Advances in Radiation Oncology (2019) **4**, 15-19

advances
in radiation oncology

www.advancesradonc.org

Teaching Case

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

Hiroaki Ikawa DDS, PhD [a,*], Masashi Koto MD, PhD [a], Daniel K. Ebner BS [a,b], Kazuhiko Hayashi MD, PhD [a], Ryo Takagi DDS, PhD [a], Morio Tonogi DDS, PhD [c], Takeshi Nomura DDS, PhD [d], Hiroshi Tsuji MD, PhD [a], Tadashi Kamada MD, PhD [a]

[a]Hospital of the National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan; [b]Brown University Alpert Medical School, Providence, Rhode Island; [c]Department of Oral and Maxillofacial Surgery, Nihon University School of Dentistry, Tokyo, Japan; and [d]Department of Oral Medicine, Oral and Maxillofacial Surgery, Tokyo Dental College, Tokyo, Japan

Received 26 April 2018; revised 14 August 2018; accepted 14 August 2018

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.[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.[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.[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[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.

Sources of support: This work had no specific funding.

Conflicts of interest: The authors have no conflicts of interest to disclose.

* Corresponding author. Hospital of the National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Sciences and Technology, 4-9-1 Anagawa, Inage-ku, Chiba-shi 263-8555, Japan.

E-mail address: ikawa.hiroaki@qst.go.jp (H. Ikawa).

https://doi.org/10.1016/j.adro.2018.08.016

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.

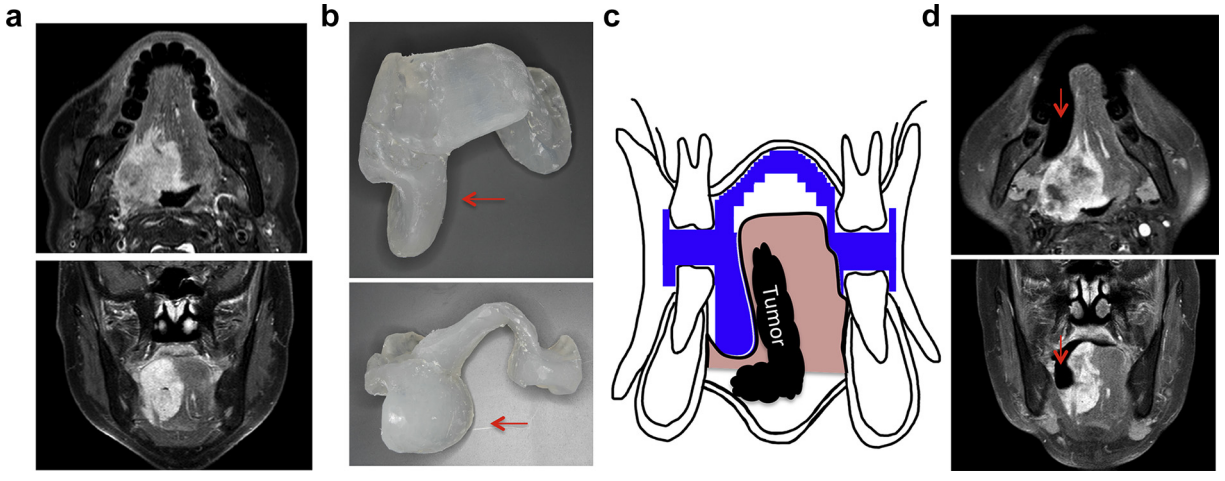

Figure 1 (a) Axial and coronal T1-weighted, contrast-enhanced magnetic resonance images before carbon-ion radiation therapy. The tumor invaded the intrinsic muscle but did not involve the mandibular bone. (b) Superior and posterior views of a custom-made mouthpiece with spacer function (red arrows). (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.

