Proton beam therapy combined with retrograde intra-arterial infusion chemotherapy for an extremely rapid growing recurrent ameloblastic carcinoma: A case report

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Abstract. Ameloblastic carcinoma (AC) is a very rare malignant odontogenic tumor. Although surgical resection is generally performed, treatment approaches have not been established for recurrent cases. Chemotherapy and radiotherapy are positioned as adjunctive therapies, and few studies investigated definitive non-operative therapy. We present the case of a 71-year-old male with recurrent secondary-type AC arising from the right maxilla, who was treated with proton beam therapy (PBT; 71.4 Gy relative biological effectiveness in 32 fractions) combined with continuous intra-arterial infusion of cisplatin (40 mg/m^2) and docetaxel (8 mg/m^2). The patient experienced acute grade 3 mucositis, dermatitis and neutropenia, which were resolved within 3 months of treatment. Late adverse events were grade 1 skin atrophy, and grade 2 right optic nerve disorder and retinopathy. After ~8 years of treatment, the patient died from another cause but did not experience any relapse or metastasis during the follow-up period of 94 months. To the best of our knowledge, this is the first report of recurrent AC treated with PBT and intra-arterial infusion chemotherapy without any severe late adverse events. This combination therapy approach may be considered as an effective therapeutic option for inoperable AC.

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Abbreviations: AC, ameloblastic carcinoma; CIT, carbon ion therapy; CT, computed tomography; FDG, ^{18}F-fluorodeoxyglucose; IAIC, intra-arterial infusion chemotherapy; MA, maxillary artery; MRI, magnetic resonance imaging; PBT, proton beam therapy; PET, positron emission tomography; PTV, planning target volume; RBE, relative biological effectiveness; SCC, squamous cell carcinoma; STA, superficial temporal artery

Key words: AC, chemoradiotherapy, head and neck cancer, IAIC, PBT, radiotherapy

Introduction

Ameloblastic carcinoma (AC) is a very rare malignant odontogenic tumor, with features of both ameloblastoma and carcinoma. An approximate male-to-female ratio of AC is 2:1 and a mandible-to-maxilla ratio is 1.7:1 (1). The common symptoms of AC are pain, swelling, and rapid growth. Clinically, AC is a typically aggressive tumor with extensive local destruction. Lymph node involvement and distant metastasis have also been reported (2-6). AC, first introduced as a distinct entity by Elzay in 1982 (1,2), is defined as a rare odontogenic malignancy that combines the histological features of ameloblastoma with cytological atypia regardless of metastasis, after considerable debate, by the World Health Organization classification of odontogenic tumors in 2005. It is classified into primary- (*de novo*) and secondary-type (malignant transformation of pre-existing ameloblastoma). Secondary-type AC is further divided into two subtypes: Intraosseous and peripheral. This classification was preserved with the 2017 update of the classification.

No standard treatment has been established for this rare tumor. Previous reports indicate complete surgical resection with wide local excision and cervical lymph node dissection as a commonly used approach (1-4,7); however, aesthetic failure and dysfunction after surgery, such as dysphagia, dysarthria, and nasopharyngeal closure dysfunction, are severe. The treatment efficacy of systemic chemotherapy and/or radiotherapy seemed poor and limited; local control rate is low and physical strength may decline due to decreased bone marrow function or difficulty in oral intake. These conservative therapies have been used as an adjunctive therapy (1). Strojan *et al* reported that cumulative dose of cisplatin in concurrent chemoradiation protocols for head and neck squamous cell carcinoma (SCC) has a significant positive correlation with survival (8). Among these

