

Treatment outcomes of real-time intraoral sonography-guided implantation technique of ^{198}Au grain brachytherapy for T1 and T2 tongue cancer

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ABSTRACT

It is often challenging to determine the accurate size and shape of oral lesions through computed tomography (CT) or magnetic resonance imaging (MRI) when they are very small or obscured by metallic artifacts, such as dental prostheses. Intraoral ultrasonography (IUS) has been shown to be beneficial in obtaining precise information about total tumor extension, as well as the exact location and guiding the insertion of catheters during interstitial brachytherapy. We evaluated the role of IUS in assessing the clinical outcomes of interstitial brachytherapy with ^{198}Au grains in tongue cancer through a retrospective medical chart review. The data from 45 patients with T1 ($n = 21$) and T2 ($n = 24$) tongue cancer, who were mainly treated with ^{198}Au grain implants between January 2005 and April 2019, were included in this study. ^{198}Au grain implantations were carried out, and positioning of the implants was confirmed by IUS, to ensure that ^{198}Au grains were appropriately placed for the deep border of the tongue lesion. The five-year local control rates of T1 and T2 tongue cancers were 95.2% and 95.5%, respectively. We propose that the use of IUS to identify the extent of lesions and the position of implanted grains is effective when performing brachytherapy with ^{198}Au grains.

Keywords: brachytherapy; ^{198}Au grain; tongue cancer; ultrasonography; local control rate

INTRODUCTION

Low-dose rate brachytherapy (LDR-BT) is often considered as an alternative to surgery for the treatment of tongue cancer [1]. Brachytherapy with ^{198}Au grains is a minimally invasive treatment that is effective for older patients or patients with poor performance status, with T1 or T2 tongue cancer [2]. Various radioactive sources have been used in LDR-BT to treat tongue cancer, such as: ^{192}Ir , ^{137}Cs , ^{222}Ra , ^{60}Co , ^{222}Rn , ^{125}I and ^{198}Au , although their local control rates differ. In the treatment groups with the aforementioned radioactive sources, except for ^{198}Au , the five-year local control rates of T1 and T2 tongue cancer patients were approximately 79–96.9% and 71–84.8%, respectively [1, 3, 4]. Conversely, the local control rates of T1 and T2 tongue cancer treated

with ^{198}Au were 66.7% and 62.5%, respectively, at two years (depending on the site) [5]. The local control rate with ^{198}Au (68%) was statistically lower than that for ^{192}Ir (86%) in T1 and T2 tongue cancers at five years [2].

Brachytherapy with ^{198}Au grains is usually applied to early (i.e. small) oral cancers as its penetration depth is relatively short, thereby minimizing radiation exposure to nearby tissues and decreasing the occurrence of adverse events [2]. Furthermore, in older patients or those with poor performance status, surgery under general anesthesia or comparatively invasive low-dose- or high-dose-rate brachytherapy with ^{192}Ir may not be feasible as a curative treatment. However, some of these patients can still be treated with ^{198}Au grains [6].

It is essential to precisely identify the volume of the target lesion since the grain size of ^{198}Au is small (2.5×0.8 mm) and the coverage volume per grain is narrow (approximately 5 mm) [5]. Therefore, careful dose planning is necessary to ensure that sufficient ^{198}Au grains are utilized in treating the tumor to avoid underdosing.

To enhance this process (i.e. in addition to inspection, palpation and contrast-enhanced computed tomography [CT] or magnetic resonance imaging [MRI]), intraoral ultrasonography (IUS) can be used in real time to locate and measure the exact volume of the lesion. This is important, as it is often challenging to determine the accurate size and shape of lesions through CT or MRI when they are very small or obscured by metallic artifacts, such as dental prostheses. Several studies have reported the ability of real-time IUS to obtain precise information about total tumor extension [7, 8]. IUS has also been shown to be beneficial in determining the exact location and guiding the insertion of catheters during interstitial brachytherapy [9]. This provides quick and reliable orientation during surgery for resection of tongue cancer, and therefore, allows precise individually tailored resection margins [8].

In this study, we retrospectively evaluated the role of IUS in assessing the clinical outcomes of ^{198}Au brachytherapy for T1 or T2 tongue cancer through a medical chart review.

