A custom mouthpiece with lip bumper for osteoradionecrosis risk reduction following carbon-ion radiotherapy for adenoid cystic carcinoma of the lip


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Title: A custom mouthpiece with lip bumper for osteoradionecrosis risk reduction following carbon-ion radiotherapy for adenoid cystic carcinoma of the lip

Short Running Title: A custom mouthpiece to reduce ORN after CIRT

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Abstract

**Purpose:** A custom mouthpiece with lip bumper for carbon-ion radiotherapy (CIRT) of tumors of the lip was developed with the goal of reducing the incidental exposure of the maxilla.

**Methods and Materials:** The mouthpiece was manufactured using a thermoplastic ethylene-vinyl acetate copolymer. This was employed in a patient with primary adenoid cystic carcinoma of the right lip without invasion of the maxilla. To evaluate spacer utility, the volume of maxilla receiving more than 50 Gy (relative biological effectiveness, V50) with and without the spacer was calculated using dose-volume histogram (DVH) analysis in a simulation study and subsequently treated.

**Results:** In the simulation study, DVH analysis demonstrated a 46% dose reduction in the high-dose area of the maxilla with mouthpiece usage (V50 = 2.21 mL) compared to non-usage (V50 = 4.11 mL). The mouthpiece was well-tolerated. Eight years after CIRT, no late dermatitis, oral mucositis, or osteoradionecrosis was observed.

**Conclusions:** A custom-made mouthpiece with a lip bumper successfully reduced the incidental exposure of the maxilla during CIRT.
Introduction

Lips are a common location for minor salivary gland tumors, including adenoid cystic carcinoma (ACC). Surgery is the preferred treatment for ACC, though patients refusing or ineligible for surgery may receive radiotherapy (RT). However, conventional RT is ineffective in treating ACC due to inherent radioresistance. Carbon-ion radiotherapy (CIRT) has demonstrated efficacy with acceptable toxicity. Consequently, CIRT has been viewed as adaptable for treating ACC of the lip.

Osteoradionecrosis (ORN) is a serious adverse event in head and neck cancer patients receiving CIRT. Grade 2 or higher maxillary ORN following CIRT was reported to be 19.0% in 2014. Further study has demonstrated that maxillary volume receiving more than 50 Gy (relative biological effectiveness [RBE], V50) CIRT delivered in 16 fractions, along with the inclusion of teeth within the planning target volume (PTV), are significant independent risk factors for ORN. To reduce the risk of maxillary ORN, a reduction of V50 is required, and intraoral devices are one modality by which the lip and jaw are positioned so as to reduce the dose. However, no devices to prevent ORN from lip cancer have been reported for CIRT.

In this technical report, we introduce and evaluate the efficacy of a custom-made mouthpiece with a lip bumper for the reduction of maxilla V50 in patients with ACC of the lip(s) treated with CIRT.

Methods and materials
Patient

An 85-year-old male patient presented to our hospital with a primary ACC located on the right side of the upper lip without invasion of the maxilla. The patient found the esthetic impact and articulatory dysfunction after surgery to be unacceptable and was subsequently referred for CIRT. The patient had no other known risk factors associated with maxillary ORN, including tobacco or alcohol usage, or a surgical history. The patient had 28 teeth and maintained adequate oral hygiene.

Mouthpiece

A custom-made mouthpiece is created in our institution for all head and neck cancer patients, as described previously.6,7 The mouthpiece is constructed using a thermoplastic ethylene-vinyl acetate (EVA) copolymer suitable for use in charged-particle therapy.8 For lip tumors, the maxilla is incorporated into the PTV because of its anatomical adjacency to the usual lip position. Therefore, a bumper moves the lip anteriorly so as to protect the maxilla from irradiation (Figure 1a, b). Lip bumpers are orthodontic devices that help create a larger space between the front of the teeth and the lip.9,10 For the lip bumper in this case, the EVA base occupied the entire oral vestibule, excluding the superior labial frenulum (Figure 1c, d).

