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Mini Review

Carbon Ion Radiotherapy for Head and Neck Cancer

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Abstract

Radiotherapy (RT) is a definitive treatment option for cancers of the head and neck. Indeed, the most common pathology of head and neck lesions, Squamous Cell Carcinoma (SCC), is radiosensitive. Recently, RT with chemotherapy has been shown to improve the local control and survival rates among patients with head and neck SCC. However, tumors arising in the head and neck region are of a variety of histological types, including adenoid cystic carcinoma, mucosal malignant melanoma, and bone and soft tissue sarcoma. Most of these tumors are resistant to RT, and therefore, RT is limited to postoperative or palliative care for these tumors. Carbon ions offer a biological advantage because, as compared with photons, carbon ions have higher linear energy transfer components in the Bragg peak. Carbon ions also provide a higher degree of physical selectivity because they have a finite range in tissue. Therefore, carbon ion RT permits better dose conformity than can be obtained with photon RT. Consequently, carbon ion RT can potentially control radio-resistant tumors while sparing normal tissues. This review summarizes clinical studies of carbon ion radiotherapy for head and neck cancers, especially non-SCCs.

ABBREVIATIONS

NIRS: National Institute of Radiological Sciences; SCC: Squamous Cell Carcinoma; RT: Radiation Therapy; LET: Linear Energy Transfer; RBE: Relative Biological Effectiveness; ACC: Adenoid Cystic Carcinoma; GyE: Gy Equivalent; MMM: Mucosal Malignant Melanoma

INTRODUCTION

Historically, ion-beam Radiotherapy (RT) was performed using proton beams at the United States' Lawrence Berkeley National Laboratory (LBNL) in 1954. Since then, the efficacies of heavier charged nuclei such as helium, carbon, nitrogen, neon, silicon, and argon have also been assessed for clinical use at LBNL. The most important pioneering work on heavy ion RT was performed at LBNL between 1977 and 1992, during the course of which most patients were treated with helium or neon ions [1,2]. In 1994, a clinical study on carbon ion RT was started at the National Institute of Radiological Sciences (NIRS) in Japan, using carbon ions generated by HIMAC, the world's first accelerator

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complex dedicated to cancer therapy. At present, carbon ion RT is performed at six facilities worldwide.

Head and neck malignancies include malignant tumors of various histologies. Squamous Cell Carcinomas (SCCs) account for the majority of these tumors. However, various rare histologies are also found, including adenoid cystic carcinoma, mucosal malignant melanoma, and soft tissue and bone sarcoma. SCC is mostly radiosensitive, and it has recently been reported that the combination of photon RT and chemotherapy improves local control and survival rates in patients with SCC of the head and neck [3,4]. On the other hand, most non-SCCs are both radio- and chemo-resistant. Therefore, achieving local control remains a challenge in patients with inoperable or macroscopic residual non-SCC tumors.

As compared with photons, carbon ions offer a biological advantage because they have higher Linear Energy Transfer (LET) components in the Bragg peak. Carbon ions also offer a higher degree of physical selectivity because they have a finite range in tissue. Therefore, carbon ion RT permits better dose conformity than can be obtained with photon RT. Consequently, carbon ion RT can potentially control radio-resistant tumors while sparing normal tissues.

CHARACTERISTICS OF CARBON IONS

Physical aspects

Photons and fast neutrons are characterized by an exponential absorption of dose with depth. Yet, the energy deposition of ion beams increases with the penetration depth, until reaching a sharp maximum at the end of their range, which is known as the Bragg peak. The peak is typically narrow, a few millimeters at the 80% level, and the dose at the peak is several times greater than the dose in the plateau that precedes it at shallower depths. The particle range is determined by the energy of the incoming particles.

The quality of the dose distribution is affected by energy spread and range straggling, the magnitude of which is smaller for carbon ions than it is for protons. Dose-distribution quality is also affected by the degree of lateral sharpness (penumbra), which depends on Coulomb scattering and becomes smaller for particles with greater masses [5]. Therefore, when comparing dose distributions between carbon ion beams and proton beams, the lateral fall-off around the target volume occurs more rapidly for carbon ion beams than it does for proton beams. However, proton beams deposit almost no dose in the region beyond the distal end of the peak, while carbon ion beams deposit a small dose because the primary carbon ions undergo nuclear interactions and fragment into particles with lower atomic numbers, producing a fragmentation tail beyond the peak. The biological effect of this fragmentation tail is small because the tail only contains fragments with low atomic numbers. Because the original peak is too narrow and sharp to treat lesions of various shapes and sizes directly, it is broadened to conform to the sizes and shapes of the lesions.

