

BMJ Open Evaluation of the efficacy of low concentration fluoride gel using custom trays to prevent radiation-related dental caries in patients with head and neck cancer: protocol for a randomised controlled phase III trial (FluCar study)

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ABSTRACT

Introduction The present study is a randomised, multicentre, open-label, phase III study, to evaluate the efficacy of low concentration of fluoride gel, applied using custom trays, in preventing radiation-related dental caries in patients with head and neck cancer who have undergone or are undergoing radiotherapy.

Methods and analysis Patients will be randomised into fluoride and control groups (1:1 ratio). In the fluoride group, patients will wear custom trays loaded with 0.145% fluoride gel after brushing every night while sleeping. In the control group, patients will receive oral hygiene instructions as usual. Patients in both the groups will be followed up every 3 months for 1 year. The primary endpoint is the incidence of newly developed dental caries. Target accrual is 80 patients with a two-sided type I error rate of 5% and 80% power to detect 80% risk reduction.

Ethics and dissemination This study was approved by the Clinical Research Review Board in Nagasaki University. The protocol of this study was registered at Japan Registry of Clinical Trials (jRCT) and University hospital Medical Information Network Clinical Trials Registry (UMIN). The datasets generated during the current study will be available from the corresponding author on reasonable request.

Trial registration numbers jRCTs 072190039 and UMIN000041426

INTRODUCTION

Multiple carious dental lesions often occur and progress rapidly after radiation therapy (RT) for head and neck cancer. This radiation-related dental caries not only reduces the quality of life of the patients severely but also causes osteoradionecrosis of the jaw. Causes of radiation-related dental caries include both saliva reduction due to salivary gland destruction and changes in hard and soft tissues of the teeth by irradiation.^{1,2} Hence,

Strengths and limitations of this study

- This is a multicentre, randomised controlled, open-label phase III trial to evaluate the effect of low concentration fluoride gel using custom trays on preventing radiation-related dental caries in patients with head and neck cancer.
- To the best of our knowledge, the present study is the first randomised controlled trial of prevention of radiation-related dental caries using low-concentration fluoride.
- The study may have high clinical implications for patients of head and neck cancer undergoing radiation therapy.
- Data centres and registration systems independent of researchers are involved in the study.
- This study has limitation of being an open trial and having a short observation period.

regular dental caries management and the use of topical fluoride are recommended as prevention methods for radiation-related dental caries.³

Dreizen *et al*⁴ first described the efficacy of topical application of 1% fluoride used in custom trays for 5 min every day to prevent radiation-related dental caries in an interventional study with a small number of patients with head and neck cancer. Some authors have recommended 1%–2% fluoride application using custom trays,^{3,5} although there have been no phase III controlled trials. However, this preventive method cannot be applied in Japan because the maximum fluoride concentration that patients can use in Japan has been limited to 0.09% for a long time. In Japan, the problem of mottled teeth had previously occurred, and the toxicity of

fluorine was unnecessarily concerned. Fluoride is not added to tap water, and the addition of fluoride to dentifrice is kept at a low concentration. For this reason, in Japan, topical application of fluoride using custom trays is not performed as a preventive method for radiation-related dental caries.

Enamel is consistently reformed as a result of competing processes both demineralisation and remineralisation to maintain the surface structure. Enamel demineralisation is strongly triggered by direct irradiation, damaging hydroxyapatite and altering its structure. If the damage is relatively early, it can be repaired by remineralisation by calcium ions present in the saliva, but this repair mechanism does not work when saliva is significantly reduced due to RT. Therefore, by using low dose fluoride, fluoroapatite is generated in the crystalline structure, and by forming high crystallinity apatite in the enamel, it is possible to maintain the tooth structure.

In 2017, regulations allowed the use of the highest concentration of 0.15% fluoride in Japan. Although it is about 1/10 of the concentration used in other countries, we aimed to obtain the same effect by extending the action time of the fluoride. First, we investigated the incidence of dental caries in head and neck cancer patients who had not received fluoride. The mean of new dental caries 1 year after RT in 31 patients with head and neck cancer undergoing RT was 2.68, while no newly developed dental caries was found in 25 patients with oral cancer who underwent surgery but not RT 1 year after the surgery.⁶ Next, as a preliminary study, 13 patients with head and neck cancer undergoing RT received topical application of 0.145% fluoride gel in custom tray during sleep every day for 1 year (figure 1), and as a result no newly developed dental carious lesion was found in all 13 patients.⁷ These results show that application of low concentration fluoride gel in custom trays during sleep every day is promising preventive method for radiation-related dental caries. Therefore, we conduct a randomised controlled phase III study (FluCar study) to evaluate the efficacy of low concentration fluoride gel using custom



Figure 1 0.145% fluoride gel loaded in a custom tray, to be worn by the study participants at bedtime.

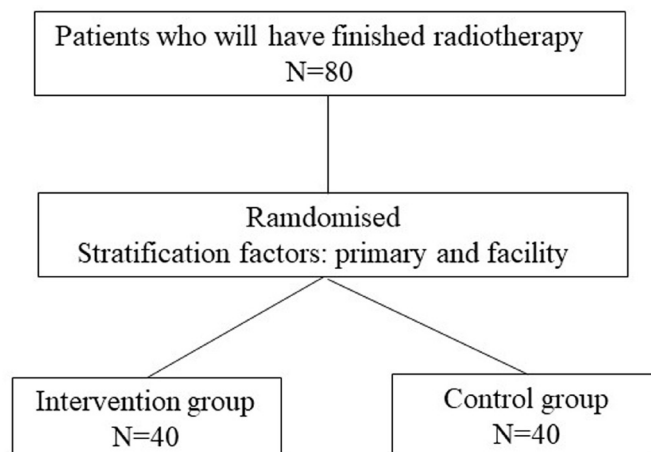


Figure 2 Flow chart of participants.

trays to prevent radiation-related dental caries in patients with head and neck cancer.

METHODS AND ANALYSIS

Digest of the study protocol

The present study is being done to check the efficacy of low concentration fluoride used in custom trays for the prevention of radiation-related dental caries. This study is of high clinical significance as the method used has the potential to reduce the incidence of dental caries after RT in patients with head and neck cancer. Hence, this study follows a superiority study design for the trial. The participant flow chart is shown in figure 2.

Purpose

The present study will examine whether the occurrence of radiation-related dental caries can be reduced by application of low concentration fluoride using custom trays in a randomised, controlled study in patients with head and neck cancer undergoing RT whose oral cavity is contained in the irradiation field.

Endpoints

(1) Primary endpoint

The number of teeth with newly developed dental caries every 3 months for 1 year after RT in patients receiving low concentration fluoride treatment and patients not receiving the treatment are considered as the primary endpoint of the present study. Dental caries was defined as the formation of cavities in the teeth by the action of bacteria, which was diagnosed by visual inspection or palpation with a probe. Dental opacity, white spots and pigmentation but no cavities (C0) were not counted as dental caries.

(2) Secondary endpoint

The number of patients who developed new dental caries every 3 months for 1 year after RT in patients receiving low concentration fluoride treatment and patients not receiving the treatment are considered as the secondary endpoint of the study.

Eligibility criteria

(1) Inclusion criteria

The patients included in the study satisfy all the following criteria

- Patients with head and neck cancer.
- Patients undergoing RT with more than 50 Gy of radiation, with or without chemotherapy.
- Patients whose oral cavity lies within the RT field during treatment.
- Patients in the age range of 20–90 years.

(2) Exclusion criteria

The patients excluded from the study are of the following groups

- Patients with edentulous upper and lower jaws.
- Patients who have received RT previously.
- Patients who are receiving RT for palliative care.
- Patients with a habit of mouth breathing.

Patient assignment and data management

Patients will be recruited from Nagasaki University Hospital, Kansai Medical University Hospital, Shinshu University Hospital, Nagoya City University Hospital and Kagoshima University Hospital, from 7 January 2020 to 31 December 2021. All patients with head and neck cancer undergoing RT are screened to determine their eligibility and asked to provide their written consent. A copy of patient consent form is available as online supplemental file 1. Participants have the right to withdraw from the study at any time without having to give a reason.

The Clinical Research Centre of Nagasaki University will allocate the patients randomly to the fluoride group and the control group in the ratio of around 1:1, using a stratified allocation method that minimises the effects of the allocation adjustment factors. The allocation algorithm will be determined by the person responsible for biostatistical analysis: primary site (oral or oropharyngeal cancer/cancer of other sites) and facility (facility name). The data will be gathered and managed using the system of Research Electronic Data Capture by the Data Centre of Nagasaki University Hospital.

Treatment and assessment schedule

Patients will be randomly allocated to the two groups after the end of their RT. ‘Treatment completion’ in the present study will be defined as patients undergoing followed up by dentists for a period of 1 year.

- Fluoride group:** Within a month after RT is completed, patients will be provided oral hygiene instruction according to the oral hygiene status by a dental hygienist, and professional oral cleaning at the patient’s visit every 3 months. Professional oral cleaning means that under the direction of a dentist, a dental hygienist perform oral hygiene instruction and cleaning of the tooth surface, tongue and oral mucosa by oral hygiene tools for patients. Impressions of the upper and lower teeth will be taken using alginate impression material and custom trays covering all teeth will be fabricated from these impressions. The custom tray will be made with soft ethylene-vinyl acetate copolymer (Bioplast, SCHEU-DENTAL GmbH, Iserlohn, Germany) of 2.0 mm thickness. A toothpaste containing 0.145% sodium fluoride (Check-Up rootcare, Lion, Tokyo, Japan) is loaded in the trays and patients are asked to wear the trays during sleep every day.
- Control group:** Within a month after RT is completed, patients will be provided oral hygiene instruction and professional oral cleaning as in the Fluoride group.