non-surgical approaches, intra-arterial infusion chemotherapy (IAIC) combined with radiotherapy has been increasingly performed in recent years for locally advanced head and neck cancers to avoid surgery. Several studies using IAIC reported that the outcomes of this organ-preserving approach were not inferior to those of surgery (9-11). Although AC is considered to be a radioresistant tumor, there are some reports of good treatment results with X-rays, gamma knife, and particle beam therapy, including proton beam therapy (PBT) and carbon ion therapy (CIT) (12-16). Particle beam therapy, which provides several advantages including a rapid dose fall-off at the distal end and the possibility to induce double strand DNA breaks leading to catastrophic damage to cancer cells (17), is an effective approach that provides high-dose irradiation to the tumor without increasing toxicity to the normal tissue (18). Although the therapeutic effect of particle beam therapy has been reported for non-SCC of the head and neck (19), few reports investigated its efficacy in AC (15,16). Here we report a case of recurrent secondary-type AC treated by PBT in combination with IAIC that resulted in a good long-term course.

Case report

A 71-year-old man was referred to the Southern Tohoku Proton Therapy Center in March 2009 with severe pain and swelling of the right palatal gingiva. In October 2007, he was diagnosed with ameloblastoma of the right maxilla based on the histopathology of biopsy and underwent partial resection several times owing to tumor recurrence. The patient was diagnosed with AC in March 2009 based on pathological assessment after the fourth surgery (Fig. 1).

At the time of admission, his hard palate on the right was swollen with bony expansion to the oral cavity, and the tumor had invaded the right alveolar ridge. He had paresthesia of the right face. Enhanced magnetic resonance imaging (MRI; Signa HDx, GE Healthcare) revealed a large, heterogeneously enhanced mass extending from the right maxillary sinus to the upper gingiva, measuring ~50x70 mm in dimensions. The medial extension reached the right nasal septum and the right ethmoid sinus. The tumor had destroyed the floor of the right maxillary sinus, perforated the anterior wall of the right maxillary sinus, and extended into the surrounding soft tissue. ^{18}F-fluorodeoxyglucose (synthesized and used in our own facility) positron emission tomography computed tomography (FDG-PET/CT; Discovery ST Elite, GE Healthcare) showed high FDG concentration in the right maxillary sinus (maximum standardized uptake value, 21.6). There were no suspicious lymph nodes or remote metastases.

The growth speed of the tumor was extremely rapid, and further surgical resection was deemed not to be sufficient for possible tumor control. Therefore, the patient was treated using PBT in combination with IAIC to the artery supplying the tumor. Written informed consent was obtained from the patient. This treatment was approved by the Ethics Committee of Southern Tohoku Research Institute for Neuroscience (approval no. 338). This study was conducted according to the principles of the Declaration of Helsinki.

IAIC. The treatment schedule is summarized in Fig. 2. The IAIC method described by Fuwa *et al* (20) was followed. Under local anesthesia (xylocaine injection 1% with epinephrine, Aspen Japan), using fluoroscopy, a guide-wire (GT wire, 0.016 inch diameter, Terumo Corp.) was inserted into the common carotid artery from the superficial temporal artery (STA), and a thin catheter (Anthron P-U catheter; tapering type, 5Fr in outer diameter, Toray, Medical Corp.) was inserted from the STA into the external carotid artery (ECA). As the main feeder of the tumor was the maxillary artery (MA), the tip of the catheter was placed slightly to the central side of the branching section of the MA. The tumor was beyond the median line of the hard palate; therefore, two catheters were inserted bilaterally. After determination of a stable position for the catheter by digital subtraction angiography using a contrast medium (Iopamirn 300), to confirm that the target area was covered, blue dye (Indigocarmine, Daiichi Sankyo) was slowly injected, and MRI was performed with slow injection of a low-dose contrast medium (Gadovist IV, Bayer) via a catheter (21). IAIC was performed after confirming good perfusion (Fig. 3). Based on their reported effect, cisplatin (Maruko, Yakult) in combination with docetaxel (Docetaxel, ELMED) was used (22). Briefly, once a week, 40 mg/m^2 cisplatin was infused over 5 h via a catheter, and 8 mg/m^2 docetaxel was infused over 2 h. During arterial cisplatin infusion, 8 g/m^2 sodium thiosulphate (Detoxol, Nichi-Iko Pharmaceutical Co. Ltd.) as a neutralizing agent for cisplatin was infused intravenously over 7 h. Cisplatin was administered seven times on both sides, for a total dose of 500 mg. Arterial docetaxel infusion was repeated five times for a total dose of 60 mg in the right (affected) side and four times for a total dose of 40 mg in the opposing side. A 5-hydroxytryptamin 3 receptor antagonist and corticosteroids were administered to minimize nausea and vomiting before intra-arterial infusion.

