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ORIGINAL ARTICLE

Retrospective analysis of tooth extraction and osteoradionecrosis after low-dose rate brachytherapy for patients with tongue cancer

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Abstract

Objectives This study aimed to investigate the incidence of osteonecrosis of the jawbones (ORN) after tooth extraction in patients undergoing low-dose rate brachytherapy (LDR-BT) and assess its safety.

Methods This study retrospectively analyzed 145 patients with tongue cancer treated at Hiroshima University Hospital from 2007 to 2021 with LDR-BT using 192Ir or 198Au alone, LDR-BT and external beam radiotherapy (EBRT) with or without chemotherapy, and LDR-BT with chemotherapy. Patients' mandible and maxilla were protected with spacers. Forty-seven patients underwent tooth extraction, and the incidence, site, and relationship of ORN with tooth extraction were recorded. A subgroup of 26 patients received additional EBRT to the neck after dissection for late cervical lymph node metastases.

Results Of 145 patients, six (4.1%) developed ORN on the same side of the mandible as LDR-BT, and EBRT was performed before and/or after LDR-BT on the sites where ORNs developed. Five of 47 (10.6%) patients who underwent tooth extraction after LDR-BT developed ORN. ORN incidence was 1.8% (2/109) in the LDR-BT and/or chemotherapy group and 11.1% (4/36) in the combination LDR-BT and EBRT and/or chemotherapy group for primary tongue cancer. Different irradiation methods (LDR-BT and/or chemotherapy and combination LDR-BT and EBRT and/or chemotherapy) and the presence or absence of tooth extraction showed significant differences ($p = 0.0335$ and $p = 0.0139$, respectively) with or without ORN.

Conclusions Mandibular tooth extraction should be avoided on the side of LDR-BT in combined EBRT cases. However, tooth extraction is feasible using a spacer in LDR-BT and/or chemotherapy.

Keywords Radiotherapy · Brachytherapy · Tooth extraction · Osteoradionecrosis

Introduction

Osteoradionecrosis of the jaw bones (ORN) is a potential complication of radiotherapy for head and neck cancers, with reported incidences ranging from 2.7 to 7.7% [1–5]. In recent years, the high precision of radiotherapy from conventional three-dimensional conformal radiation therapy to intensity modulated radiation therapy or volumetric modulated arc therapy has reduced the incidence of ORN [6, 7]. Although the incidence of ORN is low, its treatment continues to be challenging.

Tooth extraction is one of the risk factors for the development of ORN, and hence, extraction before radiotherapy is recommended for those with a poor prognosis. However, a meta-analysis comparing the incidence of ORN between groups that underwent tooth extraction before and after radiotherapy showed no statistical differences [8]. Tooth extraction after radiotherapy is contraindicated, and the timing of tooth extraction in patients treated with radiotherapy remains controversial. Nevertheless, the extraction of teeth with advanced odontogenic infection is necessary to avoid the development of osteomyelitis. Therefore, the risks and benefits of tooth preservation and extraction should be carefully considered.

Unlike external beam radiotherapy (EBRT), where dose distribution can be recorded using CT images, it is difficult to accurately determine the radiation dose with LDR-BT due to its implanted nature. Therefore, the effect of radiation

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on the jawbone should be considered when planning tooth extraction in patients treated with LDR-BT. Factors such as the site of extraction, site of the lesion treated with radiotherapy, type and location of radioactive sources used, and use of spacers should be taken into account to determine the feasibility of tooth extraction.

The purpose of this study was to investigate the incidence of ORN in patients who underwent tooth extraction after LDR-BT through a retrospective clinical chart review to assess the safety of tooth extraction.

