Association between dental extraction after radiotherapy and osteoradionecrosis: A multi-centre retrospective study

Saito, Izumi ; Hasegawa, Takumi ; Kawashita, Yumiko ; Kato, Shinichiro ; Yamada, Shin-ichi ; Kojima, Yuka ; Ueda, Nobuhiro ; Umeda, Masahiro …

(Citation)
Oral Diseases,28(4):1181-1187

(Issue Date)
2022-05

(Resource Type)
journal article

(Version)
Accepted Manuscript

Association between Dental Extraction After Radiotherapy and Osteoradionecrosis: A Multi-centre Retrospective Study

Izumi Saito, DDS, PhD‡[1], Takumi Hasegawa, DDS, PhD *[1], Yumiko Kawashita, DDS, PhD §[2], Shinichiro Kato, DDS, PhD §[3], Shin-ichi Yamada, DDS, PhD #[4], Yuka Kojima, DDS, PhD #[5], Nobuhiro Ueda, DDS §[6], Masahiro Umeda, DDS, PhD **[2], Yasuyuki Shibuya, DDS, PhD **[3], Hiroshi Kurita, DDS, PhD **[4], Tadaaki Kirita, DDS, PhD **[6], Masaya Akashi, DDS, PhD **[1]

‡Clinical Fellow, * Senior Assistant Professor, §Assistant Professor, # Associate Professor, ** Professor and Chairman

[1] Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine

[2] Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Science

[3] Department of Oral and Maxillofacial Surgery, Nagoya City University Graduate School of Medical Sciences

[4] Department of Dentistry and Oral Surgery, Shinshu University School of Medicine

[5] Department of Dentistry and Oral Surgery, Kansai Medical University

[6] Department of Oral and Maxillofacial Surgery, Nara Medical University

*Corresponding author: Takumi Hasegawa, DDS, PhD, Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. Tel: +81-78-382-6213 / Fax: +81-78-351-6229

E-mail: hasetaku@med.kobe-u.ac.jp

Running title: Dental extractions and Osteoradionecrosis

Key Words: Radiotherapy; Osteoradionecrosis; Dental extractions; Head and neck cancers; risk factor

ABSTRACT

Objective

Radiotherapy (RT) carries a substantial risk for the development of osteoradionecrosis (ORN) of the jaw. This study was performed to investigate the relationship between dental extractions after RT and the development of ORN.

Material and Methods

Thirty-two patients with head and neck cancer who underwent tooth extraction after RT were investigated for correlations between the development of ORN and various factors.

Results

Post-extraction ORN was diagnosed in 12 (12.1%) teeth of 9 patients. The RT dose against the site of tooth extraction was 62.0 and 37.4 Gy in the ORN and Non-ORN groups, respectively ($P < 0.001$). The duration from RT to tooth extraction was 41.2 and 28.2 months in the ORN and Non-ORN groups, respectively ($P = 0.025$). Tooth extraction was significantly associated with ORN in patients with a high RT dose against the site (odds ratio = 1.231) and a longer duration of time from RT (odds ratio = 1.084).

Conclusions

Extraction of non-restorable teeth and those with a poor prognosis should not necessarily be postponed even when patients are undergoing RT. However, clinicians should pay special attention to postoperative management after tooth extraction in patients with a high RT dose and longer time from RT.

INTRODUCTION

Radiotherapy (RT) is commonly used for the management of head and neck cancers. However, RT carries a substantial risk for the development of osteoradionecrosis (ORN) of the jaw. ORN of the jaw, defined as exposed irradiated bone that fails to heal during a period of 3 months with no evidence of a persistent or recurrent tumour, is a serious late complication. Quality of life can be significantly impaired, and severe cases might require mandibulectomy and reconstruction. During the last few decades, the incidence of ORN has widely ranged from 2% to 40%.[1-10] Several risk factors are thought to be associated with development of ORN, including the tumour site, radiation dose, type of radiation, fractionation of radiation, bone invasion, advanced age, sex, smoking, alcohol consumption, dental extraction, and periodontal disease.[11] We previously investigated the relationship between dental status and development of ORN and found that tooth extraction after RT is an independent risk factor for ORN.[12] Most authors have demonstrated higher rates of ORN when teeth are removed after RT. However, Koga et al.[13] reported that among 405 patients undergoing tooth extraction, 17 developed ORN and only 3 cases were related to tooth extraction (2 before and 1 after RT). Therefore, prophylactic dental extraction remains a controversial issue. No distinct definitions of infected teeth have been established, and dentists are often unable to decide whether to remove a tooth.

