

Reirradiation Using ^{198}Au Grain Brachytherapy for Recurrent Oral Cancer Cases Previously Treated by Definitive Radiotherapy

MASARU KONISHI¹, YUKI TAKEUCHI², KATSUMARO KUBO², NOBUKI IMANO²,
IKUNO NISHIBUCHI², YUJI MURAKAMI², KIICHI SHIMABUKURO³,
PONGSAPAK WONGRATWANICH³, NAOYA KAKIMOTO³ and YASUSHI NAGATA²

¹Department of Oral and Maxillofacial Radiology, Hiroshima University Hospital, Hiroshima, Japan;

²Department of Radiation Oncology, Graduate School of Biomedical and Health Sciences,
Hiroshima University, Hiroshima, Japan;

³Department of Oral and Maxillofacial Radiology,
Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Abstract. *Background/Aim:* We investigated treatment outcomes and complications during reirradiation of patients with oral cancers. *Patients and Methods:* Six patients who received definitive radiotherapy for oral cancer as the initial treatment and brachytherapy for recurrence were included. Local control and overall survival rates, soft tissue and mandibular complications, and tooth extraction were investigated. *Results:* The five-year local control and overall survival rates were 83.3% and 100%, respectively. The occurrence rate of grade 2 soft tissue and mandible complications was 33.3%, and the primary sites were the buccal mucosa and the floor of mouth. The positions of the extracted tooth in the two cases were adjacent to the tumor, and one case developed grade 2 complication of the mandible. *Conclusion:* During recurrence of the buccal mucosa and the floor of mouth cancers, reirradiation should be avoided considering mandibular complications. To avoid reirradiation-related complications, tooth extraction near the radiation field should be avoided.

Brachytherapy is often performed when considering form and function after treatment of head and neck cancer patients; however, primary lesion recurrence is occasionally

Correspondence to: Masaru Konishi, Department of Oral and Maxillofacial Radiology, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8553, Japan. Tel: +81 822575693, Fax: +81 822575692, e-mail: mkonishi@hiroshima-u.ac.jp

Key Words: Oral cancer, radiotherapy, brachytherapy, reirradiation, complication.

observed even after definitive treatment. The local recurrence rates for T1 and T2 squamous cell carcinoma (SCC) of the tongue were reported to be 4.3%-20% for T1, 16.8%-26% for T2, and 16%-28% for T1/T2 after low-dose-rate (LDR) brachytherapy (^{192}Ir , ^{60}Co , ^{226}Ra , ^{222}Rn , ^{198}Au) alone or a combination of LDR brachytherapy and/or external beam radiotherapy (EBRT) and/or chemotherapy (1-5). However, the local recurrence rates for T1 and T2 SCC of the floor of the mouth treated with ^{198}Au grain brachytherapy were reported to be 11% and 30%, respectively (6). By contrast, upon treatment with LDR ^{192}Ir brachytherapy and/or EBRT, the five-year local recurrence rates for T1 and T2 SCC were reported to be 7% and 12%, respectively (7). Furthermore, the local recurrence rate of T1/T2 SCC of the buccal mucosa treated with ^{198}Au grain brachytherapy alone or the combination of ^{198}Au grain brachytherapy and EBRT was reported to be 24.8% (8).

In the case of recurrence after definitive radiotherapy for oral cancers, surgery is often the treatment choice when the severe complications caused by excessive radiation doses are taken into consideration (9-14). However, patients who originally preferred radiotherapy for their initial treatment may also want radiotherapy during cases of recurrence. Moreover, some patients may be too advanced in age or have systemic diseases, which could limit them from undergoing surgery and lead to difficulties during decision-making in terms of treatment. In some cases, reirradiation can be considered as a treatment option.

There are some reports regarding the treatment of oral cancer recurrence with definitive radiotherapy (15-17). However, definitive conventional EBRT is not recommended for the treatment of relapse following definitive EBRT, although brachytherapy could reportedly be considered (15, 16).

Table I. Characteristics of the enrolled patients during initial treatment.

Case No.	Age	Gender	Primary site	Lesion length (mm)	Lesion thickness (mm)	TNM (UICC 8 th ed.)	Initial treatment					
							Brachytherapy	No. of ¹⁹² Ir pin or ¹⁹⁸ Au grain	Total dose, dose rate, irradiation time of brachytherapy	EBRT (dose, Gy)	Chemotherapy	Neck dissection
1	70	F	Tongue	(-) [†]	(-) [†]	T1N0M0	¹⁹² Ir-LDR*	2 hairpins	70 Gy 55 cGy/h 127 h	-	-	-
2	44	F	Tongue	38	16	T2N0M0	¹⁹² Ir-LDR*	2 hairpins	68 Gy 90 cGy/h 75 h	-	CDDP (artery injection), S-1	-
3	49	F	Tongue	24	8	T2N2bM0	¹⁹² Ir-LDR*	2 hairpins	61 Gy 65 cGy/h 94 h	30	CDDP + 5FU	+
4	61	M	Tongue	38	18	T2N0M0	¹⁹² Ir-LDR*	4 hairpins 1 single pin	55 Gy, 55 cGy/h 100 h	30	S-1	-
5	68	M	Floor of the mouth	22	7	T2N0M0	¹⁹⁸ Au-LDR*	6	69 Gy/∞ 57 Gy/7 days	30	CDGP + S-1	-
6	88	M	Buccal mucosa	18	5	T1N0M0	¹⁹⁸ Au-LDR*	7	67 Gy/∞ 56 Gy/7 days	-	-	-

