Teaching Case

The Efficacy of a Custom-Made Mouthpiece With Spacer to Reduce Osteoradionecrosis in Carbon-Ion Radiation Therapy for Tongue-Base Tumor

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Introduction

We previously demonstrated the efficacy and utility of carbon-ion radiation therapy (CIRT), finding acceptable toxicity with preserved speech and swallowing function in the setting of locally advanced tongue carcinoma.\textsuperscript{1} The 5-year local control rate and overall survival rate were 92.0\% and 72\%, respectively, among 18 patients with locally advanced adenoid cystic carcinoma of the tongue base. However, osteoradionecrosis (ORN) of the mandibular bone remains a serious adverse event for patients receiving CIRT. The incidence of grade 3 mandibular ORN was 11.1\%. Further study found that the volume of maxilla receiving more than 50 Gy (relative biological effectiveness [RBE]) across 16 fractions (maxilla V50 Gy [RBE] [mL]) and the presence of teeth within the planning target volume (PTV) were significant independent risk factors for ORN.\textsuperscript{2} As such, reducing the volume irradiated with high dose is one key way to reduce the risk of mandibular ORN.

Spacers are widely used to prevent ORN in brachytherapy for tongue cancer.\textsuperscript{3,4} However, with regard to external photon radiation therapy (RT) for tongue carcinoma, there have been no reports on the utility of spacers focused on prevention of ORN, perhaps because of the dose distribution inherent to photon RT. CIRT offers improved lateral dose distribution with minimal target exit dose\textsuperscript{1} and thereby may benefit from the employment of a spacer-including mouthpiece.

In this technical report, we introduce and evaluate the utility of a spacer-including mouthpiece with the aim of producing reduced mandible V50 for the treatment of tongue carcinoma.

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Methods and materials

Patient example

A patient had a primary adenoid cystic carcinoma located in the right tongue base, with invasion of the intrinsic muscle of the tongue (Fig 1a). The tumor did not involve mandibular bone. There was no lymph node involvement and no evidence of distant metastasis at presentation. The clinical stage was evaluated as T4aN0M0. The patient declined radical surgery and was referred for CIRT. The patient had no other known risk factors to influence the development of mandibular ORN, including no history of surgery, drinking, and smoking. In addition, the number of teeth in the oral cavity was 27, and the oral hygiene condition was good.

Mouthpiece

The mouthpiece was constructed as described previously.5 For RT treatment planning of tongue-base tumors, the mandibular bone is widely included in the PTV, with natural tongue positioning. To spare the mandibular bone from irradiation, a spacer was applied to the mouthpiece (Fig 1b). The spacer, which was constructed with a thermoplastic ethylene-vinyl acetate copolymer base and occupied the entire submandibular space, was interposed between the tongue and mandibular bone to reduce the mandibular dose (Figs 1c and d). The thickness was approximately 13 mm, and device construction took approximately 100 minutes. The cost of the spacer has been described previously.5

CIRT

CIRT procedures have been previously described.6 The dose of carbon ions was expressed in photon-equivalent doses (Gy [RBE]), which were defined as the physical dose multiplied by the RBE of the carbon ions.7 The biological flatness of the spread-out Bragg peak (SOBP) was normalized by the survival fraction of human salivary gland tumor cells at the distal region of the SOBP, where the RBE of carbon ions was assumed to be 3.0. The gross tumor volume (GTV) was defined as the gross extent of the tumor as observed on intraoral endoscopy, computed tomography (CT), and magnetic resonance imaging. The clinical target volume consisted of the GTV plus an additional 5- to 7-mm margin. The PTV had an additional margin of 2 to 3 mm added to the clinical target volume. CIRT was administered on a fractionated schedule comprising 57.6 Gy (RBE) in 16 fractions over 4 weeks and was performed as previously described.5 The dose distribution and beam direction are shown in Figure 2a. The dose was delivered using 3 portals with the passive beam method.