The objective of this multi-centre, retrospective, observational study was to investigate the relationship between dental extractions after RT and the development of ORN and to suggest a new method of oral management for these patients.

MATERIALS & METHODS

This was a non-randomised, retrospective cohort study of patients with head and neck cancer. Ethics approval was obtained from the institutional review board of each university. The study involved 99 teeth of 32 patients with head and neck cancer who underwent tooth extraction after RT from 2008 to 2015 at 7 hospitals: Kansai Medical University, Nagasaki University, Kobe University, Nara Medical University, Shinshu University, Nagoya City University, and Juntendo University. In all patients, RT was administered at 1.8 to 2.2 Gy/day for 5 days/week. None of the patients underwent interstitial brachytherapy. All patients underwent a preoperative dental evaluation and panoramic X-ray examination at the first visit. Patients who were not followed up at for least 1 year were excluded from the study.

Various clinical factors and the occurrence of ORN were retrospectively examined. We investigated the following variables: age, sex, medical history (diabetes mellitus, cerebrovascular disease, osteoporosis, alcohol use history, smoking history, steroid therapy, use of bisphosphonate formulations, immunosuppressive therapy, and reconstructive surgery), tumour site, RT dose against the jaw, and dental status at the first visit (tooth mobility, acute inflammation, and bone resorption evaluated by panoramic radiographs), and surgical factors (site of tooth extraction, reason for tooth extraction, number of teeth extracted, pre-extraction antibiotic administration, suturing, and osteoplasty). The data were introduced into a multiple logistic regression model, in which patients were divided by tumour site (oral cavity or oropharynx vs. others), reason for tooth extraction (pericoronitis vs. others), and grade of tooth mobility (0 or 1 vs. 2 or 3). Each item was assessed comparatively between the ORN group and the Non-ORN group.

Statistical analysis

SPSS 22.0 (IBM Corp., Armonk, NY, USA) and Ekuseru Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan) were used for the statistical analyses. Data are presented as mean ± standard deviation. The association of each variable with ORN in patients who underwent tooth extraction after RT was tested by Fisher's exact test or the chi-squared test for categorical variables. The level of statistical significance was set at $P < 0.05$. The variables for which the number of events (yes) was 0 in the ORN group were excluded from the multivariate analysis (i.e., cerebrovascular disease, diabetes mellitus, steroid therapy, use of bisphosphonate formulations, immunosuppressive therapy, and reconstructive surgery were excluded). The remaining variables associated with ORN were introduced into a multiple logistic regression model. Forward stepwise algorithms were used, and those variables that did not significantly fit the model were rejected. Odds ratios (ORs) and 95% confidence intervals were also calculated. Subsequently, the relationships between all variables and the cumulative occurrence rate of ORN were analysed by multivariate Cox proportional hazard model analyses.

The discriminatory ability of the duration of time from the index day to the first tooth extraction day and the RT dose against the tooth extraction site to serve as indicators of possible ORN events was evaluated with a receiver operating characteristic (ROC) curve. This ROC curve was used to determine the cut-off values for clinical tests. The area under the ROC curve (AUC) measures the accuracy of this discrimination and ranges from 0.5 to 1.0. The cut-off value was chosen to minimise the number of false-positive and false-negative results.

RESULTS

The patients in the ORN group had a mean age of 65.0 years (range, 30–85 years), and those in the Non-ORN group had a mean age of 61.2 years (range, 37–80 years). The main tumour site was the oral cavity in six teeth and the oropharynx in five. The mean RT dose against the tooth extraction site was 62.0 ± 5.9 Gy in the ORN group and 37.6 ± 20.9 Gy in the Non-ORN group. Post-extraction ORN was diagnosed in nine patients. Among the 99 teeth evaluated, 12 (12.1%) were affected by ORN (Table 1). The univariate analysis showed a significant difference in the incidence of ORN between male and female patients ($P = 0.025$). The tumour site was associated with the development of ORN; specifically, oral cavity or oropharyngeal cancer was significantly correlated with the occurrence of ORN ($P = 0.013$). There were significant differences in the development of ORN according to a total RT dose exceeding 58 Gy and a duration of time from the index day to the first tooth extraction day exceeding 35 months ($P = 0.002$). There were no differences in other demographic factors, such as medical history, alcohol use, and chronic smoking history, between the patients with and without ORN. Forty-two teeth in the anterior region and 57 teeth in the molar region were removed. The reason for tooth extraction was severe marginal periodontitis in 38 teeth, periapical periodontitis in 10, marginal/periapical periodontitis in 3, pericoronitis in 4, odontoclasis in 3, caries in 37, other conditions in 3, and an unknown condition in 1 (Table 1). Tooth extraction in the molar region was a significant predictor of ORN, as was extraction of teeth with pericoronitis ($P = 0.011$ and $P = 0.004$, respectively). Dental status-related factors such as bone resorption, grade of tooth mobility, and acute inflammation were not significant risk factors for ORN. Similarly, procedure-related factors such as preoperative antibiotic administration, use of surgical staples, and performance of osteoplasty were not significant risk factors.

Through application of a logistic regression model and forward stepwise algorithms, we found that the RT dose against the site of tooth extraction (OR = 1.231) and the duration of time from RT to tooth extraction (OR = 1.084) were significantly associated with ORN (Table 2). However, through application of the multivariate Cox proportional hazard model, there was no significant factor associated with the cumulative occurrence rate of ORN.

The AUC for the duration from RT to extraction was 0.70, a value generally considered inaccurate. Maximisation of the harmonic mean of the specificity and sensitivity put the cut-off of the duration from RT to tooth extraction for predicting post-extraction ORN at 35 months (Fig. 1). The resulting sensitivity was 0.75, and the specificity was 0.72. Similarly, the AUC for the RT dose was 0.89, a value generally considered inaccurate. Maximisation of the harmonic mean of the specificity and sensitivity put the cut-off of the RT dose against the tooth extraction site for predicting post-extraction ORN at 58 Gy (Fig. 2). The resulting sensitivity was 0.92, and the specificity was 0.78.

DISCUSSION

In this retrospective study, we analysed the relationship between dental extraction after RT and the development of ORN with the aim of suggesting a new method of oral management for these patients. Many reports have addressed the incidence of ORN after dental extraction in irradiated patients. During the last few decades, the incidence of ORN has widely ranged from 2% to 40%. Recently, however, Horiot et al.[14] reported that the incidence of ORN after dental extraction in irradiated patients was 9.1%, and Epstein et al.[15] found an incidence of 7.1% among 42 patients who underwent 137 dental extractions. A systematic review by Nabil and Samman[16] showed that the incidence of ORN after dental extraction in irradiated patients was 7%. In the present study, post-extraction ORN was diagnosed in 12 teeth (12.1%) of 9 patients. This rate is higher than in other recent studies. Our cases of ORN might have included patients who had already developed ORN before tooth extraction because it is difficult to distinguish early ORN from tooth infection, and the Japanese guideline for oral cancer suggests the avoidance of tooth extraction if possible.[17]

The relationship between the primary lesion and the ORN site was assessed, and we found that ORN can occur in patients with oral cavity cancer (6 patients), oropharyngeal cancer (4 patients), and hypopharyngeal cancer (1 patients). Oral cavity or oropharyngeal cancer was significantly correlated with the occurrence of ORN. The irradiation field for oral cavity and oropharyngeal cancer often involves both the maxilla and mandible. Severe radiation-induced salivary gland damage frequently occurs in these patients. Therefore, prophylactic dental extraction of teeth with severe caries and periodontitis is needed in patients who are scheduled for RT for treatment of oral cavity and oropharyngeal cancer.

Most cases of ORN occurred in the premolar or molar region of the lower jaw in this study. This result is similar to the findings in other studies. Koga et al.[13] reported 17 cases of ORN: 16 in the mandible (14 in the premolar and molar regions and 2 in the incisor region) and 1 affecting the maxilla. Nabil and Samman[16] found that when extraction was performed in the maxilla, only 1% of the sockets developed ORN; in contrast, the risk of ORN was three times higher when extraction was performed in the mandible. Raguse et al.[11] reported that most cases of ORN occurred in the molar region. This finding is in accordance with the literature in that injury and irritation associated with the presence of a prosthesis have been described as risk factors for ORN, with the molar region as a site of predilection.

Dental extraction remains controversial. A recent systematic review showed that the incidence of ORN after post-irradiation dental extraction was low. Some studies have shown no apparent benefit of pre-ORN extractions in terms of reducing the risk of ORN.[16,18,219] However, these authors noted that a complete dental evaluation by an experienced practitioner is strongly recommended before RT and that it is important to discuss with patients the implications of extraction versus retaining teeth in the proposed high-dose RT field.[19] The highest risk of developing ORN was in patients who received a radiation dose of more than 60 Gy and had dental extractions within the radiation field.[16] Tsai et al.[7] found that head and neck RT at a dose of <50 Gy has a much lower risk than that at >60 Gy. They considered that if the dose can be lowered to <50 Gy, the incidence of ORN might decrease.[7,20] Since 2000, intensity-modulated RT (IMRT) has gained wide popularity. Studer et al.[21] reported that IMRT can reduce the incidence of ORN against conventional RT because of less radiation exposure in the maxilla and mandibular bones. In the present study, however, there was no significant difference between conventional RT and IMRT in the univariate and multivariate analyses. The radiation dose among patients with ORN was significantly higher than that among patients without ORN. The cut-off value for the radiation dose that increased the risk of ORN was 58 Gy based on the results of the ROC curve. Therefore, tooth extraction may be acceptable until reaching a radiation dose of 58 Gy. However, patients should be instructed by oral surgeons, head and neck surgeons, and radiation therapists to undergo an oral examination by a dentist.

A systematic review by Nabil and Samman[16] showed that dental extraction within 1 year after RT resulted in a 7.5% risk of ORN. The risk of ORN caused by dental extraction increased to 22.6% from 2 to 5 years after RT and then decreased to 16.7% after 5 years.[16,22] Chen et al.[19] found that their institute avoided dental extraction within 2 years after RT because the average duration between RT and dental extraction was 27.3 months. In the present study, the cut-off value for the duration from RT to tooth extraction that increased the risk of ORN was 35 months based on the results of the ROC curve. Previously, we indicated that the cumulative occurrence rate of ORN increased over time.[12] Therefore, the incident risk of ORN after extraction may not be decreased even after the lapse of time from RT. This suggests that teeth that cannot be preserved for a long time should be extracted before the start of RT. Kojima et al.[12] reported that a pre-RT periapical focus is an independent risk factor for the development ORN. In this study, extraction of teeth with pericoronitis was a significant predictor of ORN, although that was not significant by multivariate analysis. Therefore, non-restorable teeth and those with a poor prognosis should be extracted before the development of inflammation even when patients are undergoing a high dose of RT. We suggest that minimal trauma or atraumatic extraction can reduce the risk of ORN. Other investigators have suggested that the teeth should be extracted by limited mucoperiosteal disruption and minimal bone injury.[13,23] However, we recommend post-extraction removal of bone edges and mucosal wound closure. This point may be controversial; therefore, further prospective studies are necessary to provide definitive scientific evidence for these recommendations.

Finally, we must mention the limitations of this study. First, this was a retrospective study with a small sample size. Second, the number of patients treated with IMRT was small. Gomez et al.[24] demonstrated that the incidence of ORN in their population of patients being treated with IMRT was very low at approximately 1% (2 of 168 patients). They concluded that IMRT likely offers an advantage over conventional and three-dimensional conformal techniques in preventing this adverse event. Causal teeth with severe infection and severe pain should be extracted even in patients undergoing RT.[24,25] To reduce the incidence of ORN, we should conduct a prospective study including a large sample size of patients undergoing IMRT in the near future.

In conclusion, we found that the RT dose against the site of tooth extraction and the duration from RT to tooth extraction were significantly associated with ORN through application of a logistic regression model and forward stepwise algorithms. However, through application of a multivariate Cox proportional hazard model, there was no significant factor associated with the cumulative occurrence rate of ORN. Extraction of non-restorable teeth and those with a poor prognosis should not necessarily be postponed even when patients are undergoing RT. However, clinicians should pay special attention to postoperative management after tooth extraction in patients with a high RT dose and longer time from RT. We hope that these criteria can be used for selection of tooth extraction in the irradiation area.

ACKNOWLEDGEMENTS

We received no sources of study funding, including those of an institutional or departmental nature. We thank Angela Morben, DVM, ELS, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

Table 1. Characteristics and incidence rates of ORN in patients who underwent tooth extraction after RT

Variables	ORN n (%)	Non-ORN n (%)	P value
Number of teeth	12 (12.1)	87 (87.9)	
Sex			
Male	11 (11.1)	49 (49.5)	0.025*
Female	1 (1.0)	38 (38.4)	
Age			
Range (Years)	30-85	37-85	0.360**
Mean ± SD	65.0 ± 18.3	61.2 ± 15.9	
Smoking history			
Yes	5 (5.1)	17 (17.2)	0.157***
No	5 (5.1)	46 (46.5)	
Unknown	2(2.0)	24 (24.2)	
Alcohol use history			
Yes	5 (5.1)	24 (24.2)	0.510***
No	5 (5.1)	38 (38.4)	
Unknown	2 (2.0)	25 (25.3)	
Cerebrovascular disease			
Yes	0 (0)	0 (0)	
No	12 (12.1)	87 (87.9)	
Unknown	0 (0)	0 (0)	
Diabetes mellitus			
Yes	0 (0)	3 (3.0)	1.000*

No	12 (12.1)	84 (84.8)	
Steroid therapy			
Yes	0 (0)	0 (0)	
No	12 (12.1)	87 (87.9)	
Unknown	0	0	
Use of bisphosphonate formulation			
Yes	0 (0)	1 (1.0)[a]	1.000*
No	12 (12.1)	86 (86.9)	
Unknown	0 (0)	0 (0)	
Immunosuppressive therapy			
Yes	0 (0)	0 (0)	
No	12 (12.1)	87 (87.9)	
Unknown	0 (0)	0 (0)	
Reconstructive surgery			
Yes	0 (0)	13 (13.1)	0.357*
No	12 (12.1)	74 (74.7)	
Unknown	0 (0)	0 (0)	
Tumour site			
Oral cavity	6 (6.1)	45 (45.5)	
Oropharynx	5 (5.1)	5 (5.1)	
Hypopharynx	1 (1.0)	22 (22.2)	
Nasal/Sinus cavity	0 (0)	2 (2.1)	
Unknown primary	0 (0)	4 (4.0)	
Others	0 (0)	12 (12.1)	
Unknown	0 (0)	0 (0)	

Time period from RT to extraction			
Range (months)	3-67	0-71	0.025**
Mean ± SD	41.2 ± 17.0	28.2 ± 27.6	
Time period from RT to extraction			
≤ 35 months	3 (3.0)	24 (24.2)	0.002*
> 35 months	9 (9.1)	63 (63.6)	
Site of tooth extraction			
Maxillary	3 (3.0)	35 (35.4)	0.360*
Mandibular	9 (9.1)	52 (52.5)	
Anterior region	1 (1.0)	41 (41.4)	0.012*
Molar region	11 (11.1)	46 (46.5)	
RT dose against the site of tooth extracted			
Range (Gy)	50-70	5-70	<0.001**
Mean ± SD	62.0 ± 5.9	37.6 ± 20.9	
Total RT dose			
≥ 58 Gy	11 (11.1)	19 (19.2)	<0.001*
< 58 Gy	1 (1.0)	68 (68.7)	
RT method			
3D-CRT	10 (83.3)	82 (94.3)	0.200*
IMRT	2 (16.7)	5 (5.7)	
Root			
Single	5 (5.1)	65 (65.7)	0.300*
Multiple	7 (7.1)	22 (22.2)	
Reason of tooth extraction			
Marginal periodontitis	3 (3.0)	35 (35.4)	
Periapical periodontitis	2 (2.0)	8 (8.1)	

Marginal/Periapical periodontitis	0 (0)	3 (3.0)	
Pericoronitis	3 (3.0)	1 (1.0)	
Odontoclasis	1 (1.0)	2 (2.0)	
Caries	0 (0)	37 (37.4)	
Others	2 (2.0)	1 (1.0)	
Unknown	1 (1.0)	0 (0)	
Pericoronitis			
Yes	3 (3.0)	1 (1.0)	0.004***
No	8 (8.1)	86 (86.9)	
Unknown	1 (1.0)	0 (0)	
Bone resorption			
Severe	5 (5.1)	36 (36.4)	1.000***
Mild	6 (6.1)	51 (51.5)	
Unknown	1 (1.0)	0 (0)	
Grade of tooth mobility			
0	5 (5.1)	17 (17.2)	
1	0 (0)	7 (7.1)	
2	4 (4.0)	33 (33.3)	
3	1 (1.0)	19 (19.2)	
Unknown	2 (2.0)	11 (11.1)	
Acute inflammation			
Yes	6 (6.1)	29 (29.3)	0.339***
No	6 (6.1)	57 (57.6)	
Unknown	0 (0)	1 (1.0)	
Preoperative antibiotics administration			

Yes	5 (5.1)	30 (30.3)	0.749*
No	7 (7.1)	57 (57.6)	
Surgical staple			
Yes	7 (7.1)	56 (56.6)	0.676***
No	1 (1.0)	22 (22.2)	
Unknown	4 (44.4)	9 (9.1)	
Osteoplasty			
Yes	3 (3.0)	12 (12.1)	0.140***
No	5 (5.1)	66 (66.7)	
Unknown	4 (4.0)	9 (9.1)	

*Fisher's exact test. **Mann–Whitney U test. ***Chi-squared test.

