Accurate delineation of mucosal lesions in treatment planning computed tomography using iodine paste markers for oral mucosal melanoma

Hiroaki Ikawa DDS, PhD, Masashi Koto MD, PhD, Tapesh Bhattacharyya MD, DNB, Takashi Kaneko MD, Hirotoshi Takiyama MD, PhD, Makoto Shinoto MD, PhD, Akihiro Nomoto MD, PhD, Shigeru Yamada MD, PhD, Hiroshi Tsuji MD, PhD

PII: S1879-8500(22)00048-0
DOI: https://doi.org/10.1016/j.prro.2022.01.009
Reference: PRRO 1477

To appear in: Practical Radiation Oncology

Received date: 27 December 2021
Revised date: 25 January 2022
Accepted date: 27 January 2022

Please cite this article as: Hiroaki Ikawa DDS, PhD, Masashi Koto MD, PhD, Tapesh Bhattacharyya MD, DNB, Takashi Kaneko MD, Hirotoshi Takiyama MD, PhD, Makoto Shinoto MD, PhD, Akihiro Nomoto MD, PhD, Shigeru Yamada MD, PhD, Hiroshi Tsuji MD, PhD, Accurate delineation of mucosal lesions in treatment planning computed tomography using iodine paste markers for oral mucosal melanoma, Practical Radiation Oncology (2022), doi: https://doi.org/10.1016/j.prro.2022.01.009

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc. on behalf of American Society for Radiation Oncology.
Accurate delineation of mucosal lesions in treatment planning computed tomography using iodine paste markers for oral mucosal melanoma

Hiroaki Ikawa, D.D.S., Ph.D.¹, Masashi Koto, M.D., Ph.D.¹, Tapesh Bhattacharyya, M.D., DNB², Takashi Kaneko, M.D.¹, Hirotsushi Takiyama, M.D., Ph.D.¹, Makoto Shinoto, M.D., Ph.D.¹, Akihiro Nomoto, M.D., Ph.D.¹, Shigeru Yamada, M.D., Ph.D.¹, and Hiroshi Tsuji M.D., Ph.D.¹.

¹QST Hospital, National Institutes for Quantum Science and Technology, Chiba, Japan.
²Tata Medical Center, Kolkata, India

Corresponding Author Name & Email Address
Hiroaki Ikawa, D.D.S., Ph.D.
QST Hospital, National Institutes for Quantum Science and Technology
4-9-1 Anagawa, Inage-ku, Chiba-shi 263-8555, Japan
Tel: +81 - 43 – 206 - 3306, FAX: +81-43-206-3069.
E-mail: ikawa.hiroaki@qst.go.jp

[Author Responsible for Statistical Analysis Name & Email Address]
Hiroaki Ikawa: ikawa.hiroaki@qst.go.jp
Masashi Koto: koto.masashi@qst.go.jp
Tapesh Bhattacharyya: tapesh27@gmail.com
Takashi Kaneko: t.kaneko.niigata1024@gmail.com
Hirotsushi Takiyama: takiyama.hirotsoshi@qst.go.jp
Makoto Shinoto: shinoto.makoto@qst.go.jp
Akihiro Nomoto: nomoto.akihiro@qst.go.jp
Shigeru Yamada: yamada.shigeru@qst.go.jp
Hiroshi Tsuji: tsuji.hiroshi@qst.go.jp

Conflict of Interest: None.
Funding: None.
Data Availability Statement for this Work
Research data are not available at this time.
Acknowledgements
Not applicable.
Abstract

We introduce the utility of iodine paste markers using endodontic materials for the accurate contouring of mucosal lesions of oral mucosal melanoma (OMM), which are difficult to delineate on imaging during the planning of carbon-ion radiation therapy (CIRT). The patient had a primary OMM located in the palatal mucosa without palatal or maxillary bone invasion. A dental root canal filling material, which is a calcium hydroxide/iodoform non-hardenable paste, was used as a marker. We first performed treatment planning computed tomography (CT) without an iodine paste marker for mucosal lesions. Subsequently, we placed an iodine paste marker on the palatal mucosal lesion to accurately delineate the mucosal lesions of the palate. Finally, we took reference CT with an iodine paste marker. CT without the marker was fused to the reference CT with markers during treatment planning, and the gross tumor volume (GTV) was contoured. Thereafter, CIRT was delivered without markers. During CIRT, expected acute mucositis was observed in the area of the planning target volume (PTV), including melanosis, in accordance with the dose distribution. The use of iodine paste markers for localized mucosal lesions, which are difficult to delineate on CT and MRI, may be useful for contouring GTVs on treatment planning CT accurately.
Introduction
We previously demonstrated the efficacy and utility of carbon-ion radiation therapy (CIRT) with acceptable toxicity and preserved oral function in treating oral mucosal melanoma (OMM).\textsuperscript{1,2} CIRT provides an excellent conformal physical dose distribution because of its Bragg peak property and sharper lateral penumbra.\textsuperscript{3} Therefore, the delineation of gross tumor volume (GTV) must be sufficiently accurate to obtain optimal local control with minimal side effects in high-precision RT.

