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Original research article

Review of carbon ion radiotherapy for skull base tumors (especially chordomas)

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ABSTRACT

Aim: To review the clinical feasibility of carbon ion radiotherapy (C-ion RT) for skull base tumors, especially for chordomas which are often seen in the skull base area.
Background: Skull base tumors treated by C-ion RT consist of primary chordomas and chondrosarcomas, and enormously extended head and neck cancer with a histology of adenoid cystic carcinomas, adenocarcinomas and malignant melanomas. These tumors are located on anatomically complex sites where they are close to important normal tissues and therefore demand better physical dose distribution to avoid unnecessary doses for surrounding normal tissues. These tumors are also known as radio-resistant tumors for low linear energy transfer (LET) radiotherapy and show favorable results after treatment by high LET carbon ion radiotherapy.
Materials and methods: Biological reports of C-ions for the chordoma cell line, clinical results of C-ion RT for skull base tumors, dose comparative studies between two representative facilities and tumor control probability (TCP) of chordomas by C-ion RT were reviewed.
Results: C-ion RT for skull base tumors, especially for chordomas, shows favorable results of tumor control and acceptable complications. The C-ion dose of 57.36 gray equivalent (GyE)/16 fractions/4 weeks will deliver 90% of local control for chordomas. The limiting doses for surrounding normal tissues are clearly revealed. The dose difference between institutes was assumed within 10%.
Conclusions: C-ion RT is recommended for skull base tumors because of high LET characteristics and clinical results.

1. Background

Skull base tumors are arising in complex anatomical regions and adjacent to the important normal tissues like the brain, cranial nerves, brainstem, eyeball and acoustic system. Also skull base tumors consist of various histological and clinical types including chordomas, chondrosarcomas, and other primary tumors; adenoid cystic carcinomas, adenocarcinomas, malignant melanomas and other metastatic and direct

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invasive tumors from neighboring anatomical sites. Surgical resection is recommended as the first therapeutic strategy, acquiring histological details with tumor removal.[1] Due to the proximity of critical normal tissues, complete surgical resection can result in severe complications of surrounding normal tissues. In such a situation, highly conformed radiotherapy, like intensity modulated radiotherapy (IMRT), stereotactic radio-surgery (SRS) and charged particles will be recommended. Charged particles, like protons and carbon ions, have a Bragg peak and show better dose distribution than conventional X-rays, resulting in less doses to the surrounding normal tissues.[2] For these tumors, high linear energy transfer (LET) radiotherapy is occasionally recommended because the biological characteristics have a high relative biological effectiveness (RBE). Carbon ions (C-ions) are charged particles the same as protons, and are characterized as high LET radiotherapy, different from low LET protons. The target tumors of high LET charged particles will be chordomas, chondrosarcomas, malignant meningiomas and non-squamous cell malignancies of the head and neck.

2. Aim

In this review article, the evidence of the high RBE feature of C-ions for skull base tumors, especially primary chordomas, which is the most popular histology in skull base tumors, was investigated in terms of biology, beam delivery, clinical results and dose comparative studies.

3. Materials and methods

3.1. *Biology of high LET radiation for a chordoma cell line*

A chordoma is a rare and slow growing malignancy arising from the remnants of the fetal notochord[3] and there exist a few cell lines of chordomas established for biological study.[4,5] Also, the characteristics of the slow growth in chordomas make it difficult to investigate the behaviors in radiation exposure. Kato et al. investigated the nature of the U-CH1-N cell line which is a subpopulation of U-CH1 chordoma cells with a short doubling time.[6] They reported the cell doubling time of U-CH1-N as 3 days which was a longer time than other cell lines, like HeLa (uterine cervix – 18 h) and U87-MG (malignant glioma – 24 h). Using this short-doubling-time cell line, they reported the RBE values of U-CH1-N at 10% survival as 1.30 in 13 keV/μm C-ion, 2.45 in 70 keV/μm C-ion and 3.86 in 200 keV/μm iron-ion.

Fujisawa et al. followed the comparative study of RBE between C-ion and proton therapy for chordomas using the U-CG1-N cell line.[7] RBE values were calculated based on the D_{10} values. The RBE value of 70 MeV proton was 0.89, of 13–20 keV/μm C-ion was 0.85, of 20–30 keV/μm C-ion was 1.27, and >30 keV/μm C-ion was 1.69. C-ion killed cells depending on both the dose and the LET, while protons depended on the dose alone. They concluded the carbon ion radiotherapy may have an advantage for chordoma radiotherapy because of a higher cell-killing effect with high LET doses from biological observation in their studies.

3.2. *Beam delivery and treatment planning system*

A present, there are two representative beam delivery systems for C-ion RT.

One is a passive beam delivery system at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, and is based on the relationships between RBE and LET of human salivary gland tumor (HSG) cells for flattening the spread out Bragg peak (SOBP) and on the clinical experience with fast neutrons for determining the clinical RBE.[8] Accelerated beams are broadened laterally by wobbler magnets and a scatterer; and they are longitudinally spread out by a ridge filter. A collimator and a compensator are used to clip the irradiation fields and to conform the distal shape of the irradiation field to those of the planned target volume of a patient, respectively. SOBPs were designed for the carbon beam to have uniform biological responses throughout the SOBP. The physical dose distributions of the beam agreed very well with the predicted depth dose distributions; also, the biological responses were satisfactorily flat in the SOBP. RBE values of carbon beams were determined based on experimental results of cell responses, on values expected with the linear-quadratic model, and on experiences with neutron therapy. They use fixed RBE values independent of dose levels, and the RBE system depends only on LET of the C-ion radiation fields. The clinical dose is obtained by multiplying a ratio between the biologic dose at the neutron-equivalent point and the clinically observed RBE value, 3.0 to the entire biologic dose distributions.

Another system is a dynamic beam delivery at Gesellschaft fuer Schwerionenforschung (GSI) in Darmstadt, Germany.[9] The RBEs are determined for each single beam through the local effect model (LEM) which assumes that equal local doses should lead to equal local effects, independent of the radiation quality. The first version, LEM I, is based on a radial dose distribution of each charged particle crossing into a cell nucleus, as well as on the radiosensitivity and repair capacity of the tissue. They reported that the original version of the LEM I underestimated the ratio of RBE in the Bragg peak region as compared with the RBE in the entrance. The next extension of the LEM II still showed the same tendency. Implementation of the modified track structure LEM III almost completely compensates for these systematic deviations, and predictions of RBE by LEM III for high and low energetic C-ions show good agreement for a wide panel of different cell lines, as well as for the tolerance of the rat spinal cord.

3.3. *Clinical results of carbon ion radiotherapy*

Since December 1997, C-ion radiotherapy (RT) has been performed at the GSI by means of the intensity-controlled raster scan technique for patients with chordomas and low-grade chondrosarcomas of the skull base. The median total dose was 60 gray equivalent (GyE) (57–70 GyE) (weekly fractionation of 7 fractions with a fraction dose of 3.0 GyE) delivered in 20 fractions within 3 weeks. Schulz-Ertner et al. reported the preliminary results of C-ion RT in 96 patients with chordomas of the skull base in 2007.[10] The actuarial 3- and 5-year local control rates were 80.6% and 70.0%, respectively, and the overall 3- and 5-year overall survival (OS) rates were 91.8% and 88.5% with acceptable toxicity. Delivery of target doses exceeding