CIRT

The CIRT technique has been described previously.13 Following positioning
and replicable immobilization, the gross tumor volume (GTV) was defined on fusion of magnetic resonance imaging (MRI) with 2-mm computed tomography (CT) imaging, with clinical target volume (CTV) including a 5–7 mm expansion of the GTV. PTV was generated with an additional 2–3-mm margin from CTV. In this case, 57.6 Gy (RBE) CIRT was delivered in 16 fractions over four weeks, with four treatments per week in line with institutional scheduling. Treatment planning was performed using Xio-N (ELEKTA, Stockholm, Sweden, and Mitsubishi Electric, Tokyo, Japan). The dose distribution and port angles are shown in Figure 2a. Two ports were used, and scanning CIRT was employed.

**Follow-up and ORN evaluation**

After CIRT, maxillary ORN was evaluated based on clinical symptoms, macroscopic examination, and the findings of CT and MRI conducted every 2–3 months. The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used to define toxicity.

**Simulation study**

A simulation study was conducted to evaluate spacer utility. Maxillary V50 with and without the spacer was calculated. Dose-volume histogram (DVH) analysis was performed using the MIM software (MIM Software Inc., Cleveland, OH, USA) to compare the irradiation dose to the maxilla volume with and without the mouthpiece.
Pre-treatment diagnostic CT images in the same case were used to simulate the treatment without a mouthpiece (Figure 2b). Maxillary DVH included both the alveolar and palatine processes of the maxilla; the maxillary sinuses were excluded.

**Results**

CIRT was completed over a period of 29 days, as scheduled. During CIRT, grade 1 dermatitis and grade 3 mucositis appeared in the upper lip and labial gingiva, respectively, but no mucositis was observed in the palatal mucosa. The mouthpiece itself elicited pain during treatment due to its direct contact with the oral mucosa, which was controlled with nonsteroidal anti-inflammatory drugs and 2% lignocaine gel. And during the treatment, there was no change in the gingiva, but the upper lip swelled slightly. However, it was not significant enough to affect the accuracy of the treatment.

Eight years after CIRT, no late dermatitis (Figure 3a); oral mucositis; dental issues such as dental caries, periapical abscesses, and periodontitis (Figure 3b); or ORN was observed (Figure 3c), and lip ACC was controlled clinically and radiologically.

In the simulated treatment without the mouthpiece, the maxilla was irradiated with a high dose (Figure 2b). With mouthpiece usage, the upper lip was extended and the tumor laterally enlarged compared to non-usage. In the comparison study, DVH analysis demonstrated a reduction in dose in the high-dose area of the maxilla with mouthpiece usage (V50 = 2.21 mL) compared to non-usage (V50 = 4.11 mL) (Figure 2c). One and four teeth were present in the PTV when the mouthpiece was and was not
used, respectively.

Discussion

In limited cases, CIRT may be indicated for head and neck non-squamous cell carcinoma (SCC).\textsuperscript{4} In patients with lip ACC who find the esthetic change and articulatory dysfunction caused by resection unacceptable, CIRT appears to be a potential alternative for definitive treatment. Therefore, upon consideration of ORN risk, which may ultimately lead to surgical intervention, careful deployment of dose volumes while maximally sparing the maxilla is required. Herein, an ACC of the lip in close proximity to the maxilla was treated with CIRT using a custom-fitted mouthpiece so as to reduce the maxillary dose.

A previous study has reported the independent risk factors for developing maxillary ORN after CIRT. On multivariate analysis, V50 (≥ 3.0 mL) and the presence of teeth in the PTV were identified as independent risk factors.\textsuperscript{5} Consequently, efforts to reduce the volume of the maxilla receiving a radiation dose of >50 Gy (RBE) have been ongoing. Herein, DVH analysis revealed a reduction in V50 from 4.11 mL to 2.21 mL with a mouthpiece. The lip bumper seems to be effective in reducing maxillary dose and, by extension, the risk of maxillary ORN for lip ACC treated with CIRT.