Patients and methods

The study involved patients with tongue cancer who were treated with LDR-BT using ^{192}Ir or ^{198}Au alone or in combination with chemotherapy or in combination with EBRT and/or chemotherapy at Hiroshima University Hospital between 2007 and 2021. Of the 172 patients with tongue cancer treated with LDR-BT, 27 were excluded from the study due to inadequate medical records, edentulous jaws, re-irradiation, LDR-BT on both sides of the tongue, and lesions located in the midline of the tongue. The remaining 145 patients were included in this study. Patients who developed late cervical lymph node metastasis after primary treatment for tongue cancer and underwent neck dissection followed by postoperative EBRT of the neck were also irradiated to the jawbone; therefore, the effect of radiation on the jawbone was also investigated. The patient selection and characteristics are shown in Fig. 1 and Table 1. The mean patient age was 60.2 years, with 88 male and 57 female patients. All patients had histopathologically confirmed squamous cell carcinoma, and the absence of metastases was confirmed using ultrasonography, CT, and/or PET/CT. The median follow-up period was 83 months (range, 13–180 months). Of the 145 patients, 47 underwent tooth extraction. The data were reviewed in February 2023.

Table 1 Patient characteristics ($n = 145$)

Age at diagnosis (years, mean ± S.D.)	60.2 ± 14.0
Sex (male/female)	88/57
Follow-up period (months), (median (min.-max.)	83 (13–180)
T-factor (is/1/2/3/4)	6/39/89/11
Treatment	
Brachytherapy alone	99
Combination with EBRT and chemotherapy	34
Combination with EBRT	2
Combination with chemotherapy	10
Radioactive sources	
^{192}Ir	88
^{198}Au	57
Tooth extraction	
Present	47
Absent	98
Neck dissection	48/145
Late cervical lymph node metastasis	44/145
Postoperative EBRT after neck dissection	26/44

EBRT external beam radiotherapy

LDR-BT was performed as reported in previous reports [9, 10]. A spacer, used for dental impressions and made of silicone rubber of approximately 10 mm in thickness, including a lead plate of approximately 4 mm in thickness, was used to protect the mandible and maxilla in all patients [10, 11]. EBRT was administered in combination with LDR-BT at doses of 30 Gy (2 Gy/fraction at a rate of 5 fractions/week with a total of 15 fractions

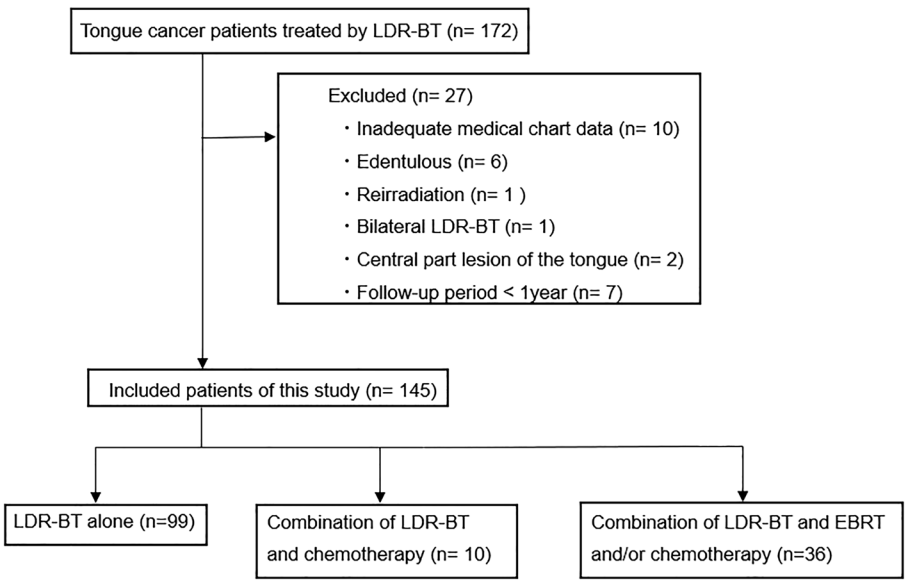

Fig. 1 Flowchart of patient selection. *LDR-BT* low-dose rate brachytherapy, *EBRT* external beam radiotherapy

over a 3-week period). A 4- or 6-MV X-ray through a lateral field, lateral parallel opposed fields, or orthogonal fields to a volume encompassing the primary site and upper neck area was used. The chemotherapy regimens included S1 (tegafur, gimeracil, and oteracil potassium) alone, UFT (tegafur and uracil) alone, nedaplatin alone, docetaxel hydrate alone, cisplatin and 5-fluorouracil combination, S1 and cisplatin combination, and nedaplatin and S1 combination.

