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Teaching Case

# Re-irradiation With Carbon Ion Beams for Recurrent Adenoid Cystic Carcinoma of the Tongue Base: A Case Report

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## Introduction

Adenoid cystic carcinoma (ACC) is a rare cancer that accounts for 1% of all head and neck tumors and 10% of all salivary gland tumors.[1] It has a slightly higher incidence in middle-aged patients (50-60 years) and is more common in women.[2] It is a slow-growing tumor characterized by multiple and late recurrences.[3] Surgery and radiation therapy are the standard treatment options.[3] However, recurrence or resistance to therapy might make choosing the correct treatment in some patients difficult.

Carbon ion radiotherapy (CIRT) combines the high linear energy transfer (LET) and superior biological efficacy of carbon ions with the precise dose distribution characteristic of charged particle beams.[4] LET refers to the energy deposited per unit length as radiation travels through matter, with high LET radiation, such as carbon ions, creating dense ionization clusters that cause complex, difficult-to-repair DNA damage in cancer cells.[4] Charged particle beams, including carbon ions, are defined by the Bragg peak, which concentrates most of the dose at a specific depth, minimizing damage to surrounding healthy tissues.[4] Although proton therapy also uses the Bragg peak, CIRT offers higher LET, resulting in greater lethality to radioresistant tumors, and reduced lateral scattering for sharper dose delivery. These advantages make CIRT a more potent and targeted therapy compared with x-rays or proton therapy.

The efficacy of CIRT in managing ACC has already been demonstrated in previous studies. A multicenter study by Sulaiman et al[5] on CIRT for head and neck ACC evaluated 289 patients treated with CIRT. The results showed high local control rates, with 2-year and 5-year local control rates of 88% and 68%, respectively. Acute and late adverse events of grade 3 (Common Terminology Criteria for Adverse Events [CTCAE], version 5.0) or higher were reported in 32% and 15% of patients, respectively. CIRT has been increasingly evaluated as a treatment option for ACCs over the past few years.[5]

Herein, we present a case report of re-irradiation (reRT) with CIRT for ACC of the tongue base, without recurrence or serious adverse events after treatment at our hospital. We expect this to be an important achievement in the expansion of treatment options.

## Case Report

We report the case of an 80-year-old man with ACC of the tongue base. He visited an otolaryngologist with sore throat that had worsened over the past 5 to 6 years. A tumor was detected at the tongue base because of

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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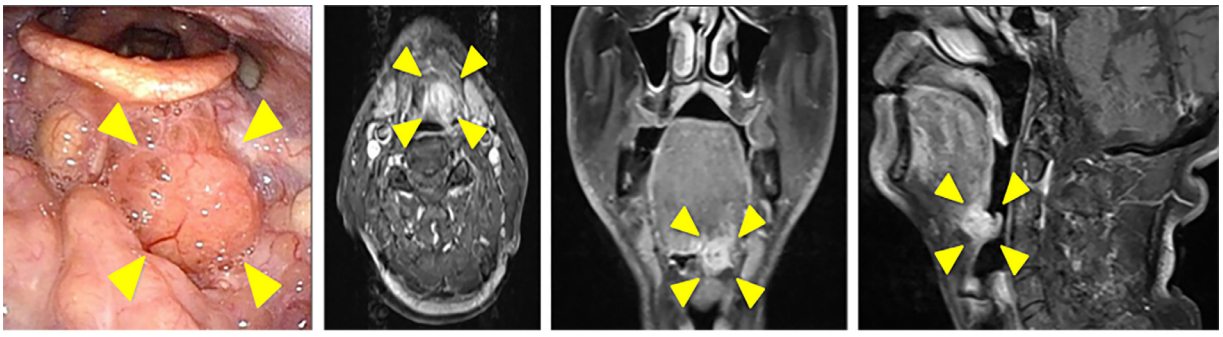



**Figure 1** Findings at the time of initial visit to our hospital. (a) Nasopharyngoscopy: tumor, 21 mm in diameter, extending from the tongue base to the epiglottis valley (yellow arrow). (b) Contrast-enhanced magnetic resonance imaging: contrast nodule 21 mm long on the left side of the tongue base (yellow arrow).

nasopharyngoscopy; he was referred to our otorhinolaryngology department. At the initial visit, the nasopharyngoscopy showed a tumor with a 21-mm diameter extending from the tongue base to the glottis valley (Fig. 1a); contrast-enhanced magnetic resonance imaging (MRI) showed a contrast nodule with a 21-mm diameter on the left side of the tongue base (Fig. 1b). After a biopsy of the lesion, a diagnosis of ACC was made. No lymph nodes or distant metastases were found; a diagnosis of cT2N0M0 stage II (Union for International Cancer Control (UICC), 8th ed.) was made.