PBT. The patient was positioned and immobilized with a thermoplastic head mask to ensure high target repositioning accuracy. CT images with 1-mm scan thickness were obtained using a 16-slice large-bore helical CT scanner (Aquilion LB; Canon). Diagnostic MRI scans with 3-mm thickness were combined with planning CT images for target delineation. A three-dimensional treatment planning system (Xio-M, Elekta; and Hitachi) was used for PBT planning. Gross tumor volume (GTV) 1 was outlined on CT images, and clinical target volume (CTV) 1 was defined as GTV1 with a 4-mm margin in all directions, while avoiding critical organs at risk (brain stem, spinal cord, optic nerves, optic chiasma, and mandible bone). CTV1 was expanded by 3 mm in all directions to create planning target volume (PTV) 1 with the aim to compensate for setup uncertainty. Because of the presence of penumbra and range of the radiation, the following beam-specific margins were set: Proximal, distal, and lateral margins as well as the smearing margin as a margin for bolus (23). The planning CT/MRI images for the boost plan were captured after 15 episodes of irradiation, and GTV2 was outlined. CTV2 was defined by adding a 3-mm margin around GTV2 and modified to exclude organs at risk. PTV2 was created in the same way as that for PTV1. Two portals of 150-MeV noncoplanar beams were arranged at optimal angles to avoid excess-dose exposure to the normal tissue. Doses were calculated based on a pencil-beam algorithm. A spread-out Bragg peak was

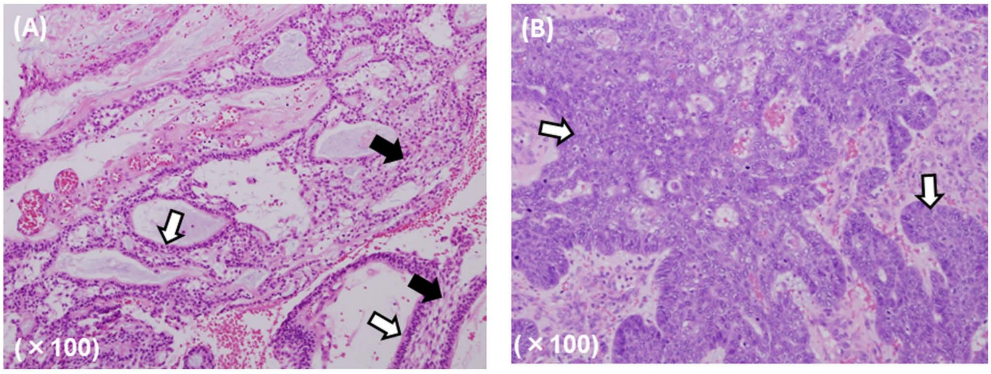

Figure 1. Histological findings by hematoxylin-eosin staining. (A) Ameloblastoma: Histological specimen of the first biopsy in October 2007. The outer layer comprises several sheets of high columnar cells (white arrows) and, in an inner site, asteroid-shaped cells exhibit a loose and irregular arrangement (black arrows). The diagnosis is follicular-type ameloblastoma. (B) Ameloblastic carcinoma: Histological specimen of the fourth biopsy in March 2009. The specimen shows pleomorphism, nuclear hyperchromatism, increased mitotic ratio, cytologic atypia, foci of keratinization, and presence of several clear cells and tumor cells as seen in ameloblastoma along with marked cytological atypia (white arrows). The diagnosis is ameloblastic carcinoma. Magnification, x100.