OMM localized to the mucosa without bone invasion can be missed with volumetric imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI). Although intraoral endoscopic findings are helpful, it is difficult to accurately identify and contour the exact tumor site on treatment planning CT.

The accurate delineation of mucosal lesions in treatment planning CT is of utmost importance for the accurate delivery of RT. However, no method has been reported to accurately delineate mucosal lesions in treatment planning CT.

This technical report introduces a method to accurately delineate mucosal lesions using endodontic materials as markers for palatal mucosal melanoma.

Methods and materials
An example of a patient
The patient had a primary OMM located in the palatal mucosa and left maxillary gingiva without palatal and maxillary bone invasion (Fig 1a). In this case, the lesion was localized to the mucosa and was difficult to detect by contrast-enhanced MRI and CT. There was no lymph node involvement or evidence of distant metastasis at presentation. The clinical stage was evaluated to be T3N0M0. The patient declined radical surgery and was referred for CIRT. The patient had no history of iodine-induced allergies.

Iodine pastes markers
In this study, Vitapex (Neo Dental International Inc., Tokyo, Japan), a calcium hydroxide dental root canal filling material commonly used in endodontic treatment,\textsuperscript{4,7} was used as the marker. The main ingredients of Vitapex are iodoform (40.4%), calcium hydroxide (30.3%), and silicone 22.4%.\textsuperscript{8} The iodoform content provides contrasting properties. Vitapex is a non-hardenable paste that is delivered through a syringe with disposable tips.\textsuperscript{9} The material is viscous and non–irritating;\textsuperscript{9} therefore, it can be placed stably on moist areas of the oral mucosa without iodine allergy (Fig. 1b). In addition, it is not injected into the body, meaning that it can be easily removed after CT imaging by rinsing or wiping.

Mouthpiece
The mouthpiece was constructed as described in our previously published article.\textsuperscript{10} It was constructed with a thermoplastic ethylene-vinyl acetate copolymer, which is suitable for use in charged-particle therapy (Fig. 2).\textsuperscript{11}

Results
Radiation therapy planning and treatment setup
The CIRT method used at our institute has been described previously.\textsuperscript{1} CT images with a slice thickness of 2 mm were obtained in the following order. First, we performed treatment planning CT without the iodine paste marker for palatal lesions (Fig. 3a). To accurately delineate mucosal lesions of the palate on CT, we placed an iodine paste marker on the palatal mucosal lesion. Finally, we took a reference CT with an iodine paste marker (Fig. 3b). The iodine paste was removed immediately after CT imaging.
During the treatment planning CT, no adverse events, such as mucosal pain and redness, were observed due to iodine paste markers. GTV was contoured on treatment planning CT without markers after fusing it with CT with markers for the palatal lesion using MIM (MIM Software Inc., Cleveland, OH). CIRT was delivered without the markers. During CIRT treatment, expected acute mucositis was observed in the high-dose area of the prescribed dose in accordance with the dose distribution. No mucositis was noted outside the PTV.

**Discussion**

CIRT has shown promising results for patients with inoperable OMM. With T3 diseases, the lesion was localized to the mucosa and was difficult to detect by treatment planning CT. GTVs on treatment planning CT could be contoured using intraoral endoscopic examination findings or gross visual observation, yet they may be inaccurate. Owing to the uncertainty in GTV delineation, a robust CTV was considered as the CTV margin expanded. Simultaneously, the lesion was close to the maxillary bone, and there was a high risk of osteoradionecrosis (ORN). et al. reported that Grade ≥2 ORN was observed in 36.8% of patients after CIRT for OMM. Widening the CTV margins may increase ORN incidence and severity. Therefore, the GTV should be delineated accurately, enabling optimal CIRT planning.

Fiducial markers for target localization and positional verification are widely used in RT. Few reports have demonstrated the use of radiopaque markers, such as lipiodol injection and implanted gold markers, for target volume delineation optimization in patients with oropharyngeal cancer. For oral lesions, there have been no reports on the utility of the markers in contouring GTV on treatment planning CT.