The eligibility for treatment and assessment of patient suitability were reviewed by our hospital's Cancer Board, a multidisciplinary panel comprising specialists from otolaryngology; oral and maxillofacial surgery; and radiation oncology, convened to discuss the management strategies for head and neck tumor cases. They determined that the carcinoma was inoperable because of the need for extensive resection. CIRT was recommended.

CIRT was applied, with a total dose of 57.6 Gy relative biological effectiveness (RBE) in 16 fractions (fr). The patient was treated according to the criteria of the existing protocol and irradiated with 36.0 Gy (RBE)/10 fr and 21.6 Gy (RBE)/6 fr in the first and second halves, respectively.[6,7] The XiO-N system (Elekta) was used for treatment planning. Gross tumor volume (GTV) was used to define the tongue-based tumor. The GTV was primarily delineated based on computed tomography (CT) and MRI imaging. According to the protocol, the definition of the clinical target volume (CTV) differed between the first and second halves of the treatment.[6,7] In the first half, CTV1 was defined to include the GTV + 5 mm margin, as well as the tongue base, full circumference of the oropharynx, and entirety of the ipsilateral midinternal jugular node region. Planning target volume (PTV) 1 was defined as CTV1 + 2 mm margin (Fig. 2a). In the second half, CTV2 was limited to the GTV + 5 mm margin; PTV2 was defined as a CTV2 + 2 mm margin (Fig. 2b). The patient was immobilized using a thermoplastic shell (Shellfitter; Kuraray) and positioned in customized cradles (Moldcare; Alcare). To prevent swallowing and occlusal movement, a customized mouthpiece was secured mouth. CIRT was conducted under inpatient management. However, this was not because of a decline in the patient's general condition or severe symptoms. Rather, inpatient care was chosen because the patient did not live close enough to the facility to undergo outpatient treatment. Toxicity was assessed by medical examination and nasopharyngoscopy. The acute adverse events were limited to grade 1 (CTCAE, version 5.0) for dermatitis, mucositis, and dysgeusia.

Nasopharyngoscopy and contrast-enhanced MRI were performed 1, 6, and 12 months after treatment completion. The lesion reduced in size and was undetectable 12 months after completion (Fig. 3). At the time, CIRT was considered a relatively new treatment, predicting the long-term course after therapy was challenging. Therefore, we prioritized extended follow-up beyond 5 years, paying particular attention to the potential emergence of late severe adverse events. The patient remained free of recurrence or serious late adverse events 96 months after treatment.

During routine otorhinolaryngology visit 106 months after treatment, the nasopharyngoscopy showed ulcerative changes in tumor localization (Fig. 4a). Contrast-enhanced MRI did not reveal any lesions; positron emission tomography–computed tomography (PET/CT) showed abnormal accumulation on the left side of the tongue base (Fig. 4b). When the localization of the accumulation was compared with that in the initial treatment plan, it was located within the irradiation field and in the high-dose area of the GTV (Fig. 4c). Biopsy results confirmed that the histologic type was ACC rather than sarcoma, leading to the diagnosis of a true recurrence in the irradiated field a long time after CIRT.