MATERIALS AND METHODS

Population

Between January 2005 and April 2019, 46 patients with previously untreated T1N0M0 ($n = 21$) and T2N0M0 ($n = 25$) tongue cancers were treated with ^{198}Au grains. One patient with a tumor on both side of the tongue, both of which were treated with ^{198}Au brachytherapy, was excluded. The remaining 45 patients were included in the study. Distribution of the patients was by tumor size according to the 7th edition/2009 version of the Union for International Cancer Control's TNM classification of malignant tumors [10] is shown in Table 1. The lesions included the superficial tumor type, with tumors on the outermost surface of the mucosa; the exophytic type, with most of the tumor located on the surface of the mucosa; and the infiltrative type, with most of the tumor beneath the surface of the mucosa with or without ulceration. Lesions with a mixed appearance were classified as the infiltrative type. Tumor thickness was measured using IUS. The median age of the patients was 62.5 years (range, 30–93 years). All patients had histopathologically confirmed squamous cell carcinoma, and the absence of metastases was confirmed by CT and/or positron emission tomography (PET)/CT. The median follow-up period was 72.5 months (range, 10–133 months). All patients were followed up until death or March 2021. Their data were reviewed in March 2021.

Treatment

The indication criteria of ^{198}Au grain brachytherapy in our hospital are as follows: for lesions with a thickness of approximately 5 mm or less, we use ^{198}Au grain brachytherapy alone; for lesions thicker than 5 mm, external beam radiotherapy (EBRT) and/or chemotherapy are used in combination with ^{198}Au grain brachytherapy, or LDR-BT with ^{192}Ir is applied. Thirty-eight patients were treated using

^{198}Au grains alone, and the other seven patients were treated with a combination of EBRT and ^{198}Au grains. One patient with T1 and six with T2 tongue cancer were treated with EBRT prior to ^{198}Au brachytherapy, mainly for infiltrative disease. Six of the seven patients received chemotherapy concurrently with EBRT before ^{198}Au brachytherapy. The chemotherapy regimens were S-1 (tegafur, gimeracil and oteracil potassium) alone (three cases), a combination of cisplatin and 5-fluorouracil (one case), a combination of S-1 and cisplatin (one case) and a combination of nedaplatin and S-1 (one case).

The ^{198}Au grain implantation technique is described as follows: the grains were arranged 10 mm apart, and the outermost grains were implanted 5 mm outside of the lesion which was a Lugol-unstained area. ^{198}Au grain implantations were carried out under local anesthesia, and positioning was confirmed by IUS, to ensure that they were in the appropriate position to cover the deep border of the tongue lesion. A case of T1 tongue cancer treated with 10 grains is shown in Fig. 1. The ProSound SSD-3500 plus[®] (Hitachi Aloka Medical, Tokyo, Japan) with a 38- or 50-mm linear probe (7.5 MHz) was used in all examinations. A 10-mm thick acoustic coupling material was placed on the surface of the probe and covered with a rubber probe cover filled with water. The probe was placed in contact with the surface of the tongue lesion, and the cross-sectional maximum thickness was measured and visualized (Fig. 1C) [11].

The initial ^{198}Au grain activity was approximately $185 \text{ MBq} \pm 10\%$ per grain at noon on Wednesday, and single-plane implants were routinely used. In patients treated with ^{198}Au grains alone, a permanent dose of 85–100 Gy was prescribed for the treatment volume determined by inspection, palpation, IUS and Lugol's staining. Spacers made of silicon rubber material, used for dental impressions of approximately 10-mm thickness, containing a lead plate of approximately 4-mm thickness, were used to protect the mandible and maxilla.

A combination treatment with EBRT and/or chemotherapy, and ^{198}Au grain brachytherapy was mainly applied for infiltrative and thick lesions. Comparing the tumor thickness between the group without EBRT and/or chemotherapy and the group with EBRT and/or chemotherapy, the tumor thicknesses were 3.7 ± 1.7 mm (mean \pm standard deviation [SD]) and 6.2 ± 1.7 mm (mean \pm SD), respectively. The Wilcoxon rank-sum test showed a statistically significant difference ($P = 0.0039$). EBRT was usually applied in combination with ^{198}Au brachytherapy at doses of 30 Gy (2 Gy/fraction, 5 fractions/week, 15 fractions). 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 the upper neck area was used for this. The interval between the end of EBRT and the beginning of ^{198}Au brachytherapy was a median of 16 days (range, 6–35 days) to alleviate any acute mucosal reaction. In the case of the combination of EBRT and ^{198}Au brachytherapy, ^{198}Au grains were implanted 24 hours after the 185 MBq per grain was measured to control the total dose to the tumor site. One patient received 15 Gy EBRT a month after ^{198}Au brachytherapy for suspected residual disease.

No prophylactic neck dissection was performed. The patients were examined for cervical lymph node metastasis monthly, during the first year after the brachytherapy, using ultrasonography or contrast-enhanced CT.

Table 1. Patient characteristics

Primary lesion	T1	T2	P-value
Number	21	24	n.s.
Age (years) (median, range)	62.0 (34–90)	66.0 (30–93)	n.s.
Sex (male/female)	8/13	12/12	n.s.
Follow up period (months) (median, range)	63.0 (10–159)	74.5 (13–154)	n.s.
Combination of EBRT and/or chemotherapy	1	6	n.s.
Growth type			n.s.
Superficial	11	16	
Exophytic	4	2	
Infiltrative	6	6	
Tumor thickness by IUS (mm, median [range])	3.0 (1.3–8.3)	4.4 (1.5–8.4)	n.s.

n.s.: not significant.