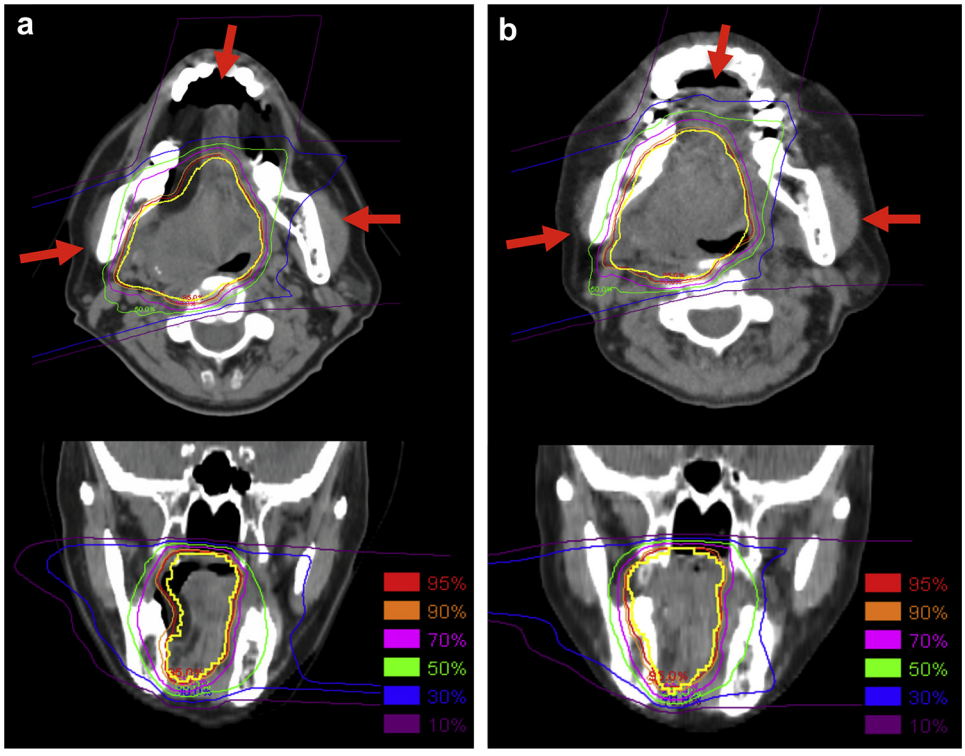

Figure 2 (a) Dose distributions of carbon-ion radiation therapy. Carbon-ion radiation therapy was administered at 57.6 Gy (relative biological effectiveness) in 16 fractions using 3 portals. Isodose lines corresponded to 95%, 90%, 70%, 50%, 30%, and 10% dose areas. The planning target volume was demarcated by yellow lines. (b) A simulated dose distribution of carbon-ion radiation therapy without mouthpiece.

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

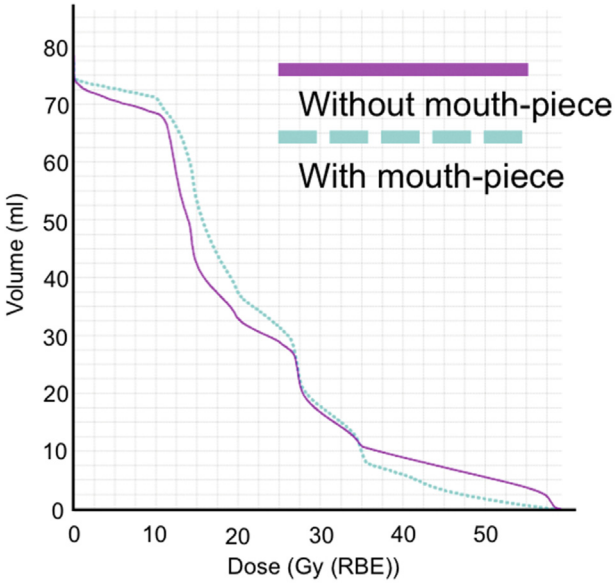

Figure 3 Dose-volume histogram for the mandibular bone with and without the mouthpiece.

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.[8] 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.[2] 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 radioresistant tumors, such as salivary gland carcinoma and mucosal melanoma.[6] Squamous cell carcinomas, the most common of oral cancers, are well indicated for brachytherapy and photon RT with and without chemotherapy.[3,4,9] Spacers have been employed in brachytherapy for tongue squamous cell carcinomas, reducing irradiation of the mandibular bone.[3,4] Murakami et al[3] 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.[4] reported on 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[10] 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.[11,12] The MD Anderson Head and Neck Cancer Symptom Working Group[12] 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,[13] 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.