After review by the in-hospital Cancer Board, salvage surgery was not indicated because of the localization and irradiation history. Drug therapy was feasible but considered less effective in treating ACC. An excessive dose to

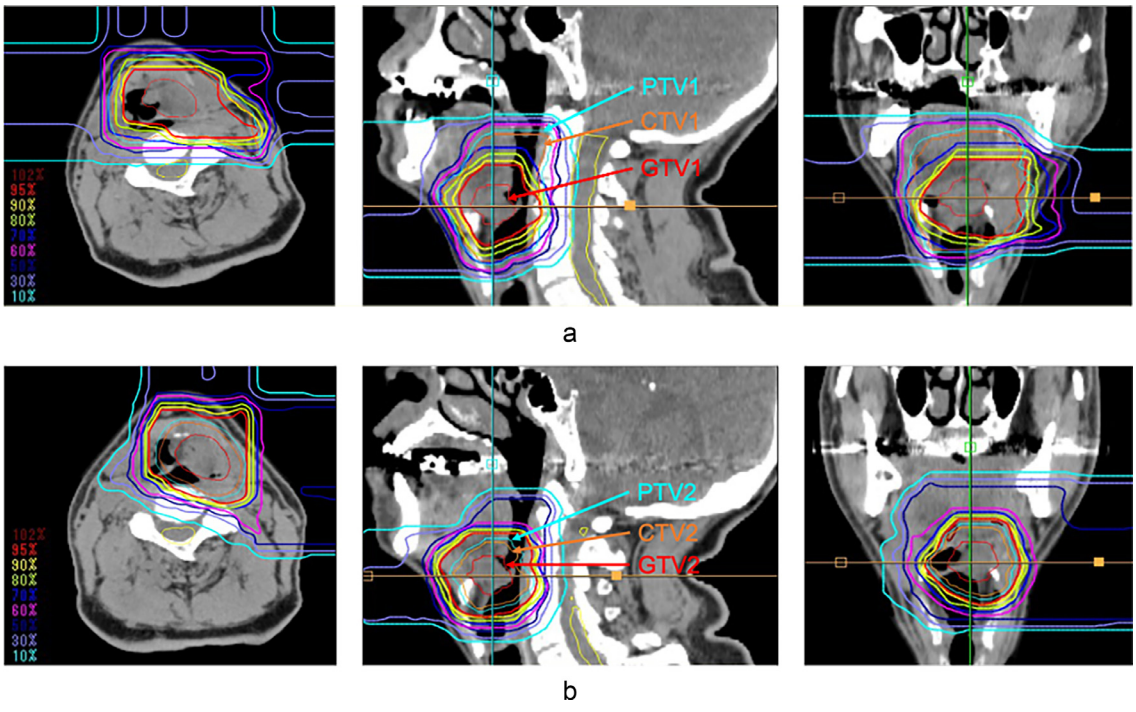



**Figure 2** CIRT (initial treatment). Total dose 57.6 Gy (RBE)/16 fractions. (a) First half of the plan: irradiated up to 36.0 Gy (RBE)/10 fractions. (b) Second half of the plan: CTV2 was limited to GTV + 5 mm margin, and the remaining 21.6 Gy (RBE)/6 fractions were irradiated.
*Abbreviations:* CIRT = carbon ion radiotherapy; CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume; RBE = relative biological effectiveness.

the pharyngeal mucosa is a concern in CIRT. However, reRT is feasible if caution is exerted concerning the overlap of irradiation fields and prescribed doses. Therefore, reRT with carbon ions was decided on.

During reRT with CIRT, the margin was set to minimize the dose to the epiglottis and pharyngeal mucosa as much as possible; GTV was defined as a recurrent tumor that was delineated based on PET/CT imaging,