EBRT: external beam radiotherapy.

IUS: intraoral ultrasonography.

Statistical analysis

The Wilcoxon rank sum test and Fisher's exact test were used to compare the patient characteristics. Local control, cause-specific survival (CSS), overall survival (OS) and cervical lymph node metastasis rates were generated using the Kaplan–Meier method. Outcomes in the different groups were compared using a log-rank statistical test. JMP[®] version 12 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Statistical significance was set at $P < 0.05$.

Ethical approval

The study was approved by the local institutional ethics committee (registration: E-458) and was 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

Local control

The two- and five-year local control rates in patients with T1 tongue cancer were 95.2%. The two- and five-year local control rates in patients with T2 tongue cancer were 100% and 95.5%, respectively (Fig. 2A). There were no statistically significant differences in local control rates between patients with T1 and T2 tongue cancer ($P = 0.74$). Three out of 45 patients (6.7%) did not achieve primary lesion control during the entire follow-up period. Two of the three patients with T1 tumors had recurrences within the irradiated field. One patient with a T2 tumor had a marginal recurrence. All patients were successfully treated through surgery.

Survival rate

The two- and five-year CSS rates were 84.2% in patients with T1 tongue cancer and 100% and 95.5% in patients with T2 tongue cancer, respectively (Fig. 2B). The two- and five-year OS rates were 84.2% and 77.7% in patients with T1 tongue cancer, respectively, and 95.8% and 86.1% in patients with T2 tongue cancer, respectively (Fig. 2C). There were no statistically significant differences in the CSS ($P = 0.19$) and OS

($P = 0.59$) rates between patients with T1 and T2 tongue cancer. Seven of the 45 patients died. Four patients (three with T1 and one with T2) died because of uncontrolled cervical lymph node metastases. Three patients (one with T1 and two with T2) died from other conditions.

Cervical lymph node metastasis

Seven out of the 21 patients with T1 tongue cancer and seven out of the 24 patients with T2 tongue cancer developed cervical lymph node metastases after the ¹⁹⁸Au brachytherapy. The rates of metastases to cervical lymph nodes at two and five years were 25.3% and 31.1% respectively, for T1 tumors, and 23.8% and 33.3%, respectively, for T2 tumors (Fig. 2D). There were no statistically significant differences between patients with T1 and T2 tongue cancer ($P = 0.89$). In the 14 cases included our study, lymph node metastases occurred at a median of eight months (range, 4–66 months) post-therapy in patients with T1 tongue cancer, and a median of five months (range, 2–39 months) post-therapy in patients with T2 tongue cancer. There were no statistically significant differences between patients with T1 and T2 tongue cancer ($P = 0.44$) in this regard. When comparing treatment regimens with and without the combination of EBRT and/or chemotherapy, late cervical lymph node metastasis was observed in only one patient in the EBRT and/or chemotherapy group. In contrast, 13 patients in the group without EBRT and/or chemotherapy had late cervical lymph node metastasis.

DISCUSSION

In this study, we report the treatment outcomes of ¹⁹⁸Au brachytherapy guided by IUS for early stage primary tongue cancer through a retrospective medical chart review. Previous studies reporting the local control rate of tongue cancer patients treated with only ¹⁹⁸Au brachytherapy as the radioactive source are sparse. One study reported a two-year local control rate of 71% [2]. As we were not able to find reports of ¹⁹⁸Au brachytherapy for patients with only tongue cancer, we searched for treatment results including other subsites in the oral cavity. Horiuchi *et al.* reported that the two-year local control rate was 88.7% for T1 and 76.5% for T2 tongue, floor of the mouth, buccal mucosa

