Phys 61:492–498. doi:10.1016/j.ijrobp.2004.05.051
11. Ozaki T, Flege S, Liljenqvist U, Hillmann A, Delling G, Salzer-Kuntschik M, Jurgens H, Kotz R, Winkelmann W, Bielack SS (2002) Osteosarcoma of the spine: experience of the Cooperative Osteosarcoma Study Group. Cancer 94:1069–1077
12. Matsunobu A, Imai R, Kamada T, Imaizumi T, Tsuji H, Tsujii H, Shioyama Y, Honda H, Tatezaki S, Working Group for the Bone and Soft Tissue Sarcomas (2012) Impact of carbon ion radiotherapy for unresectable osteosarcoma of the trunk. Cancer 118:4555–4563. doi:10.1002/cncr.27451
13. Kamada T, Tsujii H, Tsuji H, Yanagi T, Mizoe JE, Miyamoto T, Kato H, Yamada S, Morita S, Yoshikawa K, Kandatsu S, Tateishi A, Working Group for the Bone and Soft Tissue Sarcomas (2002) Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. J Clin Oncol 20:4466–4471. doi:10.1200/JCO.2002.10.050

14. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH (1948) The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. Cancer 1:634–656. doi:10.1002/1097-0142
15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–656
16. Schoenfeld AJ, Hornicek FJ, Pedlow FX, Kobayashi W, Garcia RT, DeLaney TF, Springfield D, Mankin HJ, Schwab JH (2010) Osteosarcoma of the spine: experience in 26 patients treated at the Massachusetts General Hospital. Spine J 10:708–714. doi:10.1016/j.spinee.2010.05.017
17. Mankin HJ, Hornicek FJ, Rosenberg AE, Harmon DC, Gebhardt MC (2004) Survival data for 648 patients with osteosarcoma treated at one institution. Clin Orthop Relat Res 429:286–291
18. Hundsdoerfer P, Albrecht M, Rühl U, Fengler R, Kulozik AE, Henze G (2009) Long-term outcome after polychemotherapy and intensive local radiation therapy of high-grade osteosarcoma. Eur J Cancer 45:2447–2451
19. Blattmann C, Oertel S, Schulz-Ertner D, Rieken S, Haufe S, Ewerbeck V, Unterberg A, Karapanagiotou-Schenkel I, Combs SE, Nikoghosyan A, Bischof M, Jakel O, Huber P, Kulozik AE, Debus J (2010) Non-randomized therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with non-resectable osteosarcoma. BMC Cancer 10:96. doi:10.1186/1471-2407-10-96
20. Okada T, Kamada T, Tsuji H, Mizoe JE, Baba M, Kato S, Yamada S, Sugahara S, Yasuda S, Yamamoto N, Imai R, Hasegawa A, Imada H, Kiyohara H, Jingu K, Shinoto M, Tsujii H (2010) Carbon ion radiotherapy: clinical experiences at National Institute of Radiological Science (NIRS). J Radiat Res 51:355–364
21. Barendsen GW (1996) RBE-LET relationships for lethal, potentially lethal and sublethal damage in mammalian cells: implications for fast neutron radiotherapy. Bulletin du cancer Radiotherapie 83(Suppl):15s–18s
22. Skarsgard LD (1998) Radiobiology with heavy charged particles: a historical review. Phys Med 14(Suppl 1):1–19
23. Ogata T, Teshima T, Kagawa K, Hishikawa Y, Takahashi Y, Kawaguchi A, Suzumoto Y, Nojima K, Furusawa Y, Matsuura N (2005) Particle irradiation suppresses metastatic potential of cancer cells. Cancer Res 65:113–120
24. Tamaki T, Iwakawa M, Ohno T, Imadome K, Nakawatari M, Sakai M, Tsujii H, Nakano T, Imai T (2009) Application of carbon-ion beams or gamma-rays on primary tumors does not change the expression profiles of metastatic tumors in an in vivo murine model. Int J Radiat Oncol Biol Phys 74:210–218. doi:10.1016/j.ijrobp.2008.12.078
25. Akino Y, Teshima T, Kihara A, Kodera-Suzumoto Y, Inaoka M, Higashiyama S, Furusawa Y, Matsuura N (2009) Carbon-ion beam irradiation effectively suppresses migration and invasion of human non-small-cell lung cancer cells. Int J Radiat Oncol Biol Phys 75:475–481. doi:10.1016/j.ijrobp.2008.12.090
26. Matsumoto K, Imai R, Kamada T, Maruyama K, Tsuji H, Tsujii H, Shioyama Y, Honda H, Isu K, Working Group for the Bone and Soft Tissue Sarcomas (2013) Impact of carbon ion radiotherapy for primary spinal sarcoma. Cancer 119:3496–3503. doi:10.1002/cncr.28177
27. Imai R, Kamada T, Tsuji H, Tsujii H, Tsuburai Y, S-i Tatezaki (2006) Cervical spine osteosarcoma treated with carbon-ion radiotherapy. Lancet Oncol 7:1034–1035