For mucosal lesions, it is difficult to perform CT imaging with metallic materials, such as gold markers, placed in the mucosa. Moreover, the local injection of radiopaque materials, such as lipiodol, may affect the accuracy of treatment owing to the error in the stopping power ratio of the particle beam as uncertainty. A removable paste marker can eliminate marker uncertainty and can easily be applied with no invasion to the patient. Therefore, applying a removable paste marker to the oral mucosa is a reasonable option. Additionally, it is adaptable for all types of external beam RT, although it is limited to the oral cavity, including the buccal mucosa and floor of the mouth, which can be approached directly. RT is also used for early-stage oral squamous cell carcinoma, which may be difficult to identify on CT and MRI. In such cases, the present method may be adaptable.

**Conclusion:**

Iodine paste markers for localized mucosal lesions, which are difficult to delineate on CT and MRI images, may be useful for contouring GTVs on treatment planning CT accurately.
References

1. *******************
2. *******************
3. 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.
4. Cartwright JW, Todd MJ. A comparison of endodontic medications. Gen Dent. 1982;30:334-337.
5. Nurko C, Garcia-Godoy F. Evaluation of a calcium hydroxide/iodoform paste (Vitapex) in root canal therapy for primary teeth. J of Clin Pediatr Dent. 1999;23:289-294.
6. Ishikawa T. The healing process of improved calcium hydroxide paste “Vitapex”. Nippon Dent Rev. 1980;460:56-64.
7. Smail-Faugeron V, Glenny AM, Courson F, et al. Pulp treatment for extensive decay in primary teeth. Cochrane Database Syst Rev. 2018;5:CD003220.
8. National Center for Biotechnology Information. PubChem Compound Summary for CID 121861, Vitapex. 2021. Retrieved November 12, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Vitapex.
9. Barnhart BD, Chuang A, Lucca JJ, et al. An in vitro evaluation of the cytotoxicity of various endodontic irrigants on human gingival fibroblast. J Endod. 2005;31:613-635.
10. *******************
11. *******************
12. Makishima H, Yasuda S, Isozaki Y, et al. Single fraction carbon ion radiotherapy for colorectal cancer liver metastasis: A dose escalation study. Cancer Sci. 2019;110:303-309.
13. Kasuya G, Tsuji H, Nomiya T, et al. Prospective clinical trial of 12-fraction carbon-ion radiotherapy for primary renal cell carcinoma. Oncotarget. 2019;10:76-81.
14. Yasuda S, Kato H, Imada H, et al. Long-Term Results of High-Dose 2-Fraction Carbon Ion Radiation Therapy for Hepatocellular Carcinoma. Adv Radiat Oncol. 2019;5:196-203.
15. Yamamoto N, Miyamoto T, Nakajima M, et al. A Dose Escalation Clinical Trial of Single-Fraction Carbon Ion Radiotherapy for Peripheral Stage I Non-Small Cell Lung Cancer. J Thorac Oncol. 2017;12:673-680.
16. van Asselen B, Dehnad H, Raaijmakers CP, et al. Implanted gold markers for position verification during irradiation of head-and-neck cancers: a feasibility study. Int J Radiat Oncol Biol Phys. 2004;59:1011-1017.
17. Haderlein M, Mercen R, Stojanovic A, Speer S, Scherl C, Fietkau R, Ott OJ. Lipiodol injections for optimization of target volume delineation in a patient with a second tumor of the oropharynx: A case report. Strahlenther Onkol. 2015;191:681-686.
18. Hamming-Vrieze O, van Kranten SR, van Beek S, et al. Evaluation of tumor shape variability in head-and-neck cancer patients during the course of radiation therapy using implanted gold markers. Int J Radiat Oncol Biol Phys. 2012;84:e201-e207.
19. Hosni A, Chiu K, Huang SH, et al. Non-operative management for oral cavity carcinoma: Definitive radiation therapy as a potential alternative treatment approach. Radiother Oncol. 2021;154:70-75.
20. Pałasz P, Adamski Ł, Górska-Chrząstek M, et al. Contemporary Diagnostic Imaging of Oral Squamous Cell Carcinoma - A Review of Literature. Pol J Radiol. 2017;82:193-202.
Figure legends.

Figure 1. Intra-oral endoscopic examination findings. a) A finding at the time of initial examination. b) A finding of an iodine paste marker applied to a lesion on the palatal mucosa.

Figure 2. The mouthpiece was put on after the marker was applied to the lesion.
Figure 3. Sagittal image of computed tomography. a) Treatment planning computed tomography image without marker application. b) Reference computed tomography with an iodine paste marker.