[a]This patient had received bisphosphonate for the past 3 years.

ORN: osteoradionecrosis, RT: radiotherapy, SD: standard deviation, 3D-CRT: three-dimensional chemoradiotherapy, IMRT: intensity-modulated radiotherapy

1

Table 2. Results of multivariate logistic regression analysis of risk factors for ORN

			95 % CI	
Variable	P value	Odds ratio	Lower	Upper
RT dose against the site of tooth extracted	0.024	1.231	1.027	1.476
The duration from RT to tooth extraction	0.018	1.084	1.014	1.160

ORN: osteoradionecrosis, RT: radiotherapy, CI: confidence interval

REFERENCES

[1] Grant BP, Fletcher GH. Analysis of complications following megavoltage therapy for squamous cell carcinomas of the tonsillar area. *Am J Roentgenol Radium Ther Nucl Med* 1966;96:28-36.

[2] Maccomb WS. Necrosis in treatment of in treatment of intraoral cancer by radiation therapy. *Am J Roentgenol Radium Ther Nucl Med* 1962;87:431-440.

[3] Withers HR, Peters LJ, Taylor JM, et al. Late normal tissue sequelae from radiation therapy for carcinoma of the tonsil: patterns of fractionation study of radiobiology. *Int J Radiat Oncol Biol Phys* 1995;33:563-568.

[4] Muray CG, Herson J, Daly TE, Zimmerman S. Radiation necrosis of the mandible: a 10 year study. Part II. Dental factors; onset, duration and management of necrosis. *Int J Radiat Oncol Biol Phys* 1980;6:549-553.

[5] Lee IJ, Koom WS, Lee CG, Lee CG, et al. Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. *Int J Radiat Oncol Biol Phys* 2009;75:1084-1091.

[6] Reuther T, Schuster T, Mende U, Kübler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumor patients – A report of a thirty year retrospective review. *Int J Oral Maxillofac Surg* 2003;32:289-295.

[7] Tsai CJ, Hofstede TM, Sturgis EM, et al. Lack of osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys* 2013;85:415-420.

[8] Ben-David MA, Diamante M, Radawski JD, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys* 2007;68:396-402.

[9] Niewald M, Mang K, Barbie O, et al. Dental status, dental treatment procedures and radiotherapy as risk factors for infected osteoradionecrosis (IORN) in patients with

oral cancer: a comparison of two 10 years' observation periods. *Springerplus* 2014;3:263.

[10] Monnier Y, Broome M, Betz M, Bouferrache K, Ozsahin M, Jaques B. Mandibular osteoradionecrosis in squamous cell carcinoma of the oral cavity and oropharynx: incidence and risk factors. *Otolaryngol Head Neck Surg* 2011;144:726-732.

[11] Raguse JD, Hossamo J, Tinhofer I, et al. Patient and treatment-related risk factors for osteoradionecrosis of the jaw in patients with head and neck cancer. *Oral Maxillofac Surg* 2016;121:215-221.

[12] Kojima Y, Yanamoto S, Umeda M, et al. Relationship between dental status and development of osteoradionecrosis of the jaw: a multicenter retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2017;124:139-145.

[13] Koga DH, Salvajoli JV, Alves FA. Dental extractions and radiotherapy in head and neck oncology: review of the literature. *Oral Dis* 2008;14:40-44.

[14] Horiot JC, Bone MC, Ibrahim E, Castro JR. Systematic dental management in head and neck irradiation. *Int J Radiat Oncol Biol Phys* 1981;7:1025-1029.

[15] Epstein JB, Rea G, Wong FL, Spinelli J, Stevenson-Moore P. Osteonecrosis-study of the relationship of dental extractions in patients receiving radiotherapy. *Head Neck Surg* 1987;10:48-54.

[16] Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. *Int J Oral Maxillofac Surg* 2011;40:229-243.

[17] The Japanese Society of Oral Oncology. Japanese Clinical Practice Guideline for Oral Cancer, 2013.