Evaluation

The follow-up of acute mucosal reactions consisted of daily inspection until sequelae resolution post-CIRT. A diagnosis of mandibular ORN was indicated on the basis of clinical symptoms, macroscopic observation, and the findings of CT and magnetic resonance imaging conducted every 2 to 3 months. Oral mucositis and ORN were assessed per the Common Terminology Criteria for Adverse Events, version 3.0.

Figure 1  (a) Axial and coronal T1-weighted, contrast-enhanced magnetic resonance images before carbon-ion radiation therapy. The tumor invaded the intrinsic muscle but did not involve the mandibular bone. (b) Superior and posterior views of a custom-made mouthpiece with spacer function (red arrows). (c) Diagrammatic representation of the custom-made mouthpiece with spacer function. The mouthpiece was interposed between the tongue and mandibular bone. (d) Axial and coronal T1-weighted, contrast-enhanced magnetic resonance images of the tongue-base tumor with the spacer mouthpiece (red arrows). The tongue was displaced to the left and separated from the mandibular bone.
Comparison study

To evaluate the utility of the mouthpiece, a simulation study was performed. A mandible V50 with and without the mouthpiece was calculated. To simulate CIRT without a mouthpiece, pretreatment diagnostic CT images without the mouthpiece were used. Identical GTV, margins, and beam directions were reproduced. The mandibular bone included the chin to the temporomandibular joint. Additionally, the root portion of each tooth embedded in the mandibular bone was included, although the crown was excluded. A dose-volume histogram analysis was performed to compare the mandible V50 with and without the mouthpiece, calculated using MIM (MIM Software Inc., Cleveland, OH). We evaluated the percent change of mandible V50, as well as the number of teeth irradiated, with and without the mouthpiece.

Results

Grade 3 acute mucositis was observed in the dorsal surface and lateral border of the tongue during CIRT treatment. No mucositis was noted on the right lingual gingiva. Although the mouthpiece touched the oral mucosa during CIRT, eliciting pain, this was controlled with nonsteroidal anti-inflammatory drugs alone. Two years after treatment, ORN has not been observed in the right mandibular bone.

A simulated dose distribution of CIRT without the mouthpiece is shown in Figure 2b. A dose-volume histogram analysis demonstrated that high dose to the mandible was reduced using the mouthpiece (Fig 3). In the comparison study, mandible V50 with the mouthpiece

![Figure 2](image_url)

(a) Dose distributions of carbon-ion radiation therapy. Carbon-ion radiation therapy was administered at 57.6 Gy (relative biological effectiveness) in 16 fractions using 3 portals. Isodose lines corresponded to 95%, 90%, 70%, 50%, 30%, and 10% dose areas. The planning target volume was demarcated by yellow lines. (b) A simulated dose distribution of carbon-ion radiation therapy without mouthpiece.

![Figure 3](image_url)

Dose-volume histogram for the mandibular bone with and without the mouthpiece.
was 1.7 mL, but the mandible V50 without the mouthpiece was 5.46 mL, a 69% reduction of mandible V50. The number of teeth in the PTV with the mouthpiece was 0, whereas that without the mouthpiece was 2.

**Discussion**

In CIRT, a precise conformal dose distribution to the target is possible because of the unique physical characteristics of heavy-ion particle beam RT, including the ability to form SOBPs with minimal lateral scattering. Therefore, a custom-made mouthpiece with spacer function has the potential not only to fix the tongue and jaw but also to reduce the development of ORN and mucositis of the lower gingiva in CIRT for tongue carcinomas. Previously, V50 and the presence of teeth within the PTV have been shown to be independent risk factors for ORN. In our simulation study, spacer-mouthpiece usage decreased mandible V50 from 5.46 mL to 1.7 mL. The mouthpiece could also reduce the number of teeth in the PTV for tongue carcinomas. The patient in the case presented additionally did not develop ORN for 2 years after CIRT, but longer-term follow-up may be needed to fully evaluate the risk for this patient. A comprehensive study is needed to determine the relative risk reduction offered by mouthpiece usage.