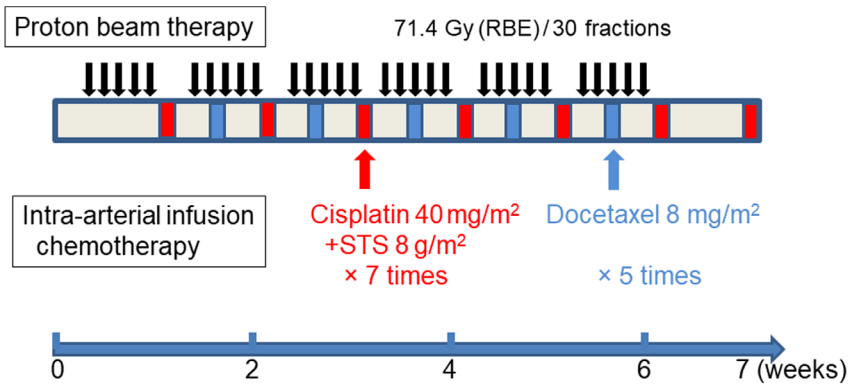

Figure 2. Treatment schedule. Concurrent therapy with daily proton beam therapy and weekly intra-arterial infusion chemotherapy. Cisplatin and docetaxel were infused once a week. STS was infused intravenously during the arterial infusion of cisplatin. STS, sodium thiosulphate; RBE, relative biological effectiveness.

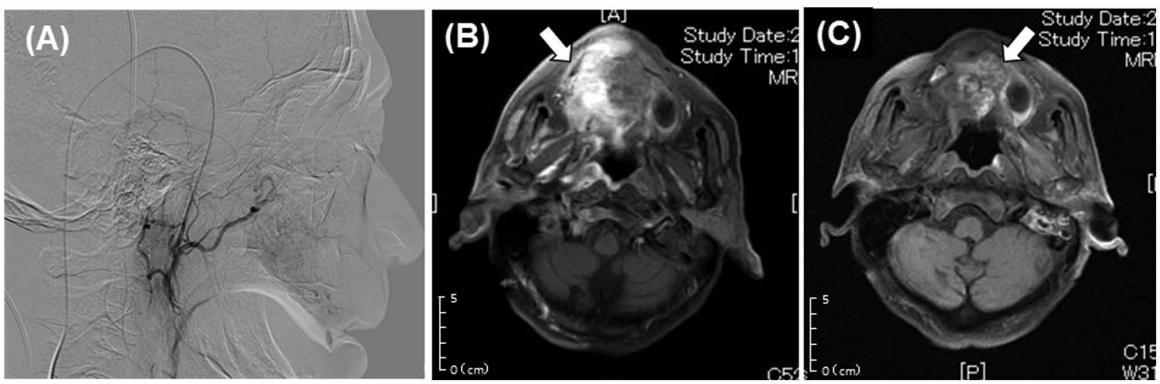

Figure 3. Flow check for the delivery of anticancer agents by contrast-enhanced T1-weighted axial magnetic resonance imaging. (A) Flow check by digital subtraction angiography using contrast medium. Flow check by enhanced magnetic resonance imaging via a catheter to cover the whole tumor; (B) the right side of the maxilla is highly enhanced (arrow), whereas (C) the left side is enhanced slightly (arrow).

tuned to the extent that was possible until PTV was exposed to a 90% isodose of the prescribed dose (Fig. 4). The PBT system (Hitachi) at our institution used a synchrotron and a passive scattering method in which a proton beam passed a bar ridge filter, a range shifter, and a bolus before entering the patient. A multileaf collimator, which could be formed into an irregular field shape, was used. Daily X-ray images were used for precise positioning. The patient was prescribed a dose of 45.0 Gy relative biological effectiveness (RBE) in 18 fractions to PTV1 (five fractions per week) as well as a dose of 26.4 Gy (RBE) in 12 fractions to PTV2 for the boost. The total irradiation dose was 71.4 Gy (RBE) in 30 fractions.