[18] Wahl MJ. Osteoradionecrosis prevention myths. *Int J Radiat Oncol Biol Phys* 2006;64:661-669.

[19] Chen J, Wang C, Wong Y, et al. Osteoradionecrosis of mandible bone in oral cancer patients associated factors and treatment outcomes. *Head Neck* 2016;38:762-768.

[20] Kuoa TJ, Leungb CM, Chang HS, et al. Jaw osteoradionecrosis and dental extraction after head and neck radiotherapy: a nationwide population-based retrospective study in Taiwan. *Oral Oncol* 2016;56:71-77.

[21] Studer G, Studer SP, Zwahlen RA, et al. Osteoradionecrosis of the mandible: minimized risk profile following intensity-modulated radiation therapy (IMRT). *Strahlenther Onkol* 2006;182:283-288.

[22] Muraki Y, Akashi M, Ejima Y, et al. Dental intervention against osteoradionecrosis of the jaws in irradiated patients with head and neck malignancy: a single-arm prospective study. *Oral Maxillofac Surg* 2019;23:297-305.

[23] A C Tong, A C Leung, J C Cheng, et al. Incidence of complicated healing and osteoradionecrosis following tooth extraction in patients receiving radiotherapy for treatment of nasopharyngeal carcinoma. Aust Dent J. 1999;44:(3):187-94.

[24] Gomez DR, Estilo CL, Wolden SL, et al. Correlation of osteoradionecrosis and dental events with dosimetric parameters in intensity-modulated radiation therapy for head-and-neck cancer. *Int J Radiation Oncology Biol Phys* 2011;81:207-213.

[25] Wanifuchi S, Akashi M, Ejima Y, et al. Cause and occurrence timing of osteoradionecrosis of the jaw: a retrospective study focusing on prophylactic tooth extraction. *Oral Maxillofac Surg* 2016;20:337-342.

LEGENDS

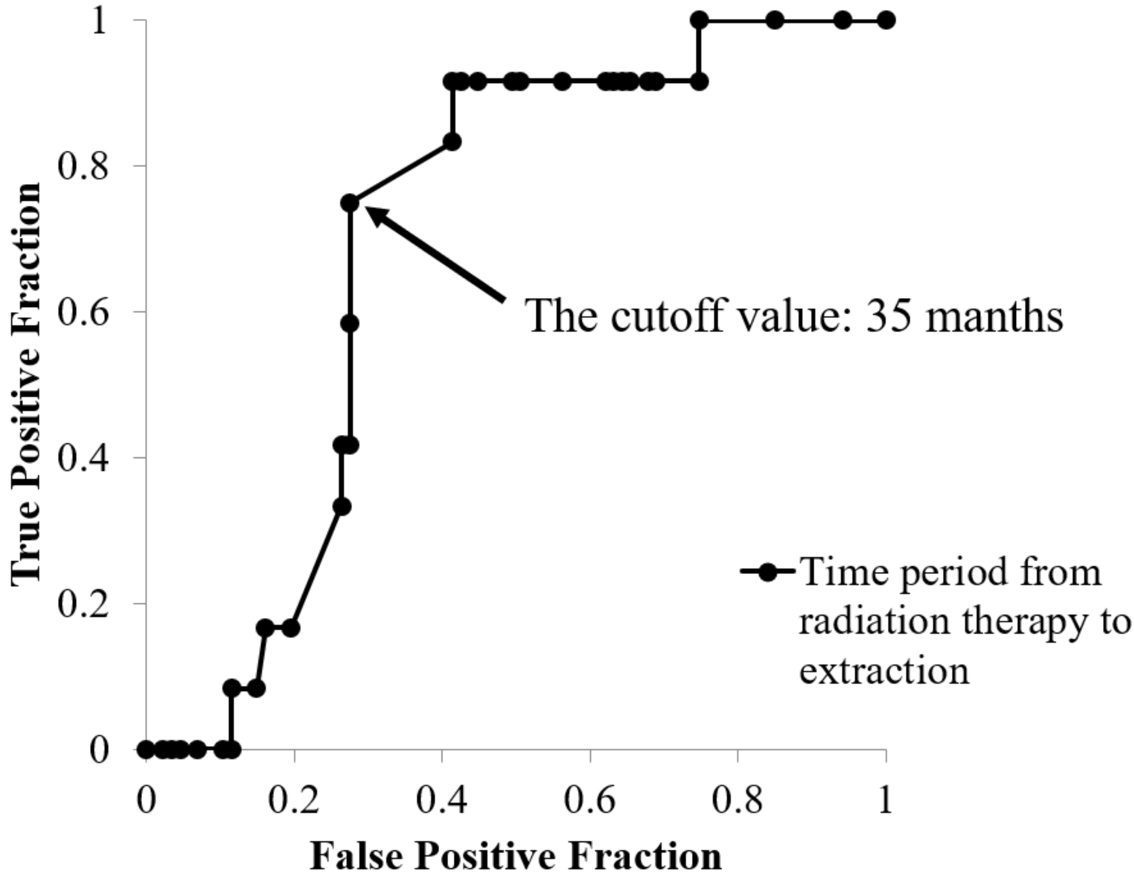
Table 1. Characteristics and incidence rates of ORN in patients who underwent tooth extraction after RT