Maesschalck et al[14] 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.[15] Takayama et al[16] 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 normaltissue 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.

Acknowledgments

The authors deeply thank Ms. Minami Ikawa for the preparation of the excellent medical illustrations.

References

1. Koto M, Hasegawa A, Takagi R, et al. Evaluation of the safety and efficacy of carbon ion radiotherapy for locally advanced adenoid cystic carcinoma of the tongue base. *Head Neck*. 2016;38:E2122-E2126.
2. Sasahara G, Koto M, Ikawa H, et al. Effects of the dose-volume relationship on and risk factors for maxillary osteoradionecrosis after carbon ion radiotherapy. *Radiat Oncol*. 2014;9:92.
3. Murakami S, Verdonschot RG, Kakimoto N, et al. Preventing complications from high-dose rate brachytherapy when treating mobile tongue cancer via the application of a modular lead-lined spacer. *PLoS One*. 2016;11:e0154226.
4. Miura M, Takeda M, Sasaki T, et al. Factors affecting mandibular complications in low dose rate brachytherapy for oral tongue carcinoma with special reference to spacer. *Int J Radiat Oncol Biol Phys*. 1998;41:763-770.
5. Hiroaki Ikawa, Masashi Koto, Daniel K Ebner. A custom-made mouthpiece incorporating tongue depressors and elevators to reduce radiation-induced tongue mucositis during carbon-ion radiotherapy for head and neck cancer. *Pract Radiat Oncol*. 2018;8:e27-e31.
6. Mizoe JE, Hasegawa A, Jingu K, et al. Results of carbon ion radiotherapy for head and neck cancer. *Radiother Oncol*. 2012;103:32-37.
7. Inaniwa T, Kanematsu N, Matsufuji N, et al. Reformulation of a clinical-dose system for carbon-ion radiotherapy treatment planning at the National Institute of Radiological Sciences, Japan. *Phys Med Biol*. 2015;60:3271-3286.
8. Kamada T. The characteristics of carbon-ion radiotherapy. In: Tsujii H, Kamada T, Shirai T, Noda K, Tsuji H, Karasawa K, eds. *Carbon-Ion Radiotherapy: Principles, Practices, and Treatment Planning*. Tokyo, Japan: Springer Science & Business Media; 2013:13-16.
9. National Comprehensive Cancer Network. Practice guidelines in oncology, version 2.2017. Available at https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed July 7, 2017.
10. Foster CC, Melotek JM, Brisson RJ, et al. Definitive chemoradiation for locally-advanced oral cavity cancer: A 20-year experience. *Oral Oncol*. 2018;80:16-22.
11. Tsai CJ, Hofstede TM, Sturgis EM, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys*. 2013;85:415-420.
12. MD Anderson Head and Neck Cancer Symptom Working Group. Dose-volume correlates of mandibular osteoradionecrosis in oropharynx cancer patients receiving intensity-modulated radiotherapy: Results from a case-matched comparison. *Radiother Oncol*. 2017;124:232-239.
13. Beadle BM, Liao KP, Chambers MS, et al. Evaluating the impact of patient, tumor, and treatment characteristics on the development of jaw complications in patients treated for oral cancers: A SEER-Medicare analysis. *Head Neck*. 2013;35:1599-1605.
14. Maesschalck T, Dulguerov N, Caparrotti F, et al. Comparison of the incidence of osteoradionecrosis with conventional radiotherapy and intensity-modulated radiotherapy. *Head Neck*. 2016;38:1695-1702.
15. Foote RL, Stafford SL, Petersen IA, et al. The clinical case for proton beam therapy. *Radiat Oncol*. 2012;7:174.
16. Takayama K, Nakamura T, Takada A, et al. Treatment results of alternating chemoradiotherapy followed by proton beam therapy boost combined with intra-arterial infusion chemotherapy for stage III-IVB tongue cancer. *J Cancer Res Clin Oncol*. 2016;142:659-667.