Prevention of dental caries using low concentration fluoride gel in custom tray in head and neck cancer patients undergoing radiotherapy: a preliminary study

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Sakiko Soutome
Oral Management Center, Nagasaki University Hospital

Souichí Yanamoto
Nagasaki University

syana@nagasaki-u.ac.jp Corresponding Author

Madoka Funahara
Kyushu Dental University School of Oral Health Sciences

Yumiko Kawashita
Oral Management Center, Nagasaki University Hospital

Masako Yoshimatsu
Oral Management Center, Nagasaki University Hospital

Maho Murata
Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences

Masahiro Umeda
Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences

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KEYWORDS
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Abstract

Background: To prevent radiation-related dental caries, some studies reported topical application of 1.0 – 2.0% fluoride gel in custom tray for 4-5 minutes every day. However, in Japan, the concentration of fluoride used by patients is limited to less than 0.15%. The efficacy of low concentration of fluoride gel in custom tray in preventing radiation-related dental caries has not been investigated.

Methods: This is a preliminary study. Thirteen patients with head and neck cancer who underwent radiotherapy were enrolled in this study. They wore custom tray containing 0.145% sodium fluoride gel during sleep every night and were examined for newly developed dental caries a year later.

Results: No new dental caries were found in the 13 patients one year after radiotherapy.

Conclusions: Low concentration fluoride gel in custom tray during sleep could prevent radiation-related dental caries. We are planning to conduct a multicenter phase III randomized controlled trial to examine the efficacy of this method in preventing radiation-related dental caries.

Trial registration: University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), UMIN000025196. Registered 9 December 2016, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000028984

Background

Radiotherapy (RT) is commonly performed in head and neck cancer patients with or without systematic therapy. It causes various adverse events such as oral mucositis, xerostomia, dysgeusia, trismus, and osteoradionecrosis (ORN) of the jaw. ORN, one of the severe late complications, is rarely cured with conservative therapy, often requires surgical treatment and significantly reduces quality of life. In a multicenter retrospective study of 392 patients with head and neck cancer undergoing RT, we reported that the major risk factors for developing ORN were periapical periodontitis, tooth extraction after RT, and radiation-related dental caries [1]. Therefore, in order to prevent ORN, it is important that the infected tooth is extracted before the start of RT and strict dental management is performed after RT to prevent radiation-related dental caries.

Radiation-related dental caries occurs after RT and progresses rapidly, sometimes even in patients who visit dentists regularly (Fig. 1) [2]. The cause of radiation-related dental caries is believed to be
increased susceptibility to demineralization due to xerostomia and direct damage to the dental hard tissue [3]. Dreizen et al.[4] reported that application of 1.0 % sodium fluoride (NaF) gel in custom tray for 5 minutes every day decreased the incidence of dental caries after RT. Wang et al.[5] applied 1.23% acidulated phosphate fluoride (APF) or 2% NaF gel in custom tray for 4 minutes every day for head and neck cancer patients undergoing RT. National Comprehensive Cancer Network (NCCN) Guideline recommends daily 1.1% NaF gel or stannous fluoride (SNF₂) gel in custom tray for dental caries prevention [6]. However, in Japan, the concentration of fluoride gel used by patients was limited to less than 0.09 % for a long time. The limit of fluoride gel concentration was changed to 0.15% in 2017. Applying fluoride gel by custom tray method for head and neck cancer patients after RT has not been performed in Japan.

Therefore, we would like to conduct a randomized controlled study to examine whether low concentration fluoride gel application in custom tray can prevent radiation-related dental caries. The purpose of this study is to perform a preliminary test before a large-scale phase III trial is undertaken.

Methods
The subjects for this study consisted of patients with head and neck cancer ranging in age from 20 to 90 years who underwent RT of 50 Gy or more at Nagasaki University Hospital between January 2017 and March 2018. Those who had 9 teeth or less, in cases where the radiation field did not include oral cavity, and those who did not follow up for a minimum of 1 year were excluded. Initially, 21 patients were registered for the study. One patient refused to wear the custom tray, seven patients did not follow-up for a year because of recurrent or metastatic tumor, therefore 13 patients were included in the study (Fig. 2). Age, sex, primary site, total RT dose, RT method, number of teeth before RT, stimulated saliva volume, wetness of the oral mucosa, and number of dental caries immediately before, after, and 1 year after RT were recorded. Stimulated saliva was examined by Saxon test [7]. Oral mucosal wetness was measured using a body component analyzer (Mucus®. Life Co., Ltd., Saitama, Japan) at the surface of bilateral buccal mucosa three times each and the average value was taken.

These 13 patients underwent topical fluoride application by custom tray method after recovering from
radiation-induced oral mucositis. Custom tray was made with soft ethylene-vinyl acetate copolymer (Bioplastt®, SCHEU-DENTAL GmbH, Iserlohn, Germany) of 2.0 mm thickness. The patients wore the tray during sleep every night after brushing their teeth with a tooth paste containing 1,450 ppm NaF (Check-Up rootcare®, Lion Co., Ltd., Tokyo, Japan) (Fig. 3). They were followed up every 3 months to examine the number of new dental caries and the study lasted for 1 year.

Results
Summary statistics of the 13 patients are shown in Table 1. Ten patients were men and three women, with an average age of 60.9 years. The primary site of cancer was the oral cavity or the oropharynx in seven patients and other sites in six patients. Three-dimensional conformal radiotherapy (3D-CRT) was performed in four patients, while intensity modulated radiotherapy (IMRT) was performed in nine patients. Stimulated saliva decreased after RT and oral wetness did not differ between pre- and post RT.

Oral examination 1 year after RT revealed no new dental caries in all 13 patients. There were no adverse events caused by custom tray and fluoride gel.