*LDR: Low-dose rate brachytherapy. [†](-): No description in the medical chart. 5FU: 5-Fluorouracil; M: male; F: female; CDDP: cisplatin; EBRT: external beam radiotherapy; S-1: tegafur, gimeracil, and oteracil potassium.

An increase in adverse events due to overdose is a problem during cases of reirradiation. Therefore, a more accurate dose to the lesion or surrounding tissues should be identified before reirradiation treatment. However, in the case of LDR brachytherapy, the dose is calculated not from computed tomography (CT) images but from plain radiographs of the head, making it difficult to more accurately calculate the radiation dose of the surrounding tissues, such as the mandible. In addition, brachytherapy may be combined with EBRT, making it increasingly difficult to assess the biological effects on the surrounding tissues.

Therefore, in the present study, we evaluated the treatment outcomes and the relationships between the radiation dose and the complications in patients who were mainly treated with ¹⁹⁸Au grain brachytherapy for recurrent oral cancers; in particular, we considered the biological effects to the surrounding tissues, and the analysis primarily involved patients who were treated with LDR brachytherapy.

Patients and Methods

Patients. Among the 186 patients who underwent LDR brachytherapy using the radioactive sources ¹⁹²Ir or ¹⁹⁸Au for oral and oropharyngeal cancer between 2003 and 2011 at Hiroshima University Hospital, 19 had local recurrence. Six of the 19 patients

who again underwent definitive interstitial brachytherapy were included in the study. The other 13 patients were treated by surgery. Among all the included participants, reirradiation was chosen when the patients rejected surgery. Although it is difficult to distinguish recurrence from secondary primary cancer among cases that occurred near the primary tumor more than five years later, these cases were treated as recurrence.

The characteristics of the subjects during initial treatment are shown in Table I. Four patients had primary lesions in the tongue, one in the floor of the mouth, and one in the buccal mucosa. Among the participants, four were males and two were females. The median age during initial treatment was 64.5 years old (range=44-88 years). Moreover, the Union for International Cancer Control classifications (UICC) (18) for TNM during initial treatment were T1N0M0 in two cases, T2N0M0 in three cases, and T2N2bM0 in one case. The types of radioactive sources for the initial brachytherapy were ¹⁹²Ir in four patients and ¹⁹⁸Au in the remaining two patients. Three patients were treated with EBRT and chemotherapy before brachytherapy. The chemotherapy regimens included a combination of cisplatin (CDDP) and 5-fluorouracil (5-FU), S-1 (tegafur, gimeracil, and oteracil potassium) alone, and a combination of nedaplatin (CDGP) and S-1. EBRT was applied at a dose of 30 Gy (2 Gy/fraction, five fractions/week, 15 fractions) using a 6-MV X-ray through a lateral, lateral parallel, or orthogonal field to a volume encompassing the primary site. One patient received an arterial injection of CDDP and then S-1.

Treatment for recurrence. The patient characteristics during reirradiation are shown in Table II. All recurrences were

Table II. Characteristics of the enrolled patients during reirradiation by brachytherapy.

Case No.	rTNM classification	Lesion length (mm)	Lesion thickness (mm)	Interval* (month)	Treatment	No. of ¹⁹⁸ Au grain	MBq/grain	Permanent total dose of ¹⁹⁸ Au grain (Gy/∞)	Initial 7-day dose of ¹⁹⁸ Au grain (Gy/7 days)
1	rT1N0M0	12.7	4.7	63	¹⁹⁸ Au alone	7	177	88	73
2	rT2N0M0	32	5	58	¹⁹⁸ Au alone	12	186	84	69
3	rT2N0M0	14	7	13	¹⁹⁸ Au alone	9	195	69	57
4	rT2N0M0	30.1	6.4	74	¹⁹⁸ Au alone	14	178	101	84
5	rT2N0M0	22	5	27	¹⁹⁸ Au alone	5	178	79	66
6	rTisN0M0	17.4	5.1	15	¹⁹⁸ Au alone	10	189	102	85

*Interval: the period between initial treatment and reirradiation by brachytherapy.

Table III. Calculation of biological effective dose.