Similarly, dosimetric parameters have been reported as risk factors for ORN in the mandible. Musha et al. reported that doses of 30 Gy (RBE) to the mandible and teeth caused ORN at 29.5 ± 6.7 cc and 3.9 ± 1.8 cc, respectively, with cut-off values at
16.5 cc and 1.8 cc, respectively. The mouthpiece described may be applied to lower lip tumors as well, which may reduce the risk of mandibular ORN.

Lip cancer is a common cancer of the head and neck and is generally SCC. Definitive treatment of early lip SCC involves surgical resection or RT, generally incorporating either conventional photon RT or brachytherapy. While cases of lip SCC treated with RT show good disease control, there is a risk of ORN. Spacer usage has been described in the brachytherapy literature for lip SCC, but to date, there have been no such reports on photon RT. For lip cancer with no extension to the jawbone, photon RT using a lip bumper may be effective, sparing the maxilla from irradiation and preventing the risk of ORN.

In non-SCC cases requiring escalated treatment doses, charged particle therapy such as CIRT and proton beam therapy (PBT) may be considered, offering improvement in RBE and dose distribution in comparison with conventional RT. Charged particle therapy, in particular, should be considered for radioresistant diseases. To date, there has only been one report on the use of a spacer using the lip bumper technique for lip tumors in PBT. Srivastava et al. reported the fabrication and benefits of a modified radiation stent made of heat-polymerized acrylic resin with bilabial protrusion of the lips, which was used in PBT for salivary polymorphous adenocarcinoma of the upper lip. However, their clinical report did not evaluate the radiation dose to the maxilla. In our simulation study, we assessed the dose to the maxilla with and without the mouthpiece with a lip bumper and demonstrated the
usefulness of the lip bumper.

In our hospital, we are using floor-mounted kV X-ray image-guided radiation therapy systems\textsuperscript{20} for head and neck cancer patients during CIRT. While the mouthpiece material, EVA, has a low CT number of approximately - 66.85 Hounsfield unit\textsuperscript{8} and is not clearly visible on X-ray images. However, the correct fit of the mouthpiece in the oral cavity can be recognized by X-ray images of the maxilla and mandible positions. The position of the mouthpiece and lips is also confirmed by marking the position of the upper lip with a line on the mouthpiece and directly observing each irradiation.

Conclusions

A custom-made mouthpiece with a lip bumper was employed in CIRT to reduce the maxillary dose. The patient tolerated the treatment well, with acceptable treatment toxicity, and DVH simulation demonstrated a 46% reduction in maxillary dose, with expected concomitant reduced ORN risk. Further evaluation in a dedicated cohort is warranted. In addition, evaluation of the dental sequelae of CIRT is also a future concern.

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Figure captions

Figure 1.
A custom-made lip bumper to protect the maxilla from irradiation
a. Mouthpiece with the lip bumper viewed from the lingual side (arrow)
b. Mouthpiece with the lip bumper viewed from the palatal side (arrow)
c. Bumped lip position with a custom-made mouthpiece
d. T1-weighted contrast-enhanced axial magnetic resonance image of the lip tumor with the lip bumper

Figure 2.
Dose distribution in the maxilla
a. Actual clinical results of dose distribution with the mouthpiece
b. Clinical results of dose distribution without the mouthpiece in a simulated treatment
c. Dose-volume histogram for the maxilla with and without the mouthpiece
Contours: red, gross tumor volume; yellow, planning target volume

Figure 3.
Clinical results 8 years after carbon-ion radiotherapy
a. Skin findings
b. Oral findings
c. Maxillary bone findings on T1-weighed axial magnetic resonance images
Figure 2

(a) 

(b) 

(c) 

Graph showing volume vs. dose with and without mouthpiece.
Figure 3
(a)
(b)
(c)
Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: