

Investigating the displacement of radio-active sources during gold-198 grain brachytherapy for hospitalized oral cancer patients

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Abstract

Purpose: This study aimed to investigate status of displacement of gold-198 (¹⁹⁸Au) grains in patients with oral cancers as well as factors and countermeasures for the displacement of ¹⁹⁸Au grains.

Material and methods: The present study included 34 patients with oral cancers, who were exclusively treated with ¹⁹⁸Au grain brachytherapy between 2013 and 2019. Timing and duration of the ¹⁹⁸Au grain displacement from the oral cavity and reduction in radiation dose were estimated. Location of the displaced grain was classified as either inside or outside of gross tumor volume. Number and location of the displacement of ¹⁹⁸Au grains, primary lesion, and growth type were evaluated.

Results: Of the 34 patients included in this study, ¹⁹⁸Au grains were displaced in 4 patients (11.8%) during hospitalization. A total of 5 grains (1.4%) were displaced out of an overall count of 367 grains implanted in these 34 patients. Of the four patients who experienced displacement of ¹⁹⁸Au grains, three had tongue cancer, and one had lip cancer. All four patients whose grains were displaced had superficial lesions.

Conclusions: When performing brachytherapy with ¹⁹⁸Au grains for superficial lesions on the tongue or lips, care should be taken to avoid grain displacement.

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Purpose

Low-dose-rate (LDR) brachytherapy for oral cancer present a high local tumor control rate while preserving oral function and maintaining a high quality of life [1-4]. One of the radiation sources used in LDR brachytherapy is gold-198 (¹⁹⁸Au) grain, a tiny radio-active source measuring 2.5 mm in length and 0.8 mm in diameter, with minimal invasive implantation. ¹⁹⁸Au grain has a physical half-life of 2.7 days and gamma energy of 0.412 MeV. In patients with tongue cancer, it has been reported that there were fewer adverse events after treatment with ¹⁹⁸Au grain than with iridium-192 (¹⁹²Ir) in LDR brachytherapy [5].

Most oral lesions treated with ¹⁹⁸Au grain brachytherapy, in our hospital, are superficial and thin, and the grains are implanted just below the mucosal epithelium; hence, a grain may fall out of the tissue relatively early following implantation. According to the guidelines of Japan's Min-

istry of Health, Labor, and Welfare, a patient must be admitted to a radiation-controlled room for at least three days after implantation of ¹⁹⁸Au grains in case of grain displacement [6]. Early displacement of radio-active sources from the oral cavity may expose medical staff to radiation as well as patient's family or others surrounding the patient, and cause radio-active contamination. In addition, effects of such early displacement on treatment outcomes may occur. Therefore, it is necessary to prevent the displacement of radio-active source after implantation. This study aimed to investigate the status of displacement of ¹⁹⁸Au grains in patients with oral cancers as well as the factors and countermeasures for the displacement of ¹⁹⁸Au grains.

Material and methods

A total of 34 patients with oral cancer, who were treated with ¹⁹⁸Au grain brachytherapy alone in our hospital

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between 2013 and 2019 were enrolled in this study. Baseline characteristics of the 34 patients are shown in Table 1. The distribution of primary lesions included the tongue ($n = 22$; 4 carcinomas *in situ*, 10 T1, 4 T2, 1 T3, 1 rT1, and 2 rT2), floor of the mouth ($n = 7$; 1 carcinoma *in situ*, 4 T1, and 2 T2), buccal mucosa ($n = 4$; 1 carcinoma *in situ*, 1 T1, and 2 T2), and upper lip ($n = 1$; 1 carcinoma *in situ*), and were classified according to the 2017 Union for International Cancer Control TNM classification [7]. Depending on the type of tumor growth, tumors were classified into the following three types: superficial, exophytic, and infiltrative. A tumor with superficial development grew on the outermost surface of the mucosa. For a tumor with exophytic growth, most of the tumor was located on the surface of the mucosa, and grew from the surface of mucosa outward. For a tumor with infiltrative growth, most of the tumor was located beneath the surface of the mucosa, with or without ulceration. None of the patients had cervical lymph node or distant metastasis at the start of ^{198}Au grain brachytherapy.

The technique for ^{198}Au grain implantation was as follows: the longest diameter of the lesion, which was equivalent to Lugol's staining-free area, was identified, and the grains were placed at equal intervals of 10 mm. They were placed approximately 5 mm behind the lesion's posterior margin and approximately 5 mm ahead of the lesion's anterior margin. Next, the grains were arranged at approximately 10 mm above and below radiation sources of the initial arrangement. Each grain was positioned at the apex of an equilateral triangle (Fig. 1). Based on this arrangement, additional grains were placed according to the lesion's shape.

Table 1. Baseline characteristics

Characteristic	Value
Age (years), median (range)	68.5 (34-89)
Sex (male/female)	17/17
Primary lesion	
Tongue	22
Buccal mucosa	4
Floor of the mouth	7
Lip	1
Clinical T stage	
Tis	7
T1	15
T2	8
T3	1
rT1	1
rT2	2
Maximum length (mm), median (range)	24.5 (7-50)
Thickness (mm), median (range)	2.6 (0.4-7)
Growth type	
Superficial	20
Exophytic	3
Infiltrative	11
Number of implanted ^{198}Au grains, median (range)	10.5 (4-17)

^{198}Au grains were implanted in the treatment room next to patient's radiation-controlled room. Implantation of ^{198}Au grains in the oral cavity was confirmed using X-ray before the patient was allowed back to the radiation-controlled room. Subsequently, the treatment room was surveyed to ascertain that no displacement of ^{198}Au grains occurred. Thereafter, radiographs were typically taken once or twice daily in the treatment room to confirm the presence of ^{198}Au grains in the oral cavity. Each time, a radiation survey was conducted in the treatment and patient rooms to exclude the displacement of ^{198}Au grain. In case grain displacement from the oral cavity was confirmed, we tried to locate it using a radiation survey meter in the patient's room and treatment room. If the displaced ^{198}Au grain was not detected in the room, postero-anterior chest and abdominal X-rays were performed to identify possible ingestion or aspiration of ^{198}Au grain or its' hidden presence in the clothes or skin.

After ^{198}Au grain implantation, all patients always wore a removable spacer made of dental silicon impression materials, including a lead plate with a 4 mm thickness. It was only removed at mealtimes and tooth brushing. A filter was placed in the sink outlet to prevent ^{198}Au grains from being flushed down the drain during when teeth brushing. When a patient had difficulties swallowing saliva while wearing the spacer, the saliva was removed by spitting it into a tissue or using a suction tube. The saliva and tissues were stored in the patient's room until the patient left the hospital.

The patient could leave the isolation area according to the criteria prescribed by Japan's Ministry of Health, Labor, and Welfare. According to the criteria, residual radio-activity in the body should not exceed 700 MBq, equivalent dose-rate per centimeter at a point 1 m away from the patient's body surface should not exceed 40.3 $\mu\text{Sv/h}$, and the patient must stay in the hospital for at least three days in case of ^{198}Au grain displacement [6].

Permanent dose of ^{198}Au grain brachytherapy was calculated using an X-ray image taken 24 hours after ^{198}Au grain implantation. First, the treatment area was calculated based on X-ray image using the following formula:

$$\text{Treatment area (cm}^2\text{)} = \pi/4 \times \text{area calculated using X-ray image (cm}^2\text{)}.$$

According to the Manchester system (see Table 2) [8], radio-activity required to deliver 10 Gy to therapeutic

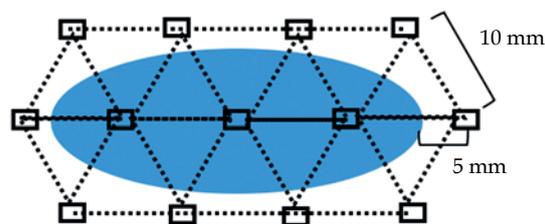


Fig. 1. Arrangement of ^{198}Au grains. The oval region shows the mucosal area without Lugol's staining, and squares represent ^{198}Au grains. Each dotted line indicates an approximately 10 mm distance between grains

area was calculated. This value was regarded as A. Next, permanent total dose was calculated as follows [9]:

$$\text{Permanent total dose (Gy}/\infty) = \text{activity/grain (MBq)} \times \text{number of grains} / 37 \times 10 / A,$$

with activity/grain representing the MBq value at ¹⁹⁸Au grain implantation, 37 representing 1 mCi = 37 MBq, and 10 representing 10 Gy.

Reduction rate in the radiation dose of a ¹⁹⁸Au grain was estimated (see Fig. 2). Location of the displaced grain was classified as either inside or outside of gross tumor volume (GTV). We defined GTV as the region that was unstained with Lugol's solution.

Number and location of the displacement of ¹⁹⁸Au grains, primary lesion, growth type, and treatment results were evaluated. Moreover, exposure dose for medical personnel was determined using a semi-conductor pocket dosimeter attached to the chest of the medical personnel during the patient's hospitalization.

The study was approved by the (anonymized for review) University Ethics Committee (registration number anonymized for review), and was conducted in accordance with the Declaration of Helsinki. According to the University Ethics Committee guidelines, we obtained opt-out informed consent.

Results

Of the 34 patients included in the study, 4 (11.8%) had at least one displacement of ¹⁹⁸Au grain during hospitalization. In terms of the number of radiation sources,

Table 2. Manchester system table [8]

Area (cm ²)	²²⁶ Ra (mg hr.)	¹⁹⁸ Au (mCi [MBq])
1	72	2.70 (100)
2	103	3.86 (143)
3	128	4.80 (178)
4	150	5.62 (208)
5	171	6.41 (237)
6	188	7.05 (261)
7	204	7.65 (283)
8	219	8.21 (304)
9	235	8.81(326)
10	250	9.38 (347)

²²⁶Ra: 1 mg = 1 mCi = 37 MBq

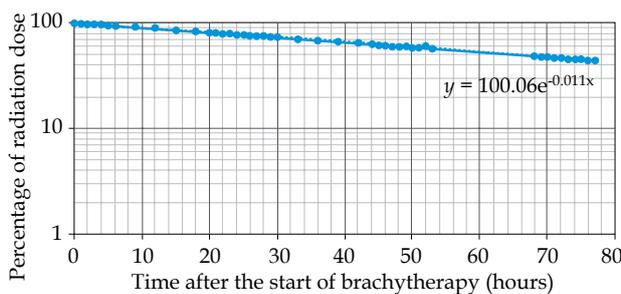


Fig. 2. Rate of radiation dose reduction per ¹⁹⁸Au grain

Table 3. Patient characteristics

Case No.	Age	Sex	Primary lesion	TNM classification	Maximum length (mm)	Thickness (mm)	Growth type	No. of implanted ¹⁹⁸ Au grains	Activity at implantation (MBq/grain)	Total dose (Gy/∞)	Initial 7-day dose (Gy/week)	Time in the hospital after implantation (hours)	Follow-up period after brachytherapy (months)
1	82	F	Tongue	T2N0M0	40	1.5	Superficial	15	178	77	64	142	41
2	47	F	Tongue	rT2N0M0	40	2	Superficial	14	185	76	63	121	34
3	87	M	Tongue	T1N0M0	14	2	Superficial	7	177	91	76	74	39
4	84	F	Upper lip	TisN0M0	15	2	Superficial	7	178	77	64	72	21

Table 4. Characteristics of displaced radio-active sources and exposure dose for medical personnel

Case No.	No. of displaced grains	Estimated time after implantation (hours)	Estimated maximum period (hours)	Estimated maximum dose reduction rate (%/grain)	Estimated total dose (Gy/∞) ¹	Initial 7-day dose (Gy/week)	Dose rate for the initial 7 days (Gy/hour)	Location of displaced grains	Duration of hospitalization after implantation (hours)	Exposure dose for medical personnel, total [during first implantation] (μSv)
1	1	70-94	24	46-36 = 10	72	60	0.36	Outside of GTV	142	497 [386]
2	2	0-30	30	100-72 = 28	71	59	0.35	Inside of GTV	121	Unknown [131]
		30-54	24	72-55 = 17	65	54	0.32	Outside of GTV		
3	1	0-∞	∞	100	78	63	0.38	Outside of GTV	74	104 [55]
4	1	52-68	16	56-47 = 9	66	55	0.33	Outside of GTV	72	120 [70]

¹Estimated total dose (Gy/∞); total dose with complete displacement of ¹⁹⁸Au grain from initial treatment, GTV – gross tumor volume

367 grains were implanted in 34 patients, and 5 grains fell out of the oral cavity, resulting in a displacement rate of 1.4%.

The characteristics of the patients and displaced grains are shown in Tables 3 and 4. The displaced grains were located on the tongue ($n = 4$) and upper lip ($n = 1$; Fig. 3). Four of the five displaced grains were located outside GTV and one inside GTV (case number 2). There was no displacement of the grains implanted in the floor of the mouth or the buccal mucosa. Three of the four patients underwent re-implantation with a ^{198}Au grain at the same location under local anesthesia. In these three cases, ^{198}Au grains were found on the floor in the patient's room and were detected using radiation survey meters. Figure 4 shows a representative case of ^{198}Au grain re-implantation (case number 4). In this patient, seven ^{198}Au grains were implanted for carcinoma in situ of the upper lip. One of the seven grains was displaced approximately 3 days after implantation (Fig. 4D). The patient's room was surveyed, and the displaced grain was found on the floor. After confirming the location of the displaced grain by radiography, it was disinfected and re-implanted in the same location (Fig. 4F).

One patient (case number 3) swallowed a grain, and it was detected in the abdomen (probably the stomach) on radiography (Fig. 5). In this case, the grain was not removed for re-implantation. Follow-up observation was conducted during hospitalization while monitoring the position of the swallowed grain on radiographs. We ex-

pected the ^{198}Au grain to be passed out with fecal matter; hence, the patient's feces were stored in a container and surveyed or radiographed to confirm the discharge of the grain. However, during the hospitalization period, the ^{198}Au grain was not passed in the stool. At the next hospital visit, an abdominal X-ray did not detect the ^{198}Au grain. Therefore, we assumed that it was spontaneously excreted in the stool following hospital discharge. The patient had no gastro-intestinal symptoms. In case number 3, the estimated time from the implantation of ^{198}Au grains to the displacement ranged from 0 to 23 hours. The estimated maximum dose reduction rate was 100% per grain displacement.

Of the four patients with ^{198}Au grain displacement, two were recurrence-free as well as without cervical lymph node and distant metastases during their respective follow-up periods (case numbers 1 and 4). One patient (case number 2) with tongue cancer had local recurrence and cervical lymph node metastasis at 8 and 38 months following ^{198}Au grain brachytherapy, respectively. A recurrent tongue lesion developed in the area adjacent to the posterior margin of the primary lesion. The local recurrent tongue lesion and cervical lymph node metastasis were treated surgically and controlled during follow-up. Another patient with tongue cancer (case number 3) died 20 months after ^{198}Au grain brachytherapy due to multiple distant metastases. In contrast, 2 of the 30 patients without ^{198}Au grain displacement experienced local recurrence (6.7%).

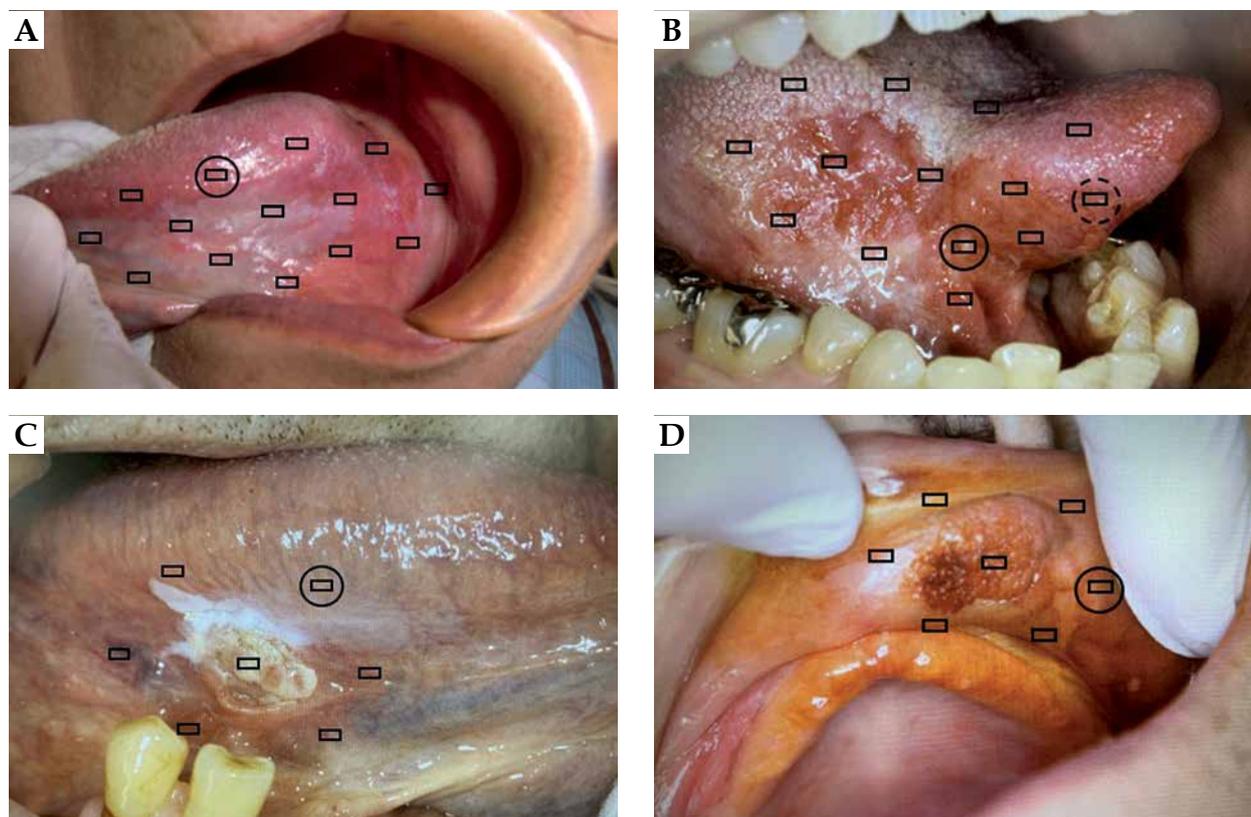


Fig. 3. Location of displaced ^{198}Au grains. **A-D)** The cases 1-4, respectively. Squares show positions of ^{198}Au grains, and the circle indicates the missing ^{198}Au grain. Solid and dotted circles represent the positions of the first and second displaced ^{198}Au grains (**B**)

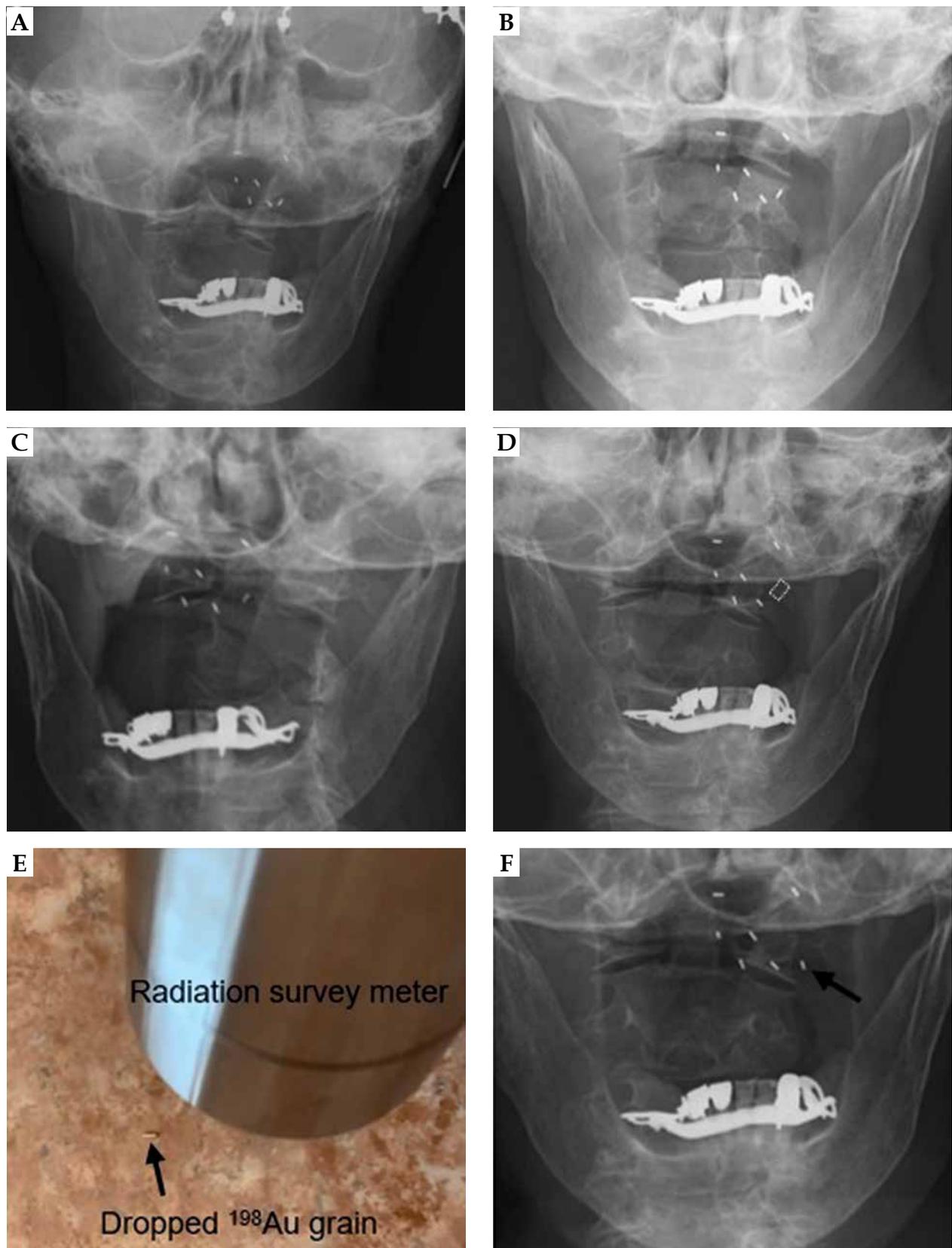


Fig. 4. Case number 4. **A-C)** Day 0, 1, and 2, respectively, after ^{198}Au grain implantation. Day 0 represents the implantation day. **D)** Day 3 after ^{198}Au grain implantation. The dotted square shows the estimated location of the displaced grain. **E)** Using a radiation survey meter, the displaced grain (arrow) was found on the floor of the patient's room. **F)** After re-implantation. The displaced grain was implanted in the same location (arrow)

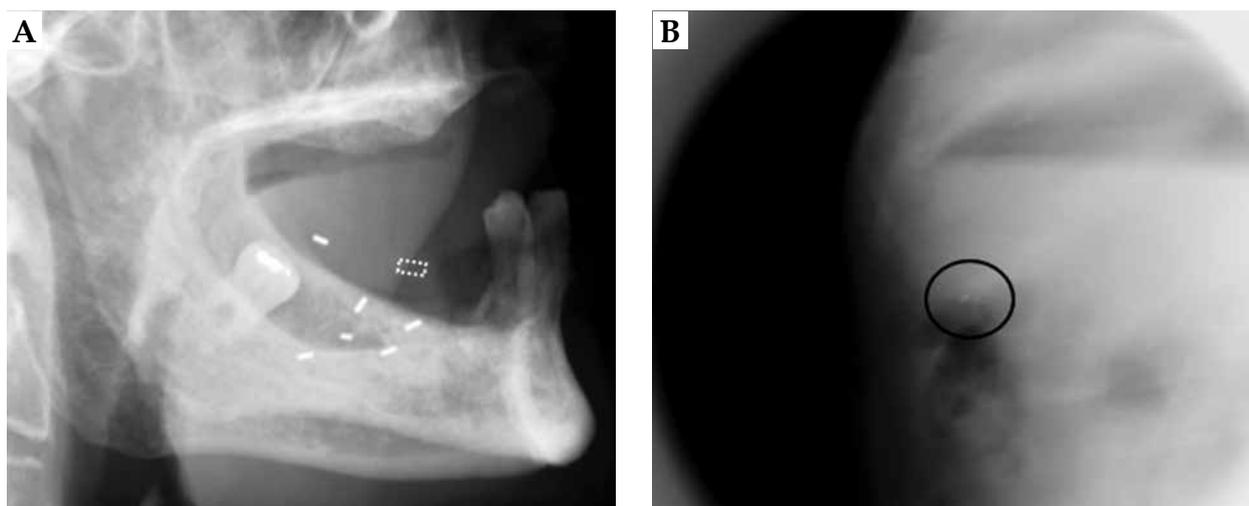


Fig. 5. Case number 3. **A)** The dotted square indicates the estimated location of the displaced grain. **B)** The ^{198}Au grain (circle) was detected in the stomach

Discussion

In the present study, we reviewed the current status of displacement of ^{198}Au grains in patients with oral cancers, and evaluated the factors and countermeasures for it. Four of the 34 patients (11.8%) had at least one displaced ^{198}Au grain during hospitalization. In terms of the number of radiation sources, 367 grains were implanted in 34 patients, and 5 grains fell out of the oral cavity, resulting in a displacement rate of 1.4%.

There are no reports on ^{198}Au grain displacement in oral cancer; however, seed migration and displacement in the treatment of prostate cancer have been mentioned. In prostate brachytherapy using ^{125}I seeds, displacement of seeds occurs in 6.0-30.4% of patients and 0.13-0.84% of total implanted seeds [10-15]. In the current study, the displacement of seeds occurred in 11.8% of the patients and 1.4% of the total implanted seeds. Displacement rates of radio-active sources in previous studies were similar to those observed in this study. As brachytherapy for prostate cancer uses many radio-active sources, a dose reduction due to displacement of a few seeds may have insignificant influence on clinical outcome [14]. In contrast, as radio-active sources in ^{198}Au grain brachytherapy in oral cancers are arranged in proportion to the size and shape of the lesion [9, 16, 17], the treatment effect may vary when one grain deviates from the scheduled position or is displaced. This may lead to recurrence depending on the location or timing of the displaced grain. However, if the possible ^{198}Au grain displacement was to be compensated by increasing the number of grains, the implantation of a larger number of grains may unnecessarily increase radiation exposure to surrounding normal tissues, and increase severity of complications. Therefore, implantation techniques should be re-considered to reduce displacement of ^{198}Au grains.

An early ^{198}Au grain displacement after implantation may be due to backflow in implantation route. To prevent this, the applicator insertion point should be approximately more than 10 mm away from the placement po-

sitions of the grains. The oral mucosal epithelium is thin, non-keratinized stratified squamous, and, unlike other gastro-intestinal mucosae, characterized by the absence of a muscularis mucosae [18]. A ^{198}Au grain arranged at the periphery of a lesion is located just below the mucosal epithelium (the lamina propria and submucosa, which are relatively sparse tissues) [19]. Moreover, the tongue and lips are highly mobile, and the mucosal epithelium is easily injured by contact with the teeth or spacer, and is fragile due to influence of ^{198}Au grain implantation. Therefore, it can be considered that a ^{198}Au grain located just below the mucosal epithelium may destroy the mucosal epithelium when the tongue or lip moves, and might fall-off from the mucosal surface. All cases of grain displacement occurred in either patients with tongue or lip cancers in the present study, and 4 out of 5 dropped-out grains were placed in the periphery of a lesion. To prevent this, the number of insertion points should be as small as possible, so that injury to the mucosal epithelium is reduced. Also, re-insertion should be performed from the same point. The position of an implanted ^{198}Au grain should be established to be deeper until it reaches the muscle layer. However, attention should be paid to the notion that the ^{198}Au grain is not located in such a deep part as to lower the mucosal surface dose. As differences in displacement rates have been reported with years of experience, therapeutic experience is also a factor in preventing source dropouts [12], and sufficient training using a phantom is required before ^{198}Au grain implantation in a patient.

Four of the five displaced ^{198}Au grains were found on the floor of the patient's room. ^{198}Au grain that had fallen out of the lesion into the oral cavity might have been discharged into the tissue paper along with saliva, and then dropped onto the floor. It is also considered that the patient with lip cancer spontaneously discharged the ^{198}Au grain from the upper lip, and it fell directly onto the floor. As a countermeasure, and for early detection of displaced ^{198}Au grains, we consider instructing the patient to care-

fully examine the tissue paper when spitting saliva and to check whether ^{198}Au grain was included in the saliva.

The exposure dose to the medical personnel at the time of implantation was similar to that reported in previous studies, except for case 1 [19, 20]. The potential reason for higher exposure dose in case 1 was the higher number of radiation sources and longer time of ^{198}Au grain implantation, as X-rays were taken to confirm the number and position of ^{198}Au grain implants. Since the exposure doses to medical personnel are expected to increase due to frequent monitoring of ^{198}Au grains during hospitalization, healthcare providers should plan essential procedures early to reduce the exposure dose. Time required for checking the ^{198}Au grain implants should be shortened, and the working distance between the healthcare provider and the patient should be increased. In addition, exposure doses for medical personnel can be reduced by allowing workers to work in shifts; hence, the number of staff should be increased. Among the four cases with ^{198}Au grain displacement, three displaced grains were found on the floor of the patient's room, and if the displacement had not been noticed, medical personnel and cleaners could have been unnecessarily exposed to radiation.