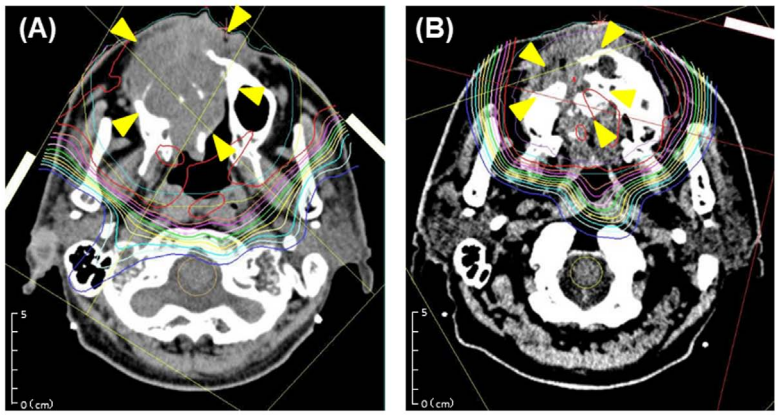

Figure 4. Dose distribution of proton beam therapy by axial computed tomography. (A) First plan: 45 Gy (RBE) in 18 fractions. (B) Boost plan: 26.4 Gy (RBE) in 12 fractions. Total dose was 71.4 Gy (RBE). Left eye, left optic nerve and optic chiasma were discharged totally in the boost plan. Yellow arrows indicate tumors. RBE, relative biological effectiveness.

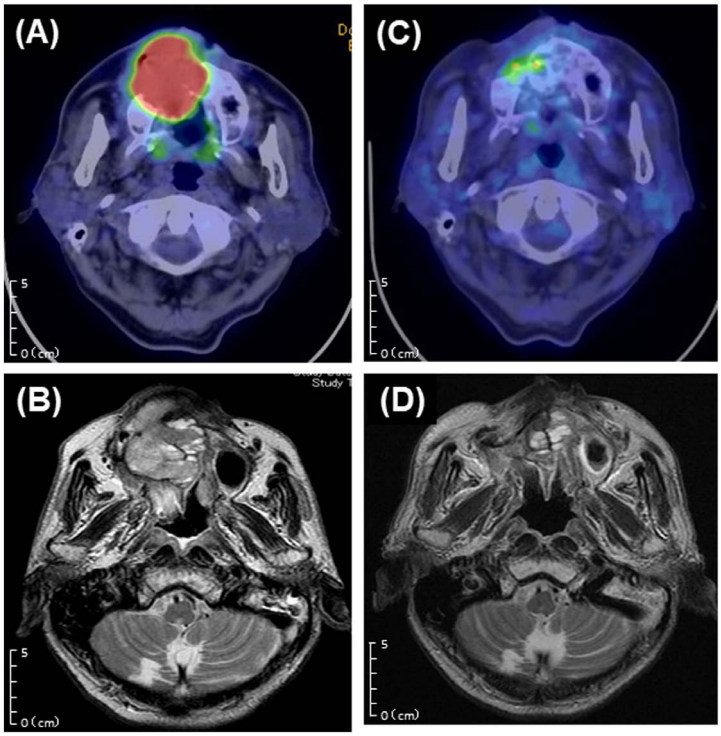

Figure 5. Comparison of before and after treatment. (A) Before treatment (FDG-PET/CT, axial, SUV_{max}=21.6). (B) Before treatment (T2-weighted MRI, axial); MRI shows a large heterogeneous mass occupying the right maxillary sinus and extending from the nasal cavity to sphenoid sinus. (C) After 3 months of treatment (FDG-PET/CT, axial, SUV_{max}=6.3). (D) After 6 months of treatment (T2-weighted MRI, axial). CT, computed tomography; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max}, maximum standardized uptake value. MRI, magnetic resonance imaging.