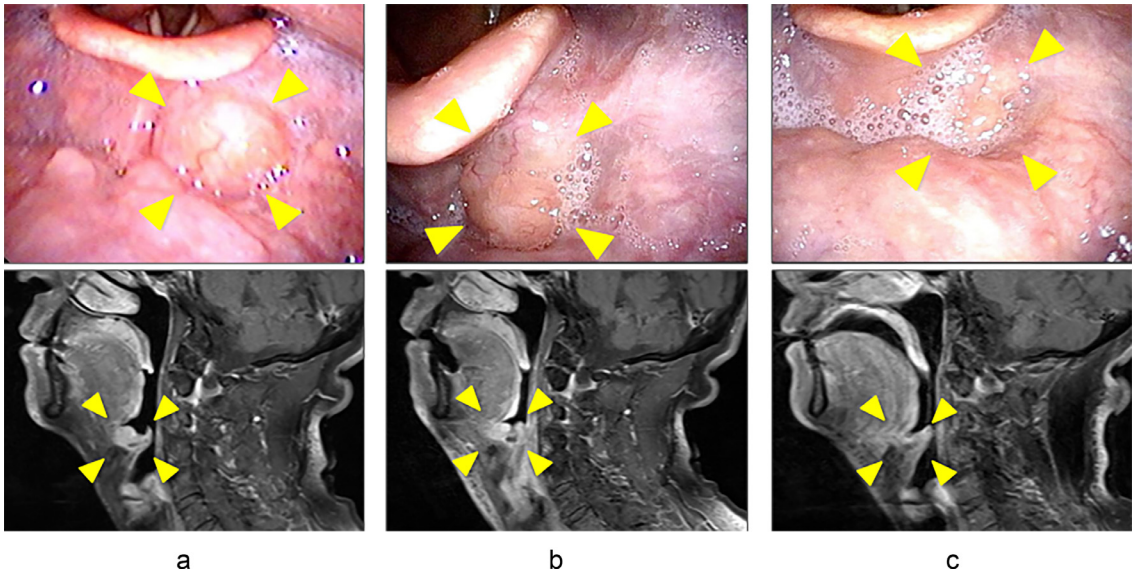



**Figure 3** Progress after initial treatment. These are nasopharyngoscopy and contrast-enhanced magnetic resonance images at 1 (a), 6 (b), and 12 (c) months after treatment. After irradiation, the tumor shrank, and the lesion was undetectable at 12 months posttreatment (yellow arrows).

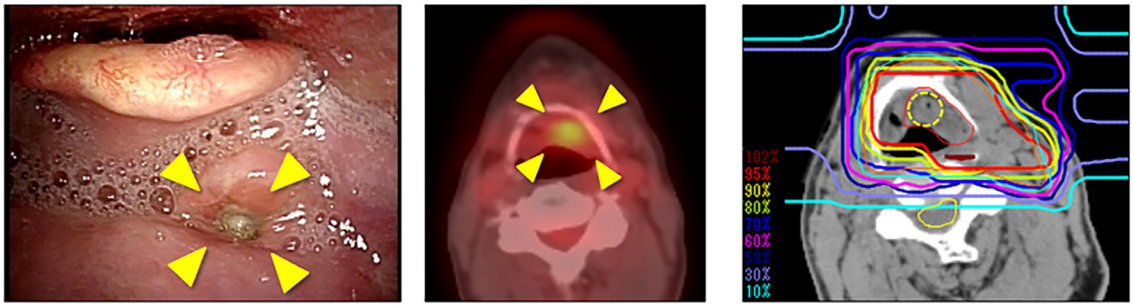



**Figure 4** Findings at the time of recurrence. (a) Nasopharyngoscopy: ulcerative changes in tumor localization at initial presentation (yellow arrow). (b) Positron emission tomography− computed tomography (PET/CT): abnormal accumulation (Standardized Uptake Value (SUV) max 3.5) on the left side of the tongue base (yellow arrow). (c) Abnormal PET/CT accumulation was fitted to the dose distribution map of the initial carbon ion radiotherapy (yellow dotted line). Abnormal accumulation was observed within the high-dose region in the irradiation field.

CTV = GTV; PTV was defined as CTV + 2 mm margin (Fig. 5a, b).

The initial plan was to combine this with the reRT plan using the MIM Maestro system ver. 7.3.2 (Euro Medi Tech), which showed that the high-dose areas overlapped in the deep pharynx. However, efforts were made to minimize overlap as much as possible, particularly in the pharyngeal mucosa surrounding the lesion, thereby reducing the radiation dose (Fig. 5a, b). The dose-volume histogram of the combined plan was also evaluated (Fig. 5c, d). This dose-volume histogram showed that despite its proximity to the tumor, the epiglottis (green line) could reduce the volume in the high-dose range. The maximum and average doses for the epiglottis were 108.8 and 79.7 Gy (RBE), respectively, and for the spinal cord (yellow line), 8.3 and 4.0 Gy (RBE), respectively. The dose constraint for the spinal cord was set at a maximum dose of <45 Gy; it was evaluated to be within this limit. The immobilization setup was the same as that during the initial treatment. Moreover, reRT was conducted under inpatient management for the same reasons as those during the initial treatment; toxicity was also assessed by the same methods as those during the initial treatment. The planned treatment was completed and the only acute adverse event was dermatitis grade 1 (CTCAE, version 5.0).