In the groups with and without displacement of ^{198}Au grains, 1 of 4 patients (25%) and 2 of 30 patients (6.7%), respectively, had local recurrence of the tumor during the follow-up period. Only four patients had ^{198}Au grain displacement in this study, but one of them developed a recurrence. In this case, the displacement of the ^{198}Au grain occurred twice, and one of the grains was located inside GTV; therefore, the dose reduction due to the ^{198}Au grain displacement might have led to local recurrence. The other three cases, in which the location of the displaced ^{198}Au grain was outside GTV had no local recurrence. It is possible that the position of the displaced radio-active source affected local control. In case 2, two ^{198}Au grains were displaced during hospitalization and the rates of estimated dose reductions were 28% and 17% in the first and second times, respectively. Local recurrence occurred after 38 months. The estimated total dose after the loss of two grains was 65 Gy, the lowest among the four cases, which may be a reason for a recurrence. However, in the case of T1 or T2 oral cancers with LDR brachytherapy alone, the radiation dose required is 60-70 Gy [21], and it was considered that the dose was not always insufficient in case 2. In addition, this patient experienced a recurrence after surgery. Recurrence after definitive treatment of head and neck cancers has been associated with a poor prognosis [22-24]. Overall salvage cure rate was reported as 21% for recurrent squamous cell carcinoma of the oral cavity [22], and two-year disease-free survival rate after definitive resection of recurrent oral cancer was 47% [23]. The more advanced the cancer stage at the time of recurrence, the poorer the prognosis: 73% in stage I, 67% in stage II, 33% in stage III, and 22% in stage IV [23]. Moreover, two- and five-year local control rates after re-irradiation with brachytherapy for recurrent oral cancers ranged from 53% to 72% [25, 26] and from 52% to 69% [26, 27], respectively. In this study, case number 2 had

a high probability of recurrence due to insufficient dosing. In this patient, the total radiation dose without the displacement of ^{198}Au grain was 76 Gy, which was reduced to 65 Gy after grain displacement, suggesting that higher doses were needed for local control.

This study has several limitations. First, no statistical analysis was performed because of the low number of cases with ^{198}Au grain displacement. However, we recognize that ^{198}Au grain displacement is a significant concern because it affects not only the treatment outcome, but also exposure to medical personnel. Future studies enrolling more patients with ^{198}Au grain displacement should evaluate the consequences on treatment outcomes and determine methods to prevent displacement. This requires regular X-ray and survey meter checks to determine whether ^{198}Au grain has fallen off after implantation, and detailed records of medical personnel's exposure dose. Second, radiation doses were calculated using plain radiographs; thus, only the dose delivered to the entire lesion could be calculated. We were not able to calculate the specific dose reduction for the lesion part with the displaced ^{198}Au grain. In the future, to examine treatment effect of missing radiation source, the dose of displaced ^{198}Au grain should be calculated in addition to the irradiation dose of the whole lesion. In prostate brachytherapy, the number of displaced seeds was reported to be relatively smaller when inserted by a radiation oncologist with long experience [12]. Although the experience of radiation oncologist might influence the displacement rate of ^{198}Au grains, we did not investigate this aspect in our study. Since the ^{198}Au grains for a single-patient were implanted by several practitioners, identifying the one who implanted the displaced grain was impossible. In the future, association of experience of practitioners involved in brachytherapy and number of seeds displaced should be examined.

Conclusions

The displacement of ^{198}Au grains occurred in 4 out of 34 enrolled patients (11.8%), and only 5 out of the 367 implanted grains (1.4%) were displaced. Of the four patients with ^{198}Au grain displacement, one had two displaced grains and experienced local recurrence. When performing brachytherapy with ^{198}Au grains for superficial lesions on the tongue or lips with significant mobility, care should be taken to avoid grain displacement. A displacement of ^{198}Au grains causes radio-active contamination of the patient's room, which unnecessarily exposes medical personnel to radiation. Furthermore, displacement of ^{198}Au grains may result in radiation underdosing and consequent tumor recurrence. Therefore, frequent monitoring of the radio-active implant is necessary for early detection of implant displacement.

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Disclosure

The authors report no conflict of interest.

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