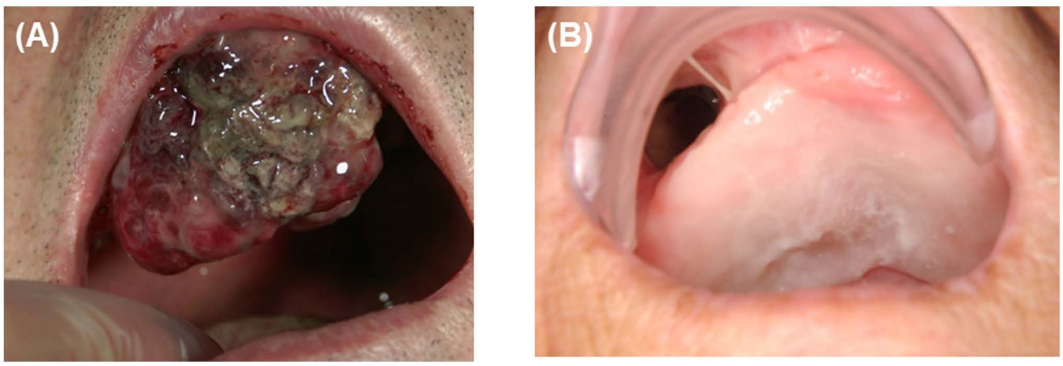

Figure 6. Comparison of the images of tumors before and after treatment. (A) Before treatment. (B) After 9 months of treatment.

Follow-up and outcomes. The treatment response was evaluated 3 months after treatment completion by contrast-enhanced MRI and clinical examination. Additional follow-up examination using CT, MRI or FDG-PET/CT was performed every 2-4 months for the first two years and every 4-6 months thereafter. The response was evaluated according to the Response Evaluation Criteria in Solid Tumors guidelines version 1.1, and the Common Terminology Criteria for Adverse Events version 4.0 was used to evaluate adverse effects (24). The patient experienced grade 3 mucositis, dermatitis, and neutropenia as early adverse events, but there was no grade 4 or higher toxicities. Additionally, as late adverse events, the patient developed grade 1 skin atrophy and hardening of the soft tissue on the right cheek after treatment and an oral maxillary fistula at the site of tumor three years after treatment. Furthermore, the patient experienced grade 2 right optic nerve disorder at four years after treatment and grade 2 radiation retinopathy of the right eye at six years after treatment. The patient achieved complete response 3 months after treatment based on the clinical assessment. The patient did not experience recurrence or distant metastases following treatment and died from another cause 94 months after the conclusion of treatment for AC (Figs. 5 and 6).

Discussion

Surgical resection is generally performed as an approach for recurrent AC. Chemotherapy and radiotherapy are not efficient and considered as treatment options for inoperable cases, with poor prognostic outcomes (7). Yoon *et al* reported that 5-year overall survival of 72.9% for AC and recurrence rate after surgical resection was reported as 28.3%, which was 92.3% in patients treated with conservative therapy using chemotherapy and radiotherapy (1). There are over 150 reports of patients treated for AC, with radiotherapy utilized in approximately one-third of the cases, especially in recent years (25-29). In majority of the cases, the therapeutic effects of conventional radiotherapy were inadequate, and high-dose radiation led to severe chronic disorders such as osteoradionecrosis (2).