Radiotherapy	Tumor site	Absorbed dose (Gy)	Biological effective dose (BED) (Gy)
External beam radiotherapy	Tongue, buccal mucosa, and floor of the mouth	Absorbed dose=tumor dose=mucosa dose=lingual surface of the mandibular gingiva dose	$BED=nd\{1+d/(\alpha/\beta)\}$
Brachytherapy with ¹⁹² Ir or ¹⁹⁸ Au	Tongue	Absorbed dose=tumor dose (tumor) Absorbed dose=1/2•tumor dose (mucosa/lingual surface of the mandibular gingiva)	$BED=(R_0/\lambda) [1+\{R_0/(\mu+\lambda)(\alpha/\beta)\}]$
	Buccal mucosa, and floor of the mouth	Absorbed dose=tumor dose=mucosa dose=lingual surface of the mandibular gingiva dose	

n: Number of fractions; d: dose/fraction; $\alpha/\beta=10$ (tumor); $\alpha/\beta=3$ (mucosa/mandibular gingiva); R0: initial dose rate of the implant; μ : repair rate constant=0.693/t1/2; t1/2=tissue repair half-time; λ : radioactive decay constant=0.639/T1/2; T1/2: radioactive half-life of the isotope.

histopathologically diagnosed by biopsy. The lesion size and form were examined through inspection, palpation, lugol staining, intraoral ultrasonography, computed tomography (CT), magnetic resonance imaging, or positron emission tomography-CT. The median interval between reirradiation and the first treatment was 42.5 months (range=13-74 months). The UICC classifications of TNM at recurrence were rTisN0M0 in one case, rT1N0M0 in two cases, and rT2N0M0 in three cases. All patients were treated with ¹⁹⁸Au grain brachytherapy alone.

The planning of ¹⁹⁸Au grain brachytherapy was determined through intraoral ultrasonographic images and lugol staining, in addition to inspection and palpation. The initial ¹⁹⁸Au grain activity was approximately 185 MBq ± 10% per grain at the start of reirradiation. The ¹⁹⁸Au grain implantation technique performed as follows: the grains were arranged 1 cm apart from every grain, and the outer side grains were implanted under local anesthesia 5 mm outside of the lesion, which had no lugol staining areas. Spacers were introduced in all patients to reduce the exposure dose to the mandible and planarize the mucosa surface. These spacers were made of silicon rubber material for dental impressions, with a thickness of approximately 1 cm. A lead plate of approximately 4-mm thickness was placed in the silicon spacer.

The permanent dose for ¹⁹⁸Au grain brachytherapy was calculated using the X-ray image taken approximately one day after ¹⁹⁸Au

grain implantation. The calculation method is described as follows: Treatment area (cm²)=π/4 × area calculated using X-ray image (cm²) The activity required to deliver 10 Gy to the therapeutic area was calculated according to Manchester system (19). This value was considered as variable A.

Permanent total dose (Gy/∞)=Activity/grain (MBq) × Number of grain/37×10/A

The biological effective dose (BED) to the tumor (BED10) as an early response and the mucosa or lingual surface of the mandibular gingiva (BED3) as a late response was calculated (20-24, see Table III).

Assessment of treatment outcomes, complications, and dental status.

Follow-up was performed every month for at least one year after the irradiation treatment, and local recurrence and cervical lymph node metastases were determined using ultrasonography or CT every month. Local control, cause-specific survival, and overall survival rates were investigated. The relationships between treatment outcomes or complications and the total radiation dose or biological effective dose of the first and second radiotherapies were investigated. The incidence of radiation-induced soft tissue and mandibular complications was also surveyed. The complication classification system used was based on that described by Shibuya *et al.* (4) (Table IV). Dental status and tooth extraction were investigated before and after brachytherapy.

Table IV. Definitions of the soft tissue and mandibular bone complications (4).

Grade	Soft tissue complication	Mandibular bone complication
0	No ulcer	No change
1	Transient ulcer disappeared within 6 months	Transient bone exposure disappeared spontaneously
2	Incurable ulcer lasted over 6 months	Bone necrosis, healed by conservative treatment
3	Severe ulcer, necessitating operation	Severe bone necrosis, necessitating operation

Table V. Complications and treatment outcomes after the second brachytherapy.

Case No.	Grade of complications		Outcome	Follow-up period after the 2 nd Br. (months)
	Soft tissue	Mandibular bone		
1	1	1	Cause-specific death (due to local recurrence and cervical lymph node metastasis) 47 months after 2 nd Br.: Local recurrence → surgery 58 months after 2 nd Br.: Local recurrence → surgery 65 months after 2 nd Br.: Local recurrence, neck metastasis → palliation	85
2	0	0	Recurrence and metastasis-free survival after 2 nd Br.	153
3	0	0	Recurrence and metastasis-free survival after 2 nd Br.	97
4	1	0	Recurrence and metastasis-free survival after 2 nd Br.	85
5	2	2	Cause-specific death (distant metastases) 14 months after 1 st Br.: cervical lymph node metastasis → neck dissection and external beam radiotherapy for neck region (50 Gy/25 fraction) and chemotherapy (CDDP + 5-FU) 38 months after 2 nd Br.: lung metastasis → surgery 39 months after 2 nd Br.: metastasis to mediastinal and hilar nodes → external beam radiotherapy (66 Gy/33 fraction) and chemotherapy (CDDP, S-1, UFT) 58 months after 2 nd Br.: metastasis to the brain → external beam radiotherapy to whole brain (30 Gy/10 fraction) 60 months after 2 nd Br.: metastasis to the femur → external beam radiotherapy (39 Gy/13 fraction)	61
6	2	2	Recurrence-free survival after 2 nd Br. 2 months after 1 st Br.: cervical lymph node metastasis → neck dissection and chemotherapy (UFT)	75