Discussion
It is well known that dental caries often occurs after RT in patients with head and neck cancer [3]. This radiation-related dental caries often progresses rapidly even if patients receive regular dental management.

We previously reported that 30 of 392 patient with head and neck cancer undergoing RT developed ORN and radiation-related dental caries. Rapidly progressing dental caries was the cause of ORN in nine patients. NCCN Guideline recommends local application of 1.1% NaF gel or SNF₂ gel every day, as well as regular dental evaluation to detect dental caries [5]. Wang et al. [5] reported that 2.0% NaF gel in custom tray prevented radiation-related dental caries in patients with head and neck cancer. In Japan, the concentration of fluoride gel that can be used by patients was limited to 0.09% for a long time. The regulation was eased in 2017 and is set at 0.15% or lower. This is because, in Japan, the occurrence of mottled teeth, a side effect of fluorine, has been a problem in some regions. Therefore, local application of fluoride gel in custom tray was not performed for head and neck cancer patients.
after RT.

We hypothesized that even low concentrations of fluoride could prevent radiation-related dental caries when applied for a long time. First, we investigated the incidence of dental caries in head and neck cancer patients who did not receive fluoride. The mean of new dental caries after RT in 31 patients with head and neck cancer was 2.68 at 1 year and 4.91 at 2 years. This increase was significantly higher than in 25 patients with oral cancer who underwent surgery but not RT, where it was 0.00 at 1 year and 0.61 at 2 years after surgery [2]. We wanted to confirm our hypothesis and performed a preliminary study to examine whether radiation-related dental caries can be prevented by long-term action of low concentration fluoride. Our results showed that no new caries was found after 1 year suggesting that this method is promising as a preventive method for radiation-related caries.

This study is a preliminary, and thus has some limitations. Firstly, the number of patients examined is too small to perform statistical analysis. Secondly, the long-term caries prevention effect is unknown because we followed-up only for 1 year. And thirdly, attaching the tray may motivate the patients to brush their teeth and there may be a bias due to improvement in oral hygiene compared to patients in the previous study. Based on these results, we have decided to conduct a multicenter phase III randomized clinical trial to determine whether topical administration of low-concentration fluoride gel in custom tray can prevent radiation-related caries.

List Of Abbreviations
UMIN-CTR, University Hospital Medical Information Network Clinical Trials Registry; RT, radiotherapy; ORN, osteoradionecrosis; NaF, sodium fluoride; AFP, acidulated phosphate fluoride; NCCN, National Comprehensive Cancer Network; SNF₂, stannous fluoride; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy

Declarations
Ethics approval and consent to participate
This study was performed in accordance with the 1964 Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Boards (IRB) of Nagasaki University Hospital. The study was registered with University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR)
(UMIN000025196). Written informed consent was obtained in each patient.

Consent for publication
Written informed consent to participate in the study and consent for publication was obtained by each participant.

Availability of data and material
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
Sakiko Soutome has received research funding to Nagasaki University Hospital from Lion Co., Ltd. The other authors declare no competing interests.

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The current study received no funding.

Authors’ contributions
SS made substantial contributions to conception and design, acquisition of data, analysis, and interpretation of data. SY has been involved in drafting the manuscript or revising it critically for important intellectual content and was a major contributor in writing the manuscript. MF participated sufficiently in the work to take public responsibility for appropriate portions of the content, and perform statistical analysis. YK, MY, and MM made substantial contributions to acquisition of data, interpretation of data, and statistical analysis. MU agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Authors’ information
1Oral Management Center, Nagasaki University Hospital, 1–7–1 Sakamoto, Nagasaki 852–8588, Japan.
2Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, 1–7–1 Sakamoto, Nagasaki 852–8588, Japan. 3Kyushu Dental University School of Oral Health Sciences, 2–6–1 Manazuru, Kokura-kita, Kitakyushu, Fukuoka 803–8580, Japan.

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Tables
Table 1  Patients characteristics

| Factor               | Category         | number of patients/mean value |
|----------------------|------------------|-------------------------------|
| Sex                  |                  |                               |
| Male                 |                  | 10                            |
| Female               |                  | 3                             |
| Age                  | mean             | 60.9 years                    |
| Primary site         | oral/oropharynx  | 7                             |
|                      | others           | 6                             |
| RT dose              | 50-59 Gy         | 1                             |
|                      | 60-69 Gy         | 6                             |
|                      | 70 Gy            | 6                             |
| RT method            | 3D-CRT*          | 4                             |
|                      | IMRT**           | 9                             |
| Number of teeth      | mean             | 22.9                          |
| Stimulated saliva (mean) | before RT | 2.0 gram                     |
|                      | after RT         | 1.2                           |
|                      | one year later   | 1.4                           |
| Oral wetness (mean)  | before RT        | 26.0                          |
|                      | after RT         | 26.8                          |
|                      | one year later   | 27.5                          |
| Total                |                  | 13                            |

*3D-CRT: Three-dimensional conformal radiation therapy

**IMRT: Intensity-modulated radiation therapy

Figures
Figure 1

Radiation-related dental caries. A 36-year-old female with tongue cancer underwent postoperative chemoradiotherapy. A: Panoramic X-ray before RT. B: Three years after RT.

Multiple dental caries were found in the mandibular teeth which were irradiated.
21 patients

Inclusion criteria:
- Head and neck cancer undergoing RT of $\geq 50$Gy
- 20-90 years old

Exclusion criteria:
- The radiation field does not contain the oral cavity
- 9 or fewer remaining teeth

- Refuse to wear the tray: 1 patient
- Follow up less than 1 year: 7 patients

13 patients

Figure 2
Flow diagram showing patient enrollment.
Figure 3

A: Toothpaste containing 1,450 ppm NaF and custom tray, B: Person wearing a custom tray