Table 2. Results of multivariate logistic regression analysis of risk factors for ORN

Fig. 1 ROC curve of the duration from RT to tooth extraction

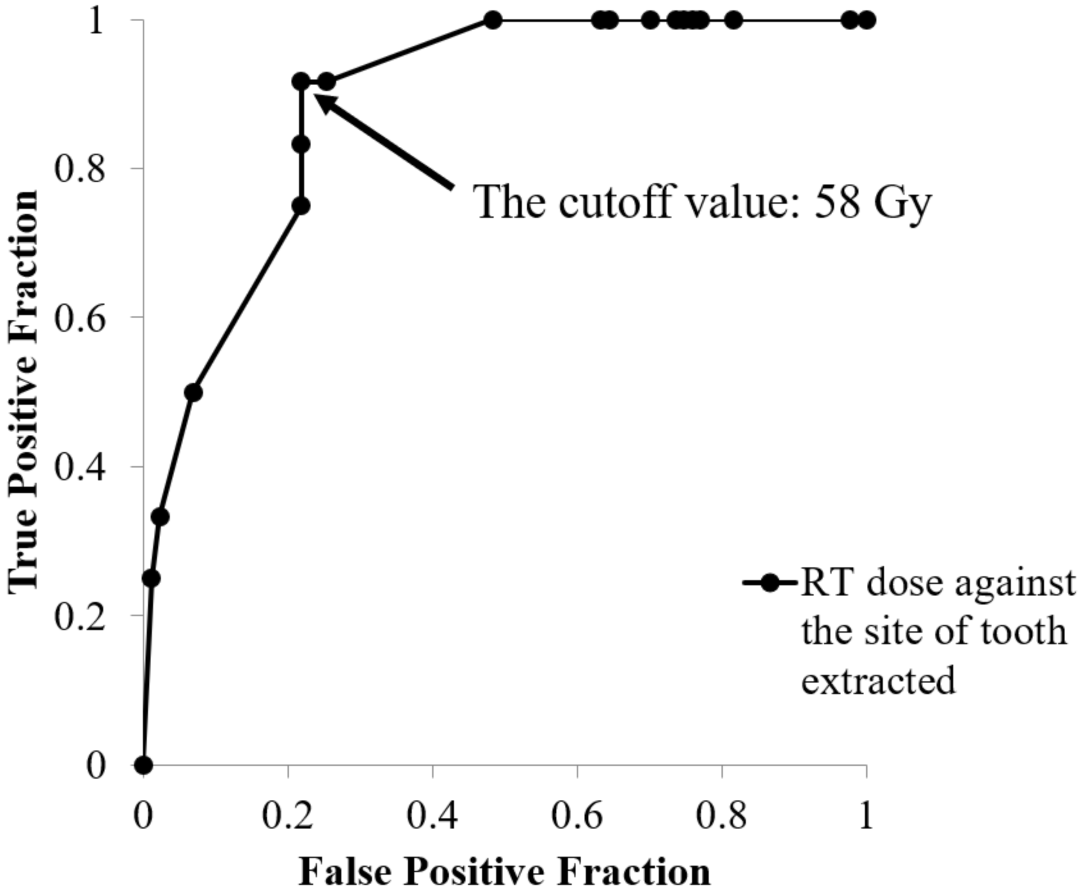
Fig. 2 ROC curve of RT dose against site of tooth extraction

Fig.1



True Positive Fraction
1
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1
False Positive Fraction
The cutoff value: 35 manths
Time period from radiation therapy to extraction

Fig.2



1
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1
True Positive Fraction
False Positive Fraction
The cutoff value: 58 Gy
RT dose against the site of tooth extracted