As shown in Fig. 2, the extraction sites were classified as category 1 for the mandible ipsilateral to brachytherapy, category 2 for the mandible contralateral to brachytherapy, category 3 for the maxilla ipsilateral to brachytherapy, and category 4 for the maxilla contralateral to brachytherapy. If more than one extraction was performed per patient, each extraction site was counted as one extraction site. The diagnosis of ORN was determined by clinical findings. ORN in this study was defined as an exposed irradiated bone that failed to heal over a period of 3 months without evidence of persistent or recurrent tumors [12].

The results were compared between groups with and without ORN using the Wilcoxon rank-sum test for numerical data, and the chi-square test and Fisher's exact test for categorical data. Statistical significance was set at $p < 0.05$. JMP Pro version 16.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. This study was approved by the local institutional ethics committee (registration: E-458-1, E2022-0159) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out in accordance with the guidelines of the local institutional ethics committee.

Results

Of the 145 patients, six developed ORN, resulting in an incidence of 4.1%. Additionally, ORN developed in 5 of 47 (10.6%) patients who underwent tooth extraction after LDR-BT. Comparisons of patients with and without ORN are highlighted in Tables 2 and 3. The incidence of ORN was 1.8% (2/109) in the treatment with LDR-BT and/or chemotherapy and 11.1% (4/36) in the treatment with combination LDR-BT and EBRT and/or chemotherapy). Statistically significant differences were observed between different irradiation methods (LDR-BT and/or chemotherapy and combination LDR-BT and EBRT and/or chemotherapy) and the presence or absence of tooth extraction ($p = 0.0335$ and $p = 0.0139$, respectively) with and without ORN. In addition, the incidence of ORN was significantly higher in the group that underwent neck dissection and postoperative EBRT after neck dissection ($p = 0.0153$ and $p = 0.0097$, respectively). The analysis of the incidence of ORN only in cases with tooth extraction showed that it was significantly associated with ORN development in the group that underwent neck dissection after LDR-BT and in the group that underwent EBRT after neck dissection ($p = 0.0396$ and $p = 0.0111$, respectively). Statistically significant differences were found in the occurrence of ORN between category 1 and the other categories (category 2, 3, and 4) ($p = 0.0496$). Forty-seven patients underwent tooth extraction after LDR-BT, with 80 sites in each category. The number of cases according to the site of tooth extraction was 24, 20, 18, and 18 in categories 1 through 4, respectively. The characteristics of patients who developed ORN are listed in Table 4. All ORN sites were on the same side of the mandible as the side of LDR-BT (category 1). There were no cases of ORN

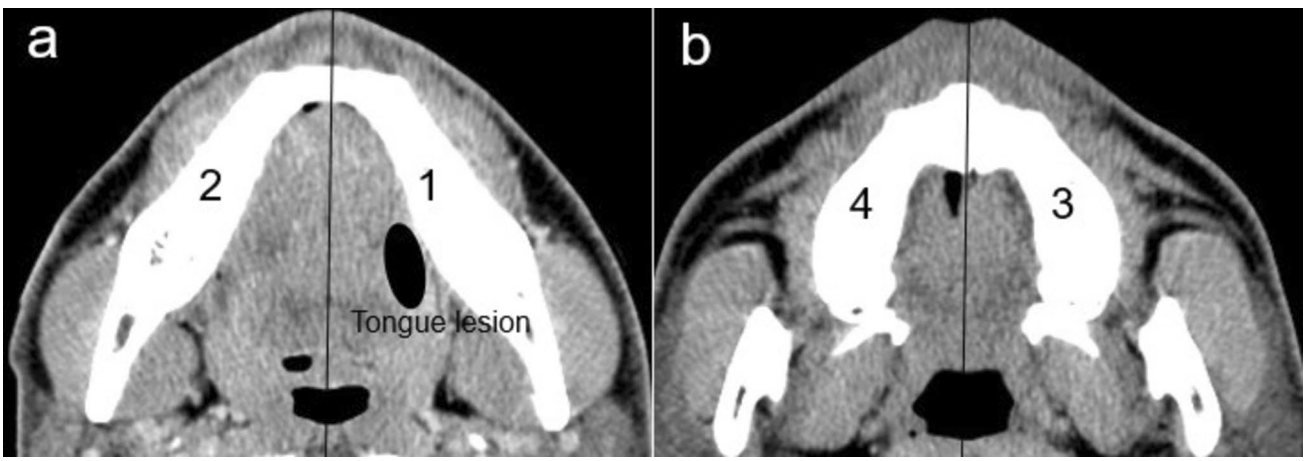

Fig. 2 Classification of tooth extraction sites by axial computed tomography images. The extraction sites were classified as category 1 for the mandible ipsilateral to the brachytherapy, category 2 for the mandible contralateral to the brachytherapy, category 3 for the maxilla ipsilateral to the brachytherapy, and category 4 for the maxilla contralateral to the brachytherapy

Table 2 Comparison of ORN incidence

	ORN ($n=6$)	Non-ORN ($n=139$)	p-value
Age (years, mean ± S.D.)	64.3 ± 10.6	60.0 ± 14.2	0.5026
Sex (male/female)	5/1	83/56	0.4036
Follow-up period (months, median (min.-max.)	116.5 (24–151)	83 (13–180)	0.3405
T-factor (is/1/2/3)	0/1/5/0	6/38/84/11	0.8444
Radioactive sources			
^{192}Ir/^{198}Au	5/1	83/56	0.4036
Irradiation method for primary tongue cancer			
Brachytherapy and/or chemotherapy ($n=109$)	2	107	0.0335*
Brachytherapy + EBRT and/or chemotherapy ($n=36$)	4	32	
Neck dissection			
Present ($n=48$)	5	43	0.0153*
Absent ($n=97$)	1	96	
Postoperative EBRT for neck region			
Present ($n=26$)	4	22	0.0097*
Absent ($n=119$)	2	117	
Tooth extraction			
Present	5	42	0.0139*
Absent	1	97	

EBRT external beam radiotherapy; *ORN* osteonecrosis of the jawbones

*Statistically significant difference

development in categories 2, 3, and 4 for all treatment types or category 1 for LDR-BT alone. Five of the six patients who developed ORN underwent tooth extraction; four of these six patients had received EBRT prior to LDR-BT, and four had received EBRT in addition to treatment after neck dissection for late cervical lymph node metastases. The sites where ORN developed were all within the EBRT irradiation field. Four of the six ORN cases were treated conservatively, while two were treated surgically.

Discussion

The incidence of ORN in this study was 4.1%, which is consistent with previously reported cases [1–5]. In this study, ORN development was observed in patients who underwent EBRT before LDR-BT (2 cases) or additional EBRT after neck dissection for late lymph node metastases after LDR-BT (2 cases) or both (2 cases). The onset of ORN was on the same side of the mandible as LDR-BT (category 1). Statistically significant differences were found in the occurrence of ORN between category 1 and the other categories. Based on the study results, which showed that no cases of ORN developed in categories 2, 3, and 4 for all treatment types or category 1 for LDR-BT alone, the mandible contralateral to brachytherapy (category 2) or the maxilla (categories 3 and 4) were considered acceptable for tooth extraction after LDR-BT. In cases of LDR-BT alone, tooth extraction in the mandible ipsilateral to LDR-BT (category 1) was considered acceptable with the use of a spacer. Previous studies have reported the effectiveness of spacers in preventing ORN in LDR-BT for tongue cancer [13–16].

Miura et al. reported that the use of a spacer during treatment with LDR-BT for patients with tongue cancer reduced the absorbed dose on the lingual surface of the lower gingiva by approximately 50% compared with that without a spacer. The incidence of ORN with and without a spacer was statistically significant ($p=0.0004$), with only 2.1% (1 of 48 patients) developing ORN with a spacer and 40.0% (22 of 55 patients) without a spacer [13]. Fujita et al. reported that in an experiment using ^{192}Ir hairpins, the dose of radiation was reduced by an average of 42.6% with a 10-mm distance and by an average of 34.1% with a 10-mm-thick silicone spacer. Measurements taken on patients treated with LDR-BT reported a reduction of 30–40% with 6–8-mm-thick silicone spacers when treated with ^{192}Ir hairpins [14]. Furthermore, Fujita et al. reported that in a patient undergoing LDR-BT, the use of a 10-mm-thick resin spacer resulted in a reduction of attenuation to 45% and further reduced attenuation to approximately 30% with the insertion of a 2-mm-thick Lipowiz metal inside the resin spacer [15]. This implies that the metal attenuation effect was approximately 15%. The lesion was irradiated with 70 Gy in LDR-BT, and the dose to the lingual surface of the mandible was estimated to be approximately 20 Gy when using a silicone spacer with metal. Despite considering the length of time the spacer was removed for medical care and eating during LDR-BT, the maximum irradiation dose to the mandible was estimated to

Table 3 Comparison of ORN incidence based on tooth extraction ($n=47$)

	ORN ($n=5$)	Non-ORN ($n=42$)	p-value
Age (years, mean ± S.D.)	66.0 ± 10.9	62.1 ± 12.8	0.5572
Sex (male/female)	4/1	28/14	0.5454
Follow-up period (months, median (min.-max.)	119 (24–151)	92 (27–180)	0.5010
T-factor (is/1/2/3)	0/1/4/0	3/8/25/6	0.7109
Radioactive sources			
^{192}Ir/^{198}Au	5/0	28/14	0.3029
Irradiation method for primary tongue cancer			
Brachytherapy and/or chemotherapy ($n=29$)	2	27	0.3568
Brachytherapy + EBRT and/or chemotherapy ($n=18$)	3	15	
Neck dissection			
Present ($n=16$)	4	12	0.0396*
Absent ($n=31$)	1	30	
Postoperative EBRT for neck region			
Present ($n=6$)	3	3	0.0111*
Absent ($n=41$)	2	39	
Tooth extraction site			
Category 1	5	19	0.2643
Category 2	0	10	
Category 3	0	8	
Category 4	0	5	
Tooth extraction site (Comparison of category 1 with other categories)			
Category 1	5	19	0.0496*
Category 2,3, and 4	0	23	

Category: category 1; the mandible ipsilateral to brachytherapy, category 2; the mandible contralateral to brachytherapy, category 3; the maxilla ipsilateral to brachytherapy, category 4; the maxilla contralateral to brachytherapy

EBRT external beam radiotherapy; *ORN* osteonecrosis of the jawbones

*Statistically significant difference

be approximately 30 Gy. In the case of LDR-BT, the dose decreases sharply as the distance increases; therefore, even if the dose was approximately 30 Gy on the lingual surface of the mandible, it would have been approximately half the dose on the buccal surface, because the width of the mandible is usually 10–15 mm or more [16]. The irradiated dose was the highest on the lingual surface of the mandible and gradually decreased toward the buccal surface. Therefore, if ORN occurs, symptoms such as bone exposure and osteonecrosis may appear in the cortical bone on the lingual side, where the radiation dose is the highest. These symptoms do not spread to the entire mandible and are often localized. When a combination of LDR-BT and EBRT is used, EBRT results in a high dose evenly distributed over the entire mandible, and ORN may spread to the entire mandible. In our study, this led to surgical intervention in one case. When using LDR-BT with EBRT, tooth extraction in category 1 cases should be avoided. The incidence of ORN was significantly higher in both groups that underwent neck dissection and those who underwent neck dissection with postoperative EBRT. A possible reason for these findings could be that postoperative EBRT was administered to four of five patients who developed ORN after cervical dissection.

This study has several limitations. First, in all cases, spacers were used to prevent ORN, resulting in only six cases of ORN, which limited the statistical analysis of ORN characteristics. Second, the dose calculation for LDR-BT in this study was not CT-based, making it impossible to calculate the radiation dose to the jawbone in individual cases. Third, the extraction dates for several patients were from other clinics, making it challenging to obtain precise dates of extractions from the hospital's medical records. Finally, since oral hygiene has also been reported as a factor associated with ORN development [1, 17, 18], it should have also been included in this study. However, since the majority of our study patients did not receive oral care intervention from the dentist and dental hygienist, oral hygiene could not be studied. In the future, it will be necessary to examine ORN development in relation to oral hygiene status as well.

In conclusion, this study suggests that tooth extraction following LDR-BT for tongue cancer using a spacer is a safe procedure. None of the cases resulted in ORN following

Table 4 Characteristics of the six patients with ORN

Age	Sex	T-factor	Radio-active sources	EBRT dose before LDR-BT	Chemotherapy before LDR-BT	Category of tooth extraction	Lesion side	Bone site	Onset of ORN after LDR-BT (months)	Treatment for ORN	Additional treatment
56	M	2	^{198}Au	30 Gy	S1	–	Right	Right mandible	13	Non-surgery	ND, EBRT 50 Gy, CDDP + 5FU
76	M	1	^{192}Ir	–	–	1	Right	Right mandible	90	Non-surgery	ND, EBRT 50 Gy, CDDP + 5FU
76	F	2	^{192}Ir	30 Gy	S1	1,3	Right	Right mandible	62	Surgery	(-)
51	M	2	^{192}Ir	30 Gy	UFT	1,2	Left	Left mandible	43	Non-surgery	(-)
59	M	2	^{192}Ir	30 Gy	CDDP + 5-FU	1,3	Left	Left mandible	89	Surgery	ND, EBRT 50 Gy, CDDP + 5FU
68	M	2	^{192}Ir	–	–	1	Right	Right mandible	19	Non-surgery	ND, EBRT 60 Gy

Category: category 1; the mandible ipsilateral to brachytherapy, category 2; the mandible contralateral to brachytherapy, category 3; the maxilla ipsilateral to brachytherapy, category 4; the maxilla contralateral to brachytherapy

Additional treatment: treatment for late cervical lymph node metastasis (-): no late cervical lymph node metastasis

EBRT external beam radiotherapy; *ORN* osteonecrosis of the jawbones; *LDR-BT* low-dose rate brachytherapy; *ND* neck dissection; *S1* tegafur, gimeracil, and oteracil potassium; *UFT* tegafur, uracil; *CDDP* cisplatin

tooth extraction at any site after LDR-BT and/or chemotherapy without postoperative EBRT for neck dissection, including tooth extraction on the mandible adjacent to the highest risk treatment site for ORN. These results suggest that properly applied spacers can be an effective preventative measure. However, caution should be exercised when considering tooth extraction from the ipsilateral mandible in patients who have undergone EBRT in combination with LDR-BT. In summary, our findings provide valuable insights for clinicians considering dental extraction following LDR-BT treatment for tongue cancer.

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Data availability The datasets generated and/or analyzed during the current study are not publicly available due to the ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Masaru Konishi, Kiichi Shimabukuro, and Naoya Kakimoto declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Informed consent Informed consent was obtained in the form of an opt-out in accordance with the guidelines of the local institutional ethics committee.

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