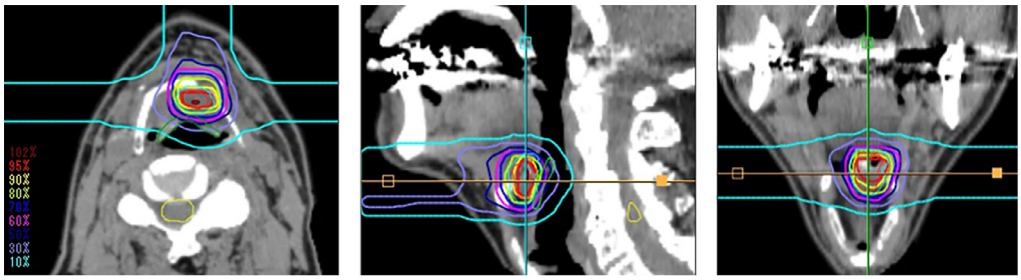
The patient was evaluated using nasopharyngoscopy and PET/CT at 5 and 12 months after reRT completion (Fig. 6). The nasopharyngoscopy showed improvement in ulcerative changes; PET/CT showed no accumulation 5 months after completing irradiation. Thirty-eight months post-reRT the patient exhibited neither recurrence nor severe adverse events, reporting only mild symptoms such as occasional coughing during swallowing.

## Discussion

According to a Japanese single-center study, the 5-year local control rate of carbon ion irradiation for ACC of the head and neck is 64.6%.[7] Approximately 35% of patients experience local recurrence within 5 years. However, in some cases, such as the present one, recurrence occurs long after treatment. At present, no studies have observed patients for >5 years after carbon ion irradiation. Studies should be conducted in the future to demonstrate the importance for long-term follow-ups of ACC.

There is no universally accepted chemotherapy regimen for ACC of the head and neck; most regimens are still in the clinical trial phase.[8] Surgery and radiation therapy are the standard initial treatments of ACC of the head and neck. Given the relatively high rate of local recurrence, whether surgical resection of the irradiation bed should be pursued for pathologic analysis or removal of microscopic residual disease or whether dose escalation should be performed to improve local control was a crucial consideration. In cases wherein reRT is planned and overlap of irradiation fields is extensive, increasing the risk of severe adverse events, surgical resection should be considered as the first option if feasible. In cases such as this, wherein the recurrent lesion was relatively small and localized, surgical resection could have been a less invasive alternative avoiding the potential risks associated with reRT. However, in this case, surgery was deemed not indicated; thus, that option could not be pursued. Our case showed no recurrence for 38 months after reRT with CIRT, suggesting that CIRT may be an effective and safe treatment option in patients with recurrent ACC of the head and neck, for which treatment options are limited.

There are few reports of reRT with CIRT for solitary recurrent ACCs, particularly in the pharyngeal region. Regarding reRT with x-rays, it has been reported that acute and late adverse events of grade 3 (CTCAE, version 5.0) or higher occur in 26% and 51% of cases, respectively.[9] Considering reRT with proton beams, it has been reported that acute and late adverse events of grade 3 (CTCAE, version 5.0) or higher occur in 23.6% and 30.3%