RADIOBIOLOGICAL ASPECTS

When penetrating the tissue, the rate at which particle beams lose energy increases with the mass of the particles, and is known as LET. Photons, electrons, and protons are sparsely ionizing, and are referred to as low-LET radiation. Fast neutrons and carbon ions are densely ionizing, and are referred to as high-LET radiation. LET has been used to evaluate the biological effects of radiations because, as LET increases, the relative biological effectiveness (RBE) also increases [6,7]. RBE is defined as the ratio of two doses from two different radiation beams given under identical conditions, including dose fractionation and the tissue that is irradiated. In contrast with neutron beams, whose LET remains uniformly high at any depth, carbon ion beams have a LET that increases steadily with greater depths until reaching a maximum in the peak region. From a therapeutic perspective, this property is extremely advantageous because the RBE of carbon ion beams increases as they advance deeper into the tumor-lying region.

Accordingly, carbon ion beams could potentially be highly effective for tumors that have deep locations and are resistant to photon beams. Tumors that are unresponsive to low-LET radiations are assumed to have high proportions of hypoxic cells, poor reoxygenation patterns, and high intrinsic repair capacities. It is also assumed that treatments for these tumors could benefit from the use of high-LET radiation. Indeed, increasing LET achieves reductions in the oxygen enhancement ratio and reduces variation in radiosensitivity that occurs at different points in the cell cycle. These observations have provided the rationale for introducing high-LET carbon ions in cancer therapy.

Treatment planning

To ensure the proper administration of carbon ion RT, it is first necessary to fabricate immobilization devices for each patient. To allow treatment planning, Computed Tomography (CT) is then performed with the patient wearing his or her immobilization devices. To determine the target volume, fusion images have frequently been employed, using CT, magnetic resonance imaging, and positron-emission tomography images. The CT image data obtained in this manner are then transferred to the treatment planning system. At this stage, irradiation parameters (the number of radiation portals and their directions) are determined in conjunction with target volume delineation.

Treatment planning for carbon ion RT has been performed using the beam-scattering method (broad beam) that was developed at NIRS or the beam-scanning method that was developed at the Gesellschaft für Schwerionenforschung (GSI). The NIRS approach is based on clinical experience with high-LET neutron beams, in which the estimation of the clinically relevant RBE values is implemented as a two-step procedure; the biological RBE is distinguished from the "clinical RBE". To shape the spread-out Bragg peak, the human salivary gland tumor cell line was selected as an *in vitro* model system [8]. The GSI approach for selecting the RBE is based on the local effect model. In essence, this model allows the biological effectiveness to be calculated based on two sets of input data: one that physically characterizes the radiation fields and another that biologically characterizes the responses of the cells or tissues, parameterized by a modified linear-quadratic approach [9].

Clinical results

Based on the results of prospective trials, it has been reported that carbon ion RT offers radiobiological advantages for cases involving histologically non-squamous cell tumors such as

Adenoid Cystic Carcinoma (ACC), Mucosal Malignant Melanoma (MMM), and various sarcomas [10–13].

Adenoid cystic carcinoma

ACC is a rare form of adenocarcinoma, which is a broad term that describes any cancer arising from glandular tissues. ACC mainly occurs in the head and neck region, most commonly in the salivary glands. Regardless of its origin, ACC tends to spread along nerves (perineural invasion) or through the bloodstream. ACC spreads to the lymph nodes in only 5–10% of cases.

The optimal treatment for patients with ACC is surgery with adjuvant RT. Complete or almost complete resection and adjuvant photon RT allows high cure rates, with locoregional control rates of 95%. However, local control rates remain poor in patients who have unresectable or incompletely resected tumors. Mendenhall et al. [14] reported the following outcomes in a series of 42 patients treated with RT alone: 5- and 10-year local control rates were 57% and 42%, respectively, and 5- and 10-year overall survival rates were 56% and 43%, respectively. Iseli et al. [15] reported on 10 patients with ACCs of the head and neck who were treated with RT alone; 5-year local recurrence-free survival and overall survival rates were 27% and 25%, respectively.

