Case Report

Unexpected radiation laryngeal necrosis after carbon ion therapy using conventional dose fractionation for laryngeal cancer

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Abstract

Carbon ion therapy is a type of radiotherapy that can deliver high-dose radiation to a tumor while minimizing the dose delivered to organs at risk. Moreover, carbon ions are classified as high linear energy transfer radiation and are expected to be effective for even photon-resistant tumors. A 73-year-old man with glottic squamous cell carcinoma, T3N0M0, refused laryngectomy and received carbon ion therapy of 70 Gy (relative biological effectiveness) in 35 fractions. Three months after the therapy, the patient had an upper airway inflammation, and then laryngeal edema and pain occurred. Five months after the therapy, the airway stenosis was severe and computed tomography showed lack of the left arytenoid cartilage and exacerbation of laryngeal necrosis. Despite the treatment, 5 and a half months after the therapy, the laryngeal edema and necrosis had become even worse and the surrounding mucosa was edematous and pale. Six months after the therapy, pharyngolaryngoesophagectomy and reconstruction with free jejunal autograft were performed. The surgical specimen pathologically showed massive necrosis and no residual tumor. Three years after the carbon ion therapy, he is alive without recurrence. The first reported laryngeal squamous cell carcinoma case treated with carbon ion therapy resulted in an unexpected radiation laryngeal necrosis. Tissue damage caused by carbon ion therapy may be difficult to repair even for radioresistant cartilage; therefore, hollow organs reinforced by cartilage, such as the larynx, may be vulnerable to carbon ion therapy. Caution should be exercised when treating tumors in or adjacent to such organs with carbon ion therapy.

Key words: radiation laryngeal necrosis, carbon ion therapy, radiotherapy, laryngeal cancer, squamous cell carcinoma

Introduction

Particle therapy, also known as particle beam radiation therapy, is a type of radiotherapy (RT). Whereas photons are used for conventional RT, beams with totally different characteristics (such as carbon ions and protons) are used in particle therapy. Particle therapies using carbon ions and protons are generally referred to as carbon ion therapy (CIT) and proton therapy, respectively.

Photons consist of waves of light and do not possess an electric charge or mass, whereas charged particles such as carbon ions and protons possess electric charge and mass. Photons emit maximal
energy near the body surface; this energy decreases gradually and passes through the entire thickness of body structures. In contrast, charged particles emit a relatively low dose near the body surface and deposit their maximum energy just before stopping in the deep interior of the body, an effect known as the Bragg peak. By modifying this peak according to the position and size of the tumor into a spread-out Bragg peak (SOBP) (1), it is possible to deliver high-dose radiation to a tumor while minimizing the dose delivered to organs at risk.

Carbon ions, which are classified as high linear energy transfer radiation, show a high ionization density and a high rate of DNA damage caused by the direct action of radiation. Carbon ions are likely to induce DNA double-strand breaks, which are difficult to repair and frequently lead to cell death (2). Thus, carbon ions have the following biological characteristics and are expected to be effective even for photon-resistant tumors: First, they have high relative biological effectiveness (RBE), showing ∼3-fold greater biological effects compared with an equal physical dose of photons. Second, they have a low oxygen enhancement ratio, meaning that they are effective for treating photon-resistant hypoxic cells. Third, they are less dependent on the cell cycle, suggesting that they may be effective for treating photon-resistant late-S phase cells. In contrast, the biological effects of protons are considered to be almost the same as photons (RBE = 1.1).

With respect to head and neck malignancies, the efficacy of CIT has been shown mainly for photon- and chemo-resistant tumors, such as mucosal melanoma (3,4), adenoid cystic carcinoma (5–7), adenocarcinoma (8) and sarcomas (9). Meanwhile, there is still controversy over the usefulness of CIT for squamous cell carcinoma (SCC), which is the most common histological type in the head and neck region (10–13). Generally, the local effects are excellent and the side effects are acceptable, but the biological effects of CIT for each organ have not been fully elucidated yet.

Here, we report a case of unexpected radiation laryngeal necrosis (RLN) after CIT using a dose fractionation equivalent to the standard photon dose for laryngeal SCC.

### Case presentation

A 73-year-old man with months-long progressive hoarseness visited his otolaryngologist. A laryngeal tumor was noted and he was referred to Department of Otorhinolaryngology-Head and Neck Surgery, Matsue Red Cross Hospital for further evaluation. A white protruded tumor was observed mainly on the left vocal cord, which was fixed (Fig. 1A). A laryngeal biopsy detected well-differentiated SCC and staging work-up including contrast-enhanced computed tomography (CT) (Fig. 2A) and 18-fluoro-deoxyglucose-positron emission tomography concluded that his disease was glottic, T3N0M0 by the 7th International Union Against Cancer (UICC) TNM classification (14). His past medical history included hypertension and gout, but not diabetes mellitus. His smoking history was 20 cigarettes per day for 55 years. The Eastern Cooperative Oncology Group (ECOG) performance status was 1. According to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 2.2014 (15), the recommended treatment options as the first line are concurrent systemic therapy/RT or laryngectomy with ipsilateral thyroidectomy; however, his tumor was adjacent to the thyroid cartilage (‘adjacent sign’) and considered to be radioresistant (16), therefore, head and neck surgeons concluded that laryngectomy was the first choice. The patient strongly desired preservation of the larynx and received explanations of concurrent chemoradiotherapy and altered fractionated RT; however, he asked for a second opinion about the indication of CIT for his disease at Hyogo Ion Beam Medical Center (HIBMC).

HIBMC was established as the first institution in the world that could use both CIT and proton therapy in 2001, and ∼4700 patients including ∼650 patients with head and neck tumors had been treated at that time. However, no patient with laryngeal cancer had been treated, and there were no reports on CIT for laryngeal SCC in the literature. Moreover, concurrent systemic therapy was not available at HIBMC because of institutional limitations. Radiation oncologists

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**Figure 1.** Endoscopic images. (A) Before the carbon ion therapy (CIT), a white protruded tumor was observed mainly on the left vocal cord. (B) At the end of CIT, only a slight white lesion remained and Grade 2 mucositis was observed. (C) One month and (D) 2 months after the CIT, the mucositis had improved, but the white lesion was still seen.
at HIBMC concluded that CIT could be used for his disease as an alternative to photon RT after thorough discussion because CIT was expected to be more effective than photon RT and could achieve carotid sparing to reduce late carotid artery stenosis, which may lead to cerebrovascular incidents (17–21). In spite of the lack of clinical evidence, the patient wished to receive CIT. This treatment was approved by the institutional review board and written informed consent was obtained.

The radiation treatment was planned on a CT-based three-dimensional treatment planning system [Xio-M (CMS, St. Louis, MO and Mitsubishi Electric Corporation, Tokyo, Japan)]. The patient was immobilized with a custom-made thermoplastic cast in the supine position, and 1 mm thick CT was performed. The target volumes and organs at risk were delineated on the CT images. The clinical target volume (CTV) was defined based on conventional photon RT technique. The planning target volume was defined as the CTV plus a setup margin of 3 mm. A dose fractionation of 70 Gy (RBE) (the particle beam dose is reported in Gy (RBE), which is defined as the physical dose multiplied by the RBE of the protons or carbon ions. For example, 2 Gy (RBE) of CIT is biologically equivalent to 2 Gy of photon RT. Biological effects of CIT at HIBMC were evaluated in vitro and in vivo, and the RBE values for carbon ion irradiation were determined to be 2–3.7 (depending on the depth in the SOBPs) (23) in 35 fractions (7 weeks), which is considered to be equivalent to the standard photon dose for T3 disease (15), was chosen. The dose distribution and digitally reconstructed radiograph in this case are shown in Figure 3. The tumor shrank gradually during the CIT, and only a slight white lesion remained at the end of radiation (Fig. 1B). Grade 2 mucositis and Grade 2 dermatitis according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) (22) were observed as acute reactions.

After the CIT, he was followed up at Matsue Red Cross Hospital. One month (Fig. 1C) and 2 months (Fig. 1D) after the CIT, the mucositis had improved, but the white lesion was still seen. Three months after the CIT, he had an upper airway inflammation, and then laryngeal edema and pain occurred (Fig. 4A). Despite treatment by the head and neck surgeons, the laryngeal edema and pain worsened (Fig. 4B). CIT showed necrosis of the larynx including the tumor, but the arytenoid cartilage was still observed (Fig. 2B). Five months after the CIT, the patient coughed up a piece of cartilage (Fig. 5A) and visited the head and neck surgeons with it. The airway stenosis was severe (Fig. 4C) and CIT showed lack of the left arytenoid cartilage and exacerbation of the laryngeal necrosis (Fig. 2C). He was admitted to the hospital and treated with antibiotics, steroids and prostaglandin E1. The head and neck surgeons recommended laryngectomy to avoid the risk of suffocation, but the patient refused. Five months and a half after the CIT, he visited the emergency room due to laryngeal bleeding. The laryngeal edema and necrosis became even worse and the surrounding mucosa was edematous and pale (Fig. 4D). CT showed extensive defect of the left larynx (Fig. 2D). The bleeding was controlled by antihemorrhagic agents, but the head and neck surgeons recommended surgical resection again and the patient finally accepted. Six months after the CIT, pharyngolaryngo-esophagectomy and reconstruction with free jejunal autograft were performed because laryngectomy only was considered to be at high risk for anastomotic insufficiency due to pharyngeal edema. The surgical specimen pathologically showed massive necrosis and no residual tumor (Figure 5B). Three years after the CIT, he is alive without recurrence.

Discussion
To our knowledge, this is the first report to describe CIT for laryngeal SCC. We encountered an unexpected RLN despite the use of a dose fractionation equivalent to the standard photon dose [70 Gy (RBE)}
Figure 3. The dose distribution and digitally reconstructed radiograph of the CIT for this patient. The CTV (cyan contour) was defined based on conventional photon radiotherapy technique. The bilateral carotid arteries (arrows) were successfully avoided.

Figure 4. Endoscopic images. (A) Three months after the CIT, laryngeal edema was observed. (B) Four months after the CIT, the laryngeal edema had worsened. (C) Five months after the CIT, the airway stenosis was severe. (D) Five and a half months after the CIT, the laryngeal edema and necrosis had become even worse and the surrounding mucosa was edematous and pale.
at 2 Gy (RBE) per fraction. The data for the incident rate of RLN in patients with advanced (T3–T4) laryngeal cancer treated with high-dose modern RT techniques is limited. Majem et al. (24) reported that RLN was observed in only one of 71 patients (1.4%) with T3 laryngeal cancer treated with hyperfractionation photon RT (76.8–79.2 Gy at 1.2 Gy per fraction, twice daily). A retrospective review of 31 patients with laryngeal/hypopharyngeal carcinoma (T3–T4: 74%) treated with concurrent platinum-based chemotherapy and intensity-modulated RT (70–72 Gy at 2.12 Gy per fraction) by Lee et al. (25) demonstrated that one patient (3.2%) developed RLN. According to these reports, the incident rate of RLN seems to be low even after high-dose RT. We might have experienced RLN in our first laryngeal SCC case by chance, but we thought that a further exploration was necessary.

The general health conditions of patients can affect the occurrence of RLN. Several authors have suggested that health conditions affecting the vasculature such as diabetes mellitus, hypertension and smoking history contribute to the progression of RLN (26–28). There have been no data showing a direct correlation between smoking and radiation necrosis; however, Rugg et al. (29) reported a significant correlation between smoking and radiation mucositis. This patient’s health conditions such as hypertension and being a long-term heavy smoker might have unfavorably affected the occurrence of RLN.

Of course, several factors were related to the RLN in our case, but our speculation is that the biological effect of CIT on cartilage is stronger than our original estimation. Chondronecrosis, which occurs with loss of microvasculature and tissue ischemia, is an essential pathology in RLN. Cartilage itself has few blood vessels and rare proliferating cells, making it resistant to photon RT, whereas the perichondrium, from which the underlying cartilage receives its nutrient supply, is highly proliferative and sensitive to photon RT (30). Chondronecrosis follows perichondritis and/or breakdown of the overlying mucosa (31). In our conception, tissue damage caused by CIT is difficult to be repaired even for radioresistant cartilage because carbon ions are likely to induce DNA double-strand breaks as stated above. Simultaneously, radiosensitive perichondrium is also damaged and the nutrient supply to cartilage stops. These phenomena lead to chondronecrosis. RBE values are calculated based on in vitro/vivo experiments (23) and are assumed to be approximately the same for all organs in the clinical setting; however, we are skeptical about this basis from our clinical experience. We have routinely treated patients with tumors adjacent to the trachea at HIBM, and the irradiation of the trachea with a high dose is inevitable in these cases. Our unpublished data showed that Grade 3 or greater tracheal hemorrhage/fistula was observed more frequently in patients treated with CIT compared with proton therapy. Because the larynx and trachea are similar in terms of being hollow organs reinforced by cartilage, taken together, the RBE values of carbon ions for these organs can be higher than 3. If so, caution should be exercised when treating tumors in or adjacent to the larynx and/or trachea with CIT.

Then, should we not have used CIT for this patient? Because his disease was considered to be photon-resistant because of ‘adjacent sign’ (16), CIT constituted a potent alternative to laryngectomy. Practically, CIT showed excellent anti-tumor effects (no pathological residual tumor in the surgical specimen) as expected. With respect to laryngeal preservation, his choice did not succeed, but his current situation (no evidence of disease; loss of voice) is similar to that if he had chosen laryngectomy as the first treatment. In that way, CIT can be an option when a patient refuses laryngectomy as the first treatment. Moreover, because of its better dose distribution compared with conventional photon RT, CIT is useful for preventing late toxicities outside the larynx such as carotid artery stenosis, which may lead to cerebrovascular incidents (Fig. 3). Recently, a carotid-sparing IMRT technique has been applied in the clinical setting (32–35), but particle therapy such as CIT and proton therapy can achieve even better dose distribution theoretically. In that way, the use of particle therapy for laryngeal cancer will increase in the future. The most important thing is that both healthcare professionals and patients understand the possibility of severe laryngeal toxicity caused by CIT.

**Conclusions**

The first reported laryngeal SCC case treated with CIT using a dose fractionation equivalent to the standard photon dose resulted in an unexpected RLN. Tissue damage caused by CIT may be difficult to repair, even that of radioresistant cartilage, because carbon ions are likely to induce DNA double-strand breaks. Therefore, hollow organs reinforced by cartilage, such as the larynx, may be vulnerable to CIT. Caution should be exercised when treating tumors in or adjacent to such organs with CIT.
Conflict of interest statement
None declared.

References