LDR: Low-dose rate brachytherapy; Br.: brachytherapy; CDDP: cisplatin; 5-FU: 5-fluorouracil; S-1: tegafur, gimeracil, and oteracil potassium; UFT: tegafur, uracil.

Medical records were reviewed in July 2021. The median follow-up period was 85 months (range=61-153 months) after reirradiation. All patients were followed up until death, or until the data cutoff time (July 2021).

Statistical analyses. Local control and overall survival rates of all patients who underwent reirradiation were assessed using the Kaplan–Meier method. Comparisons of radiation dose were conducted between the groups with and without soft tissue and mandibular complications. The Wilcoxon rank-sum test was used to compare the two groups. A *p*-value of <0.05 was considered statistically significant. JMP, version 14.0 (SAS Institute, Cary, NC, USA), was used for all statistical analyses.

Ethical approval. This study followed the Declaration of Helsinki on medical protocol and ethics, and the regional Ethical Review Board

of Hiroshima University approved the study (registration E-458). In accordance with the guidelines set by the local institutional ethics committee, informed consent was obtained in the form of opt-out.

Results

Treatment outcomes. Treatment outcomes and complications are shown in Table V. The five-year local control rate of the reirradiation treatment was 83.3%, whereas the five-year overall survival rate after reirradiation treatment was 100%. During the follow-up period, two of the six patients died due to causes related to the cancer of the tongue or the floor of the mouth. One patient with buccal mucosa cancer had cervical lymph node metastasis two months after initial

Table VI. *Dental status and tooth extraction.*

Case no. (lesion site)	Remaining teeth (before initial radiotherapy)	Remaining teeth (at latest follow-up)	Tooth extraction and site	Time of tooth extraction
1 (left tongue)	$\frac{21}{321} \frac{12378}{12345}$	$\frac{8}{321} \frac{134}{134}$	$\frac{21}{25} \frac{1237}{25}$ (Including lesion side)	Extraction between initial treatment and reirradiation brachytherapy
2 (right tongue)	$\frac{7654321}{7654321} \frac{1234567}{1234567}$	$\frac{7654321}{7654321} \frac{1234567}{1234567}$	None	-
3 (left tongue)	$\frac{7654321}{7654321} \frac{1234567}{1234567}$	$\frac{7654321}{7654321} \frac{1234567}{1234567}$	None	-
4 (right tongue)	$\frac{7654321}{7654321} \frac{123467}{1234567}$	$\frac{7654321}{7654321} \frac{123467}{1234567}$	None	-
5 (right floor of the mouth)	$\frac{7654321}{7654321} \frac{1234578}{12346}$	$\frac{7654321}{7654321} \frac{234578}{1234}$	$\frac{1}{6}$ (Not including lesion side)	Extraction between initial and reirradiation brachytherapy
6 (left buccal mucosa)	$\frac{75432}{754321} \frac{1234567}{12345}$	$\frac{7532}{54321} \frac{123567}{12345}$	$\frac{4}{7} \frac{4}{7}$ (Including lesion side)	Extraction after reirradiation brachytherapy

Table VII. *Biological effective dose of EBRT and brachytherapy.*

Case No.	Biological effective dose (Gy)									Total biological effective dose (Gy)		
	Initial treatment						Reirradiation treatment			Tumor (Gy ₁₀)	Mucosa (Gy ₃)	Gingiva (Gy ₃)
	EBRT			Brachytherapy			Brachytherapy					
	Early	Late		Early	Late		Early	Late				
Tumor (Gy ₁₀)	Mucosa (Gy ₃)	Gingiva (Gy ₃)	Tumor (Gy ₁₀)	Mucosa (Gy ₃)	Gingiva (Gy ₃)	Tumor (Gy ₁₀)	Mucosa (Gy ₃)	Gingiva (Gy ₃)				
1 (tongue)	0	0	0	81	126	63	82	118	59	163	244	122
2 (tongue)	0	0	0	85	156	78	78	110	55	163	266	132
3 (tongue)	36	50	50	73	118	59	62	86	43	171	254	152
4 (tongue)	36	50	50	64	98	49	96	144	72	196	292	172
5 (floor of the mouth)	36	50	50	63	85	85	73	102	102	172	237	237
6 (buccal mucosa)	0	0	0	61	83	83	97	147	147	158	230	230

EBRT: External beam radiotherapy. Mucosa: tongue mucosa (cases 1-4), floor of the mouth mucosa (case 5), buccal mucosa (case 6).

brachytherapy; however, it was controlled by neck dissection and chemotherapy. The other patients with tongue cancer had recurrence-free survival.

Soft tissue and mandibular bone complications. Soft tissue complications occurred in four patients (grade 0=2 cases; grade 1=2 cases; grade 2=2 cases; Table V). However, mandibular bone complications occurred in three patients

(grade 0=3 cases; grade 1=1 case; grade 2=2 cases; Table V). The incidence of grade 2 complications was the same in soft tissue and mandibular bone, with an occurrence rate of 33.3% (two of six patients).

Dental status and tooth extraction. The dental status of the study participants is shown in Table VI. Tooth extraction was conducted in three patients. Two of them underwent tooth

extraction between the initial and reirradiation brachytherapy and one underwent tooth extraction after reirradiation brachytherapy. The positions of the extracted tooth in the two cases (cases 1 and 6) were adjacent to the tumor and that in the other case (case 5) was not included in the irradiated side.

Biological effective dose and complications. The total biological effective doses are shown in Table VII. Two patients had grade 2 complications at the soft tissue and the mandible. One patient had cancer of the floor of the mouth and was treated using the combination of EBRT and ^{198}Au grain brachytherapy during their first treatment. The total effective biological dose of the initial and reirradiation treatments was 172 Gy₁₀ at the tumor and 237 Gy₃ at the floor of the mouth mucosa and lingual surface of the mandibular gingiva. Another patient had buccal mucosa cancer and received ^{198}Au grain brachytherapy alone in both the initial and reirradiation treatments. The total biological effective dose for this patient was 158 Gy₁₀ at the tumor and 230 Gy₃ at the buccal mucosa and lingual surface of the mandibular gingiva. In the case of grade 1 complications of the soft tissue and the mandibular bone (case 1), the total biological effective dose was 163 Gy₁₀ at the tumor, 244 Gy₃ at the tongue mucosa, and 122 Gy₃ at the lingual surface of the mandibular gingiva. The tooth that was close to the tumor was extracted in this case (case 1). One patient with tongue cancer developed grade 1 soft tissue complications (case 4). The total biological effective dose to the tongue mucosa in this case was 292 Gy₃, which was the highest among all cases.

Discussion

In our study, the rate of recurrence after the initial treatment was 10.2% (19 of 186 patients). In the case of recurrence after radiotherapy, reirradiation is expected to cause an increase in severe complications due to overdose, and surgery is often performed when the recurrent lesion is resectable. From this cohort, 6 of 19 patients (approximately 31.6%) were treated with ^{198}Au grain brachytherapy, and the other 13 patients were treated through surgery.

Based on our findings, the five-year local control and overall survival rates after reirradiation treatment were 83.3% and 100%, respectively. Recurrence during the follow-up period occurred in only one tongue cancer patient; however, local recurrence occurred three times in the same patient after the reirradiation treatment, with the third local recurrence accompanied by cervical lymph node metastasis. Therefore, the patient received palliative treatment and died 80 months after the reirradiation. It has been reported that the two-year local control rate after reirradiation by brachytherapy was 53% (n=62) (24), the five-year local control rate was 52% (n=54) (22), and the two- and five-year local control rates were 72% and 69% (n=70) (13).

Moreover, the five-year cause-specific survival rate was 56%-69% (12-14), and the two-year overall survival rate was 66% (24), according to previous reports. Although our study had a small number of cases, the local control and survival rates in our findings were better than those of previous reports. The improved local control rate may be attributed to the accurate evaluation of the size and extent of the lesion at the time of recurrence and the ability to implant the ^{198}Au grain in an appropriate position. The frequent follow-up after reirradiation may have enabled early diagnosis and treatment of the late cervical lymph node metastasis, which resulted in a favorable survival rate.

As for the bone complication, it is difficult to obtain sufficient distance between the source and the mandible using a spacer on the floor of the mouth or the buccal mucosa where the lesion and the mandible are close to each other, with an increase in the dose administered to the mandible considered to be the main cause. For soft tissue complications, it is considered that the irradiated dose to the oral mucosa is excessive, especially considering that the floor of the mouth and the buccal mucosa are continuous with the mucosa of the mandible. It is possible that when necrosis occurs in the mandible, the mucosa covering the mandible becomes malnourished due to poor blood flow, causing mucosal necrosis and ulceration, which may spread to the adjacent floor of the mouth and buccal mucosa. Moreover, the mucosal epithelium of the floor of the mouth is thin, and the submucosa is a loose connective tissue containing fat and minor salivary glands (25). Therefore, it is expected that the mucosa of the floor of the mouth is fragile and mucositis could likely worsen.

In a comparison of previous studies on reirradiation brachytherapy for oral cancers, Yoshimura *et al.* reported that the occurrence rate of grade 3 or 4 complications (confluent ulcer, symptomatic osteoradionecrosis-indicated intervention, tissue necrosis) according to CTCAE v3.0 was 8% (5 of 62 patients) during the treatment of recurrent SCC of the oral cavity (tongue, floor of the mouth, buccal mucosa, gingiva, and hard palate) (24). Ayukawa *et al.* reported that the occurrence rate of grade 4 complications (bone exposure) according to the RTOG/EORTC criteria was 2% (1 of 54 patients) during treatment for SCC of the tongue (26). Moreover, Kunitake *et al.* reported that the occurrence rate of soft tissue necrosis and minimal bone necrosis was 25% (3 of 12 patients) during treatment for SCC of the tongue (27). Furthermore, Mazon *et al.* reported that the occurrence rate of mucosal ulceration or necrosis was 27% (19 of 70 patients) among epidermoid cancers of the oropharynx, with only one patient dying due to severe mucosal complications (28). By comparison, two of six patients (33.3%) in our study had grade 2 soft tissue and mandibular bone complications. The dose administered to the mandible seemed high for these two cases, which could have resulted in grade 2 complications. In

case 1, the biological effective dose administered to the lingual surface of the mandibular gingiva was 122 Gy₃, which was the lowest among the six cases; nevertheless, grade 1 mandibular bone complication still occurred. The extraction of the tooth near the irradiation region could have influenced this complication. The incidence of osteoradionecrosis of the jaw bones (ORN) after the initial radiotherapy using EBRT or brachytherapy for head and neck cancers was reported to be 1.7% or 3.92%, respectively (29). As tooth extraction is one of the major risk factors for ORN (30), it should be performed before definitive radiotherapy. However, ORN still occurs in 2.2% of patients when tooth extraction is performed before radiotherapy (31). Even if the tooth is extracted before radiotherapy, we need to bear the risk of ORN in mind. For cancers of the floor of the mouth and the buccal mucosa, it is difficult to effectively reduce the radiation dose to the mandible through the use of spacers. Therefore, it is not recommended to use brachytherapy again during recurrence after radiotherapy for tumors at the floor of the mouth and the buccal mucosa considering mandibular bone complications.

This study has several limitations. First, as our study is a retrospective medical chart review, some data were not complete. Second, the statistical analysis of the relationships between the biological effective dose and the complications could not be conducted. Finally, the brachytherapy radiation dose was calculated using 2D X-ray images. Only the irradiated dose of the mandible was estimated. In future research, the radiation dose of the mandible can be evaluated according to detailed dose distribution in each region using CT images.

Conclusion

In our study, the five-year local control rate of the reirradiation treatment was 83.3%, which could show a favorable prognosis. Reirradiation using ¹⁹⁸Au grain brachytherapy with the accurate evaluation of recurrence tumors can be recommended in terms of local control. To avoid severe complications due to reirradiation, a spacer should be placed during brachytherapy for tongue cancer patients, and tooth extraction near the radiation field should be avoided. Even if the biological effective dose to the mandible is low, extraction of the teeth close to the irradiated side is discouraged. Careful consideration for reirradiation using ¹⁹⁸Au grain brachytherapy should be given for patients with cancers of the floor of the mouth or the buccal mucosa, particularly in terms of soft tissue and mandibular bone complications.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Masaru Konishi contributed to the conceptualisation, methodology, software, the data curation, writing – original draft preparation and reviewing and editing; Yuki Takeuchi, Katsumaro Kubo, Nobuki Imano, Ikuno Nishibuchi, Yuji Murakami, Kiichi Shimabukuro, and Pongsapak Wongratwanich, to the data curation and the writing – reviewing and editing; Naoya Kakimoto and Yasushi Nagata, to the writing – reviewing and editing.

References

- Mazon JJ, Crook JM, Marinello G, Walop W and Pierquin B: Prognostic factors of local outcome for T1, T2 carcinomas of oral tongue treated by iridium 192 implantation. *Int J Radiat Oncol Biol Phys* 19(2): 281-285, 1990. PMID: 2394607. DOI: 10.1016/0360-3016(90)90535-r
- Fujita M, Hirokawa Y, Kashiwado K, Akagi Y, Kashimoto K, Kiriu H, Ohtani K and Wada T: An analysis of mandibular bone complications in radiotherapy for T1 and T2 carcinoma of the oral tongue. *Int J Radiat Oncol Biol Phys* 34(2): 333-339, 1996. PMID: 8567334. DOI: 10.1016/0360-3016(95)02066-7
- Matsuura K, Hirokawa Y, Fujita M, Akagi Y and Ito K: Treatment results of stage I and II oral tongue cancer with interstitial brachytherapy: maximum tumor thickness is prognostic of nodal metastasis. *Int J Radiat Oncol Biol Phys* 40(3): 535-539, 1998. PMID: 9486601. DOI: 10.1016/s0360-3016(97)00811-0
- Shibuya H, Hoshina M, Takeda M, Matsumoto S, Suzuki S and Okada N: Brachytherapy for stage I & II oral tongue cancer: an analysis of past cases focusing on control and complications. *Int J Radiat Oncol Biol Phys* 26(1): 51-58, 1993. PMID: 8482630. DOI: 10.1016/0360-3016(93)90172-r
- Ryu Y, Shibuya H and Hayashi K: ¹⁹⁸Au grain implantation for early tongue cancer in patients of advanced age or poor performance status. *J Radiat Res* 54(6): 1125-1130, 2013. PMID: 23685669. DOI: 10.1093/jrr/rrt060
- Matsumoto S, Takeda M, Shibuya H and Suzuki S: T1 and T2 squamous cell carcinomas of the floor of the mouth: results of brachytherapy mainly using ¹⁹⁸Au grains. *Int J Radiat Oncol Biol Phys* 34(4): 833-841, 1996. PMID: 8598360. DOI: 10.1016/0360-3016(95)02164-7
- Marsiglia H, Haie-Meder C, Sasso G, Mamelle G and Gerbaulet A: Brachytherapy for T1-T2 floor-of-the-mouth cancers: the Gustave-Roussy Institute experience. *Int J Radiat Oncol Biol Phys* 52(5): 1257-1263, 2002. PMID: 11955737. DOI: 10.1016/s0360-3016(01)02761-4
- Tayier A, Hayashi K and Yoshimura R: Low-dose-rate interstitial brachytherapy preserves good quality of life in buccal mucosa cancer patients. *J Radiat Res* 52(5): 655-659, 2011. PMID: 21768751. DOI: 10.1269/jrr.11025
- Chopra S, Gupta T, Agarwal JP, Budrukkar A, Ghosh-Laskar S and Dinshaw K: Re-irradiation in the management of isolated neck recurrences: current status and recommendations. *Radiother Oncol* 81(1): 1-8, 2006. PMID: 16971009. DOI: 10.1016/j.radonc.2006.08.017
- Wong SJ, Machtay M and Li Y: Locally recurrent, previously irradiated head and neck cancer: concurrent re-irradiation and chemotherapy, or chemotherapy alone? *J Clin Oncol* 24(17): 2653-2658, 2006. PMID: 16763279. DOI: 10.1200/JCO.2005.05.3850

- 11 Salama JK, Vokes EE, Chmura SJ, Milano MT, Kao J, Stenson KM, Witt ME and Haraf DJ: Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 64(2): 382-391, 2006. PMID: 16213104. DOI: 10.1016/j.ijrobp.2005.07.005
- 12 Arnold DJ, Goodwin WJ, Weed DT and Civantos FJ: Treatment of recurrent and advanced stage squamous cell carcinoma of the head and neck. *Semin Radiat Oncol* 14(2): 190-195, 2004. PMID: 15095264. DOI: 10.1053/j.semradonc.2004.03.001
- 13 Maddalo M, Bonomo P, Belgioia L, Bacigalupo A, Donato V, Alterio D, Orlandi E, Argenone A, Merlotti A, Musio D, Trignani M, Ursino S, Arcangeli S, Furlan C, Osti MF and Italian Association of Radiation Oncology (AIRO): Re-irradiation with curative intent in patients with squamous cell carcinoma of the head and neck: a national survey of usual practice on behalf of the Italian Association of Radiation Oncology (AIRO). *Eur Arch Otorhinolaryngol* 275(2): 561-567, 2018. PMID: 29279949. DOI: 10.1007/s00405-017-4853-8
- 14 Strojanc P, Corry J, Eisbruch A, Vermorken JB, Mendenhall WM, Lee AW, Haigentz M Jr, Beitler JJ, de Bree R, Takes RP, Paleri V, Kelly CG, Genden EM, Bradford CR, Harrison LB, Rinaldo A and Ferlito A: Recurrent and second primary squamous cell carcinoma of the head and neck: when and how to reirradiate. *Head Neck* 37(1): 134-150, 2015. PMID: 24481720. DOI: 10.1002/hed.23542
- 15 Kasperts N, Slotman B, Leemans CR and Langendijk JA: A review on re-irradiation for recurrent and second primary head and neck cancer. *Oral Oncol* 41(3): 225-243, 2005. PMID: 15743686. DOI: 10.1016/j.oraloncology.2004.07.006
- 16 Cacicedo J, Navarro A, Alongi F, Gómez de Iturriaga A, Del Hoyo O, Boveda E, Casquero F, Perez JF and Bilbao P: The role of re-irradiation of secondary and recurrent head and neck carcinomas. Is it a potentially curative treatment? A practical approach. *Cancer Treat Rev* 40(1): 178-189, 2014. PMID: 23993769. DOI: 10.1016/j.ctrv.2013.08.002
- 17 Benson R, Giridhar P, Venkatesulu BP, Mallick S, Raza MW and Rath GK: Re-irradiation for head and neck squamous cell carcinoma. *J Egypt Natl Canc Inst* 29(1): 1-9, 2017. PMID: 27595192. DOI: 10.1016/j.jnci.2016.07.002
- 18 O'Sullivan B: Head and Neck Tumours. In: TNM classification of malignant tumours, eighth ed. Brierley JD, Gospodarowicz MK and Wittekind C (eds.). West Sussex, UK, John Wiley and Sons, pp. 17-54, 2017.
- 19 Dokiya T: Cancer-Radiotherapy (Gan-houshasenryouhou) '95. In: Ohkawa T (ed.). Brachytherapy. Tokyo: Shinoharashinsha publishers Inc, pp. 349, 1995.
- 20 Dale RG: The application of the linear-quadratic model to fractionated radiotherapy when there is incomplete normal tissue recovery between fractions, and possible implications for treatments involving multiple fractions per day. *Br J Radiol* 59(705): 919-927, 1986. PMID: 3756389. DOI: 10.1259/0007-1285-59-705-919
- 21 Stock RG, Stone NN, Cesaretti JA and Rosenstein BS: Biologically effective dose values for prostate brachytherapy: effects on PSA failure and posttreatment biopsy results. *Int J Radiat Oncol Biol Phys* 64(2): 527-533, 2006. PMID: 16242258. DOI: 10.1016/j.ijrobp.2005.07.981
- 22 Dutreix J: Expression of the dose rate effect in clinical curietherapy. *Radiother Oncol* 15(1): 25-37, 1989. PMID: 2748940. DOI: 10.1016/0167-8140(89)90115-1
- 23 Miura M, Takeda M, Sasaki T, Inoue T, Nakayama T, Fukuda H, Hoshi A, Hoshina M and Shibuya H: Factors affecting mandibular complications in low dose rate brachytherapy for oral tongue carcinoma with special reference to spacer. *Int J Radiat Oncol Biol Phys* 41(4): 763-770, 1998. PMID: 9652836. DOI: 10.1016/s0360-3016(98)00118-7
- 24 Yoshimura R, Shibuya H, Hayashi K, Nakagawa K, Toda K, Watanabe H, Kaida A and Miura M: Repeat brachytherapy for patients with residual or recurrent tumors of oral cavity. *Int J Radiat Oncol Biol Phys* 83(4): 1198-1204, 2012. PMID: 22099049. DOI: 10.1016/j.ijrobp.2011.09.018
- 25 Squier CA and Finkelstein MW: Oral Mucosa. In: Oral histology development, structure, and function, fifth ed. Ten Cate AR (ed.). Missouri, US, Mosby, pp. 376-379, 1998.
- 26 Ayukawa F, Shibuya H, Yoshimura R, Watanabe H and Miura M: Curative brachytherapy for recurrent/residual tongue cancer. *Strahlenther Onkol* 183(3): 133-137, 2007. PMID: 17340071. DOI: 10.1007/s00066-007-1613-5
- 27 Kunitake N, Nakamura K, Kimura M, Watanabe T, Sasaki T, Terashima H, Jingu K and Masuda K: [Reirradiation with brachytherapy for recurrent tongue cancer after initial brachytherapy]. *Nihon Igaku Hoshasen Gakkai Zasshi* 61(8): 427-430, 2001. PMID: 11524819.
- 28 Mazon JJ, Langlois D, Glaubiger D, Huart J, Martin M, Raynal M, Calitchi E, Ganem G, Faraldi M and Feuilhade F: Salvage irradiation of oropharyngeal cancers using iridium 192 wire implants: 5-year results of 70 cases. *Int J Radiat Oncol Biol Phys* 13(7): 957-962, 1987. PMID: 3597158. DOI: 10.1016/0360-3016(87)90031-9
- 29 Nabil S and Samman N: Risk factors for osteoradionecrosis after head and neck radiation: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 113(1): 54-69, 2012. PMID: 22669065. DOI: 10.1016/j.oraloncology.2011.07.042
- 30 Moon DH, Moon SH, Wang K, Weissler MC, Hackman TG, Zanation AM, Thorp BD, Patel SN, Zevallos JP, Marks LB and Chera BS: Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers. *Oral Oncol* 72: 98-103, 2017. PMID: 28797468. DOI: 10.1016/j.oraloncology.2017.07.014
- 31 Lajolo C, Gioco G, Rupe C, Troiano G, Cordaro M, Lucchese A, Paludetti G and Giuliani M: Tooth extraction before radiotherapy is a risk factor for developing osteoradionecrosis of the jaws: A systematic review. *Oral Dis* 27(7): 1595-1605, 2021. PMID: 32531873. DOI: 10.1111/odi.13485

Received October 25, 2021

Revised November 20, 2021

Accepted November 23, 2021