To date, a few studies have reported radical radiation therapy for AC (12-14). However, it may not be a desirable treatment from the view of therapeutic effect because AC is resistant to X-ray therapy. PBT is a type of particle therapy, similar to CIT. In comparison with conventional radiotherapy, particle beams are characterized by their unique Bragg peak and can deliver high-dose radiation to the tumor while sparing normal tissues (18). Additionally, compared with conventional X-ray therapy, a higher antitumor effect by direct impairment of cancer cell DNA is expected (17). Importantly, the therapeutic effect of PBT was reported in non-SCC (15,16,19). One difference between proton beams and carbon ion beams is their RBE; the RBE of protons is approximately 1.1, whereas that of carbon ions is approximately 3.0. However, no significant difference in the therapeutic effect between PBT and CIT was reported (30). To date, only two case reports of particle therapy for AC was published, including one patient treated by CIT (15) and one patient treated with PBT (16); however, AC appeared to have arisen *de novo* in both cases. Most ACs appear to be *de novo*; however, few cases of secondary-type AC arising from pre-existing ameloblastoma were reported. The current case was diagnosed with secondary-type peripheral AC, which recurred shortly after surgery, advanced extensively, and exhibited high malignancy.

Recent studies assessing IAIC for locally advanced head and neck cancers to avoid surgery reported excellent treatment outcomes. Fuwa *et al* reported good clinical outcomes of treatment with weekly IAIC and radiotherapy in a series of 92 patients with head and neck cancer, including 84 patients with oral SCC (20). Mitsudo *et al* assessed treatment results with daily IAIC and conventional radiotherapy in a series of 112 cases with stage III and IV oral SCC and reported that the 5-year local control rate and over-all survival rate were 79.3 and 71.3%, respectively (11). Our previous study in which we used PBT and IAIC in T4 SCC of the maxillary gingiva, the 3-year local control and overall survival rates were 69 and 59%, respectively (31). In the current case, treatment of aggressive AC with a combination of IAIC and PBT achieved a good therapeutic effect. To the best of our knowledge, this is the first report of a good long-term course of 94 months with radical treatment using chemoradiotherapy for postoperative recurrent secondary-type AC. During the follow-up period, the patient had skin atrophy and non-infectious fistula in the right cheek. The cheek fistula had no effect on food and conversation, and the patient did not wish for reconstructive surgery. Although the tumor was close to the right optic nerve, visual acuity was maintained for several years. However, the patient suffered from ischemic syndrome of the right eye and developed grade 2 optic nerve disorder four years after treatment. Blood flow disturbance after radiation therapy have been reported in the past (32,33), and are considered as adverse event of the treatment. It indicates that additional effort to avoid risk organ may be necessary to reduce adverse events with this therapeutic approach. In this study, a passive scattering method, which is difficult to apply for complicated cases, was used to deliver the proton beam. In the future, intensity-modulated proton beam therapy using a pencil bam scanning system can be used to reduce late adverse events.

Although case series studies with large samples are necessary for further elucidation of this treatment approach, the current case illustrates the good long-term outcome of recurrent secondary-type AC treated with PBT and IAIC. The beneficial therapeutic effect and organ preservation were achieved without any severe late adverse events, suggesting that PBT in combination with IAIC might be an effective treatment option for inoperable, locally advanced AC.

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Availability of data and materials

The data used and/or analyzed during this published article are available from the corresponding author on reasonable request.

Authors' contributions

KT and NF contributed to the study concept and clinical study design. KT and TN collected data. KT wrote the initial draft of the manuscript. KM and MM conducted the literature search. HS performed histopathological examinations. TN and TK prepared the treatment plans of the case and carried out follow-up. AT evaluated the patient's radiographs. TK established the patient's setup preparation and verifications. KT, AT, NF, TK and HS evaluated the patients and participated in the therapy. KT, KM, NF, and MM prepared the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This treatment method was approved by The Ethics Committee of Southern Tohoku Research Institute for Neuroscience. Written consent was obtained from the patient at our institution.

Patient consent for publication

The reported case has been approved by the patient for academic use only.

Competing interests

The authors declare that they have no competing interests.

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