Schulz-Ertner et al. have reported outcomes for 63 patients with ACC who were treated with photon RT alone (34 patients) or combined photon RT with a carbon ion boost (29 patients) at the University of Heidelberg between 1995 and 2003 [12]. Locoregional control rates at 4 years were 24.6% for the patients treated with photon RT alone and 77.5% for patients treated with the combination of photon RT and a carbon ion boost. However, the difference was not statistically significant. Another study analyzed 186 patients with head and neck ACCs who were treated with carbon ion RT alone between 1997 and 2013 [11]. Patients received total doses of 57.6 Gy equivalent (GyE) or 64.0 GyE in 16 fractions over 4 weeks. One hundred forty-nine patients had T4 tumors or recurrent tumors after surgery, and 36 patients had T1 to T3 tumors. The 5-years local control and overall survival rates for all patients were 75% and 74%, respectively, despite the inclusion of the 149 patients (80%) with T4 or recurrent tumors after surgery. Among these 149 patients, the 5-year local control and overall survival rates were 72% and 69%, respectively. Among the 36 patients with tumors that appeared to be locally operable, the 5-year local control and overall survival rates were greater: 85% and 94%, respectively (Table 1).

Mucosal malignant melanoma

MMM of the head and neck is a rare tumor. In the past, radical local excision was the only treatment that could potentially cure this disease, but the prognosis was generally grave. In studies of head and neck MMMs that could be radically excised, the combination of RT with surgery did not result in statistically significant improvements in local recurrence or survival. In the literature, 5-year overall survival rates of 20–45% have been reported for patients with MMMs that were treated with surgery or surgery plus RT [16-20]. Additionally, several studies have investigated the use of RT alone, reporting overall survival rates that were slightly less than those obtained with surgery [21,22]. On the other hand, Zenda et al. [23] reported the results of a pilot study of proton-beam RT for MMM. In this study of 14 patients, the local control rate was 86% and the 3-year overall survival rate was 58%.

From 1997 to 2010, a total of 218 patients with MMM were treated with carbon ion RT with or without chemotherapy at NIRS [11,24]. In the initial study of this cohort, 102 patients were treated with carbon ion RT alone, receiving 57.6 GyE in 16 fractions over 4 weeks. Although the 5-year local control rate was 80%, the 5-year survival rate was 35%, which resembled the most favorable results of surgery with or without RT or chemotherapy. This study strongly suggested the need for additional systemic therapy that could prevent distant metastasis. Therefore, in the subsequent study of 116 patients, concomitant DAV chemotherapy was also provided (Day 1: dacarbazine [DTIC] 120 mg/m^2, nimustine 70 mg/m^2, vincristine 0.7 mg/m^2; Days 2–5: DTIC 120 mg/m^2) [11]. The regimen was conducted with a 4-week interval and a total of five courses. The first course was administered at the start of carbon ion RT, the second course was administered at the completion of RT, and three courses were provided thereafter. Although the local control rate did not differ substantially from the previous study, the 5-year survival rate increased to 50% (Table 2). To date, these are the best MMM outcomes that have been reported in the literature.

Bone and soft tissue sarcoma of head and neck

Bone and soft tissue sarcomas of the head and neck are mesenchymal malignant neoplasms. They account for less than 10% of all bone and soft tissue sarcomas and constitute approximately 1% of all head and neck neoplasms. Depending on the subtype and characteristics of the individual tumor, treatment may require a combination of surgery, radiotherapy, and chemotherapy. Adjuvant radiotherapy improves local tumor control and, in selected cases, it results in complete cure with acceptable adverse effects [25]. However, the prognoses for local control and survival are poor for patients with unresectable sarcomas [26,27].

Table 1: Treatment results for adenoid cystic carcinomas of head and neck.

Authors	Treatment	N	T classification	5y-LC (%)	5y-OS (%)
Mendenhall et al. [14]	Surgery+X X	59 42	I-III/IV 44/15 I-III/IV 13/29	94 56	77 57
Iseli et al. [15]	Surgery Surgery+X X	54 95 10	I-II/III-IV 32/22 I-II/III-IV 53/42 I-II/III-IV 1/9	72 (LRFS) 73 (LRFS) 27 (LRFS)	85 76 24
Schulz-Ertner et al. [12]	X+Carbon ion X	29 34	N/A	77.5 (4-y) 24.6 (4-y)	75.8 (4-y) 77.9 (4-y)
NIRS [11]	Carbon ion	186	I-III/IV+R 36/149	75	74

Abbreviations: N: Number of Patients; LC: Local Control Rate; OS: Overall Survival Rate; X: Photon Therapy; N/A: Not Available; LRFS: Local Recurrence Free Survival Rate; R: Recurrent Tumor after Surgery.

Table 2: Treatment results for mucosal malignant melanomas of head and neck.

Authors	Treatment	N	Stage *(n)	LC (%)	3y-OS (%)	5y-OS (%)
Patel et al. [16]	Surgery±X	59	I/II/III 47/8/4	50	41	35
Lund et al. [17]	Surgery±X	58	I/II/III 58/0/0	N/A	N/A	28
Owens et al. [18]	Surgery Surgery+X	20 24	N/A	50 (5-y) 50 (5-y)	65 58	45 29
Temam et al. [19]	Surgery±X	69	I/II/III 52/17/0	46	N/A	20
Gilligan et al. [21]	X	28	N/A	61	N/A	17
Wada et al. [22]	X	31	I/II/III 27/4/0	30 (3-y)	33 (DSS)	N/A
Zenda et al.[23]	Proton	14	I/II/III 14/0/0	86	58.0	N/A
NIRS [11, 24]	Carbon ion	102	I/II/III 102/0/0	79 (5-y)	49	33
NIRS [11]	Carbon ion +C	116	I/II/III 106/0/0	80 (5-y)	65.2	50

Abbreviations: N: number of patients; * Stage I: local disease; II: regional metastasis; III: distant metastasis; LC: local control rate; OS: overall survival rate; X: photon therapy; C: chemotherapy; N/A: not available; DSS: disease specific survival

Table 3: Treatment results for unresectable bone and soft tissue sarcomas of head and neck in adults.

Authors	Years	Histology	Treatment	N	Follow up (months)	5y-LC	5y-OS
Eeles et al. [26]	1944–1988	S	X ± C	17	50	21	36
Le et al. [27]	1961–1993	S	X ± C	5	64	0	9
Willers et al. [28]	1972–1993	S	X ± C	14	50	55	63
Smith et al. [29]	1985–1996	B	X ± C	71	N/A	N/A	22
NIRS [11]	2001–2012	B & S	Carbon ion	42	42	73	53

Abbreviations: N: Number Of Patients; B: Bone Sarcoma; S: Soft Tissue Sarcoma; LC: Local Control Rate; OS: Overall Survival Rate; X: Photon Therapy; C: Chemotherapy; N/A: Not Available

In resectable cases, the 5-year local control rates for combined surgery and RT, surgery alone, and RT alone are 60–70%, approximately 54%, and 43–50%, respectively [25]. Yet, the prognosis is miserable for unresectable sarcomas [26-29]. No data have been reported for patients who received proton therapy as a sole treatment, possibly because these types of tumors are considered difficult to treat with low-LET protons. In a dose-escalation study of carbon ion RT at NIRS, the 5-year local control rate was only 24% for 64.0 or 57.6 GyE (n = 16) [11,30]. However, the 5-year local control rate increased significantly to 75% for patients receiving 70.4 GyE in 16 fractions (n = 44), and the corresponding 5-year survival rate was 52% with acceptable toxicities. To date, these are the best results for unresectable sarcomas that have been reported in the literature (Table 3).

DISCUSSION AND CONCLUSION

Because carbon ions allow a superior dose distribution, there are few reports of unexpected severe morbidity. However, the development of and risk factors for brain injury, optic nerve neuropathy, and other tumor-related toxicities have been reported. We demonstrated a dose-volume effect for the occurrence of brain necrosis after carbon ion RT, specifically showing that brain volumes receiving more than 50 GyE in a 16-fractions regimen are at risk for brain necrosis [31]. Schlampp et al. [32] also reported risk factors for temporal lobe injury after carbon ion RT for skull base tumors. Their study demonstrated a dose-volume effect for temporal lobe changes, specifically showing that the maximum dose applied to at least 1 mL of the temporal lobe was predictive of radiation-induced temporal lobe changes. Regarding optic nerve neuropathy, Hasegawa et al. [33] reported that a dose to 20% of the volume of the optic nerve was significantly associated with visual loss in a multivariate analysis. Because dose volume histogram parameters are independent risk factors for morbidity, the incidence of these morbidities may be reduced by optimal treatment planning or the introduction of new techniques of irradiation.

Carbon ion RT has been performed for radio-resistant unrespectable tumors in the head and neck region, demonstrating excellent clinical results for tumors including ACCs, MMMs, and sarcomas. Partly because these tumors are relatively rare, the total number of patients treated with carbon ion RT remains small. A limited number of studies have investigated carbon ion RT for cancers of the head and neck. At present, six carbon ion facilities (NIRS, Hyogo Ion Beam Medical Center, Gunma University and SAGA HIMAT in Japan, Heidelberg Ion Therapy Center in Germany and Centro Nationale di Adroterapia Oncologica in Italy) are running worldwide, and several more institutions are constructing carbon ion-facilities. Additional clinical data is needed to further clarify the efficacy of carbon ion RT for radio-resistant cancers of the head and neck. In conclusion, carbon ion RT is a promising treatment option for unresectable and radio-resistant cancers of the head and neck.

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