Patients in both groups will be followed up every 3 months for 1 year and also checked for dental caries. The time actually used by the custom tray will be recorded at the time of follow-up. Whenever dental caries is found in these patients, the appropriate dental treatment will be done immediately. The data collection schedule is shown in table 1. Participants will be contacted by phone the day before the follow-up date for dealing with drop-outs/lost to follow-up.

Statistical analysis

- Main analysis and assessment criteria

Table 1 Schedule for outcome measurement

	Collection time						
	After RT	booking	3 months*	6 months*	9 months*	12 months*	Cancelled
Take consent	○						
Characteristic	○						
Impression for tray†		●					
Custom tray set†		●					
Wear the tray†			●	●	●	●	●
Dental check‡	○					●	●

*These months will be after allocation day. Each consultation day has a allowance of ± 4 weeks.

†These would be evaluated only intervention group.

‡Current number of teeth, The number of newly developed dental caries, Debris Index, Wetness, Saliva volume. RT, radiation therapy.

The number of newly developed lesions of dental caries is analysed by a negative binomial regression model. Explanatory variables include the use of custom trays with fluoride and a radiation field (oral region, oropharynx or other sites). Because this study is multicentre, it seems to be a difference between centre regarding the RT. Therefore, the factor of the centre is included as an explanatory variable. The null hypothesis ‘there is no difference in the incidence of caries (number of dental caries/observation period) between the fluoride group and control group’ is tested. The length of follow-up for each patient is included as a measure of the negative binomial model as an offset. The efficacy of low concentration fluoride application using custom trays is considered good if the results of this test are statistically significant with a two-sided α -level of 5% and the incidence of dental caries is lower in the fluoride group compared with the control group. The two-sided 95% CI of the difference in incidence between the two groups will also be calculated for the purpose of analysis and interpretation.

(2) Secondary analysis

The difference in the percentage of patients who develop dental caries after RT between the fluoride and control groups is analysed by the Fisher’s exact test. The null hypothesis ‘there is no difference in the percentage of patients developing dental caries between the fluoride and the control groups’ is tested.

Sample size calculation

In this study, the sample size is calculated using negative binomial regression analysis because the outcome is count data. Based on some previous studies,^{6,7} it is assumed that the average number of radiation-related dental carious lesions that occur in the 1 year after RT is 2.5 in the fluoride group and 0.5 in the control group. The result of the overdispersion parameter calculated in the control group of a previous study⁶ is 6.2, and when the data of the fluoride group is added to this, the variation in the count data of this group can be expected to be small. Therefore, the overdispersion parameter is considered to be about 5.0. Assuming $\alpha=0.05$ and power=0.80, the required number of cases is 72, the drop-out is assumed to be 10%, and the target number of cases is 80.

Study period

The study period of this trial will be from 7 January 2020 to 31 March 2024; the participant entry period will be 7 January 2020 to 31 December 2022.

Patient and public involvement statement

This research is carried out without patient or public involvement. Neither patient nor the public is involved in the development of the research question, study design or implementation of this trial. Patients will not be invited to develop patient-relevant outcomes or interpret the results, or to participate in the writing or editing of the final manuscript for readability or accuracy. Because the interventions in our study are routine procedures during

clinical work, the burden of the intervention is assessed by the patients themselves.

ETHICS AND DISSEMINATION

This study was approved by the Clinical Research Review Board in Nagasaki University (No. CRB19-016). The protocol of this study was registered at Japan Registry of Clinical Trials (jRCT) and University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR). Details are available at the following address: <https://jrcr.niph.go.jp/en-latest-detail/jRCTs072190039> and https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000047294, respectively.

Any protocol changes that impact the study conduct, and/or participant risk–benefit profile, including changes in objectives, design, sample size, participant characteristics, staff changes or significant administrative aspects, require an approval by the relevant IRB. Minor protocol corrections and/or clarifications that do not affect study conduct or the participant risk/benefit profile are viewed as administrative changes and are documented internally.

The study investigators will have full access to and ownership of all data. Deidentified data will be made available to interested outside investigators for additional analyses, on reasonable request, following reports of primary outcomes, and with appropriate data use agreement. The findings in this study will be disseminated through scientific and professional conferences, and in peer-reviewed journal.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Obtained.

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