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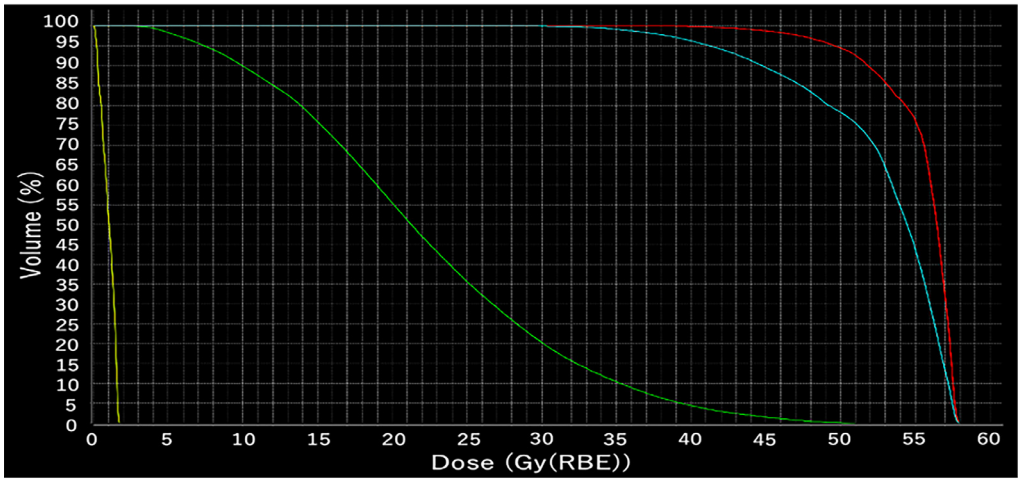


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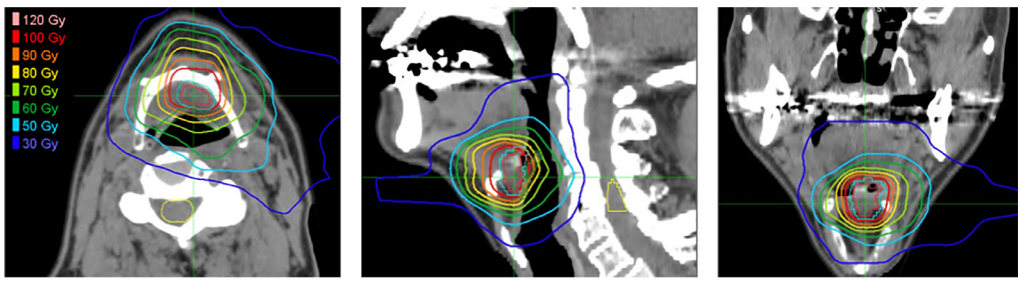


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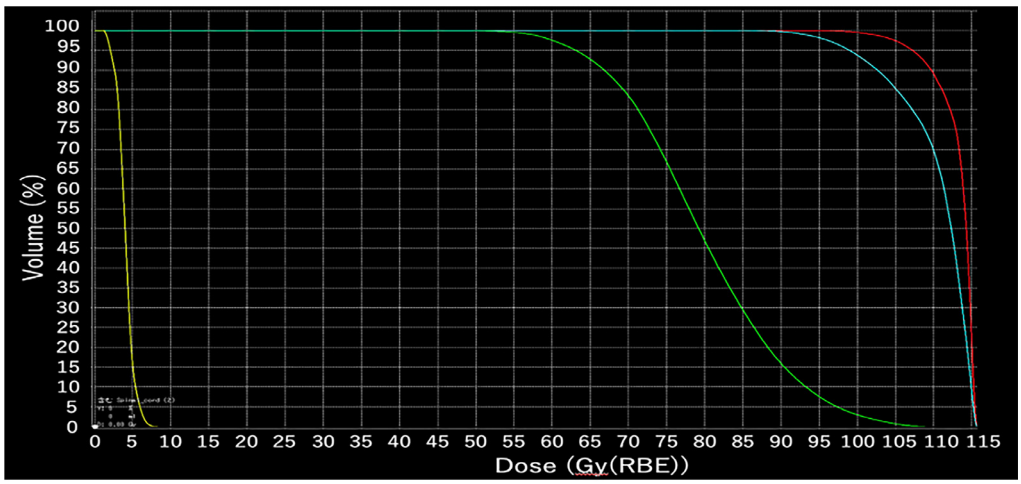


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**Figure 5** ReRT with CIRT. Total dose: 57.6 Gy (RBE)/16 fractions. (a) ReRT plan: limit margins to minimize the dose to the epiglottis (green) and pharyngeal mucosa as much as possible. (b) DVH of the reRT plan: GTV (red line) and epiglottis (green line) (generated using the XiO-N system). The maximum and average doses to the epiglottis were 52.2 Gy (RBE) and 21.7 Gy