CIRT is principally offered for treatment of radio-resistant tumors, such as salivary gland carcinoma and mucosal melanoma. Squamous cell carcinomas, the most common of oral cancers, are well indicated for brachytherapy and photon RT with and without chemotheraphy. Spacers have been employed in brachytherapy for tongue squamous cell carcinomas, reducing irradiation of the mandibular bone. Murakami et al reported the efficacy of modular, lead-lined spacers in the prevention of complications in high-dose-rate brachytherapy for mobile tongue cancer. When a 2-mm lead shield was added to the modular spacer, significantly more shielding was obtained, with absorbed doses reduced by 79%. Miura et al reported the efficacy of a spacer in the prevention of mandibular complications in low-dose-rate brachytherapy for 103 patients with oral tongue carcinoma, and found that their spacer reduced approximately 50% of the absorbed dose to the lingual side surface of the lower gingiva in the absence of a spacer. Absolute incidence of ORN was 2.1% (1 of 48) and 40.0% (22 of 55) with and without a spacer, respectively, and the difference was statistically significant by univariate analysis.

With regard to external RT for tongue carcinoma, ORN is a severe complication. Foster et al reported on a series of 140 patients with oral cancer treated with chemoradiation therapy, and the rate of ORN requiring surgery was 12.8% for patients with tongue cancer. With regard to photon RT, high-dose irradiation to the mandible has been reported previously as a risk factor for ORN. The MD Anderson Head and Neck Cancer Symptom Working Group reported the dosimetric parameters associated with ORN in 199 patients with oropharyngeal cancer treated with photon RT. In the study, the mandibular mean dose was significantly higher in the ORN cohort compared with the non-ORN cohort (48.1 vs 43.6 Gy; \( P < .0001 \)). Recently, intensity modulated RT (IMRT) has been widely employed in the treatment of head and neck tumors. In IMRT, a higher dose is localized to the GTV, with a boost dosage delivered in some cases. Although IMRT has led to reduced toxicity rates compared with conventional RT, protecting normal tissue from radiation injuries has proven to be a challenge because there are occasions when critical organs lie close to the tumor, which makes the delivery of a curative radiation dose with sufficient space for dose fall-off and organ sparing impossible.

Maeschschall et al compared the incidence of ORN after IMRT for patients with oropharyngeal cancer with that of conventional 3-dimensional conformal RT techniques, with 145 patients in the conventional RT group and 89 patients in the IMRT group. They found no difference in the rate of ORN between the groups: 16 of 145 patients (11%) had mandible ORN in the conventional RT group and 9 of 89 patients (10.2%) in the IMRT group. However, they made no mention of the use of a mouthpiece with spacer. Proton RT, compared with IMRT, can deliver high-dose radiation to a tumor while minimizing the doses delivered to the surrounding normal tissues.

Takayama et al reported on a series of 33 patients with tongue carcinoma who were treated with proton RT, combined with selective intra-arterial infusion chemotherapy using a spacer, and no grade 3 ORN was reported.

Even in CIRT and proton RT, a key method to limit exposure to the immediate adjacent organs at risk is to manually displace these organs so that they are located some distance from the tumor. This might be accomplished by introducing a spacer between them, which is seen already in various indications for IMRT and notably for CIRT of the gastrointestinal tract. However, there have been no reports on the utility of spacers focused on the prevention of ORN for patients with head and neck tumor treated with IMRT or CIRT. Here, we demonstrate an efficacious spacer-incorporating mouthpiece for CIRT in patients with head and neck cancer, which may additionally allow for improved dose targeting of tumor tissue in IMRT and improved normal tissue sparing and reduced ORN risk. Further evaluation is warranted.

**Conclusions**

A custom mouthpiece with spacer was coupled with CIRT for the reduction of incidental exposure to the
mandible and other healthy mouth structures. Reduced ORN risk was noted in a pilot study with this mouthpiece. Further evaluation in a dedicated cohort may be warranted.

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