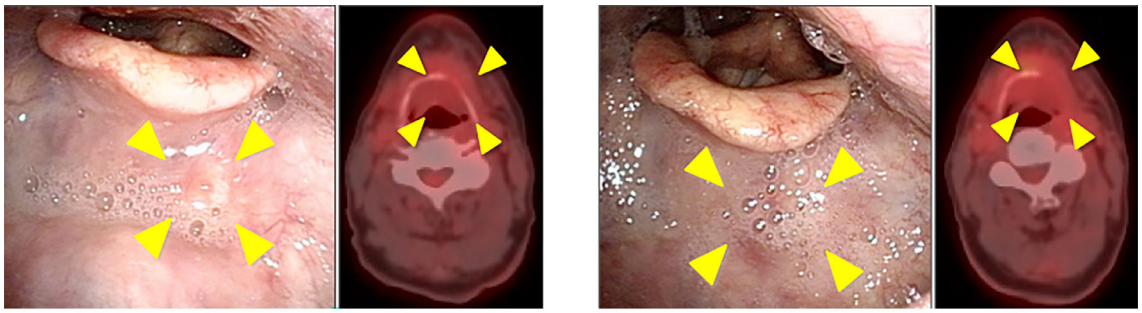


**Figure 6** Progress after re-irradiation (reRT). These are nasopharyngoscopy and the corresponding Positron emission tomography−computed tomography (PET/CT) scan at 5 months (a) and 12 months (b) after reRT, respectively. Localization of the recurrent lesion is indicated by yellow arrows. Ulcerative changes improved, and PET accumulation disappeared.

of cases, respectively.[10] Based on these findings, along with reports on other radiation modalities and the adverse events observed in this case, the high safety profile of reRT with carbon ion beams is underscored. In a previous study, the combined equivalent dose of 2 Gy to the pharynx of patients with dysphagia grade 3 or higher was 40 to 70 Gy.[11] Although an exact comparison could not be made because of different radiation qualities, the highest combined dose to the pharynx in this case was 108.8 Gy (RBE).

No studies have mentioned dose constraints on the larynx in reRT with carbon ions and proton beams. Held et al[12] examined reRT with carbon ion beams in 229 patients with recurrent head and neck cancer cases. The serious adverse events in the pharyngeal and laryngeal regions were grade 3 in 1.3% (dysphagia in 3 patients) and grade 4 in 0.9% (laryngeal edema in 2 patients) in the acute phase.[12] Serious late adverse events were mainly neurologic disorders and not observed in the pharyngeal and laryngeal regions.[12] Although the tumor and laryngeal and pharyngeal mucosa were nearby in this case, there were no serious adverse events in the same area during either the acute or late phases. The publication by Held et al[12] also reported a relatively low incidence of severe adverse events in the pharyngeal and laryngeal regions, suggesting that the outcome in this case was consistent with the findings of previous studies. The 106-month interval between initial irradiation and reRT in this case, which was longer than the median interval between initial irradiation and reRT in known publications, may also have contributed to the reduction in adverse events. Furthermore, the superior dose concentration of carbon ion beams and effort to minimize the irradiation field as much as possible during reRT were considered contributing factors. Although the discussion on the safety of reRT of the pharyngeal region with CIRT remains underdeveloped, we were able to evaluate the combined dose and confirm the safety of reRT in this case. We will continue to follow this case and study similar cases in the future.

## Conclusions

CIRT may be an effective and safe treatment option for recurrent ACC of the tongue base in an irradiated field.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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(RBE), respectively. (c) Combination with initial treatment: although the high-dose areas overlapped in the deep pharynx, the epiglottis and pharyngeal mucosa were outside the overlap of the high-dose areas, and the dose could be reduced. (d) DVH of the combined plan: GTV (red line), PTV (cyan line), epiglottis (green line), and spinal cord (yellow line); GTV and PTV are structures at recurrence.

*Abbreviations:* CIRT = carbon ion radiotherapy; DVH = dose-volume histogram; GTV = gross tumor volume; PTV = planning target volume; RBE = relative biological effectiveness; reRT = re-irradiation.

and trust throughout the treatment process. Atsushi Musha was responsible for statistical analysis.

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