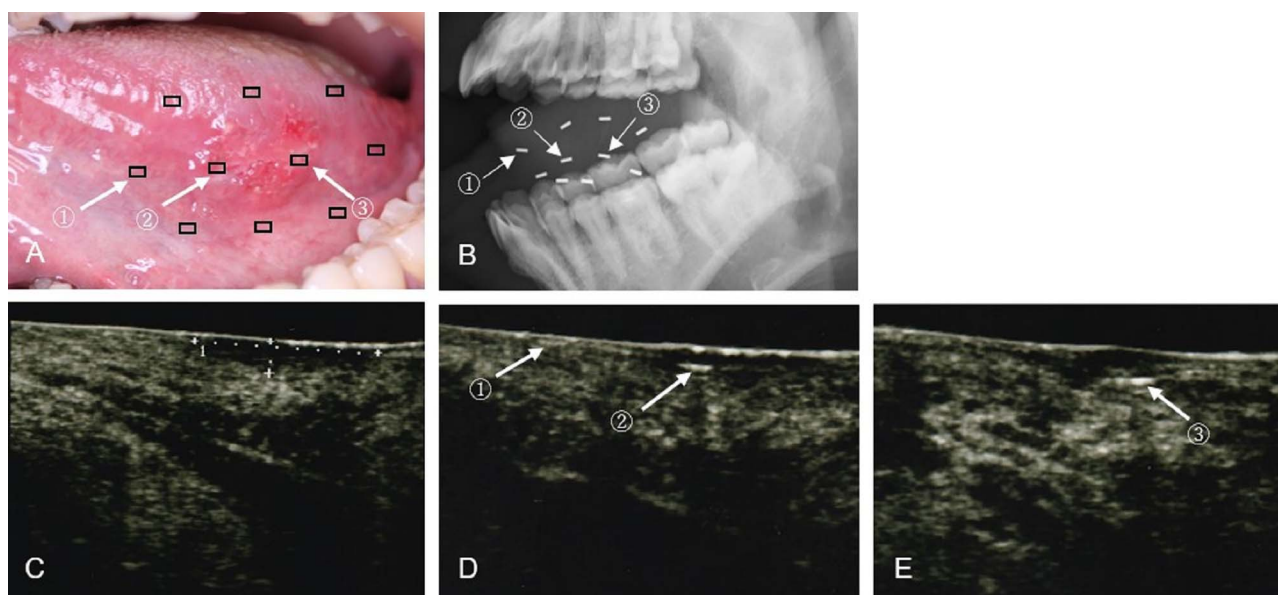


Fig. 1. Example of ^{198}Au grain implantation guided by IUS. (A) The patient has a T1 tongue cancer of the infiltrative type with erosion and erythema. As shown, 10 grains (square) are arranged. (B) The radiograph after ^{198}Au grain implantations is shown. Ten grains are implanted in the tongue. Number 1, 2 and 3 shown by arrows in the images A, B, D and E, respectively, represent the same ^{198}Au grain. (C) The degree of invasion under the lingual mucosa epithelium is considered to be the hypoechoic image region on the IUS. The length and thickness of the hypoechoic area are approximately 18.3 and 3.1 mm, respectively. (D) The locations of the implanted ^{198}Au grains are shown. IUS image shows two ^{198}Au grains (number 1 and 2) of A and B. (E) The location of the implanted ^{198}Au grain is shown. IUS image shows a grain (number 3) of A and B. It is located near the margin of the hypoechoic image.

and oropharyngeal cancer [5]. Matsumoto *et al.* reported that the two-year local control rate was 75% for T1 and T2 floor of the mouth cancer [12]. Shimizutani *et al.* reported that the local control rate for T1 was 80% and 59% for T2 tumors, in patients in whom the primary tumor originated in the floor of the mouth, tongue, oropharynx, lower gum, maxillary sinus, hard palate and the retromolar region [13]. The local control rate was 71% for ^{198}Au grains alone and 72% for EBRT combined with ^{198}Au grains [13]. Our results showed a more favorable outcome in terms of local control. We propose that this may have originated from the fact that we used IUS for all our patients during ^{198}Au grain implantation.

The dose around the ^{198}Au grain decreases by the inverse-square law; therefore, a lower dose to the border of the lesion could lead to residual or recurrent disease if the implanted position of the ^{198}Au grain is slightly dislocated from the intended site. In brachytherapy, this law is an adequate approximation at large distances from the radioactive source. A large distance generally means a distance that is at least twice the size of the source [14]. Therefore, we believe that the use of IUS can identify the lesion area and the accurate position of implanted ^{198}Au grains in real time and avoid underdosage, leading to the failure of local control.

An important indication to use ^{198}Au grain in the treatment of tongue cancer is typically small (i.e. T1 or T2) tumors that are superficial. Therefore, it is often challenging to accurately determine the size and shape of lesions using CT or MRI alone because of their small size. Additionally, small lesions may become obscured because of metallic artifacts, such as dental prosthesis. In the aforementioned

cases, we would depend on inspection and palpation to identify the exact lesion volume. When the lesion is treated surgically, we can see histologically if the lesion is completely resected. However, this information cannot be obtained for brachytherapy without surgery, although precise identification of the size and area of the lesions is essential before starting ^{198}Au brachytherapy. Consequently, we used IUS to confirm the lesion volume in addition to inspection, palpation, CT, MRI and PET/CT. Previous reports showed that the use of IUS was effective in acquiring precise information about the area of tumor extension [8, 11, 15–18]. IUS provides a quick and reliable orientation during resection of tongue cancer, and a precise delineation of the resection margins is therefore attainable [8]. The ultrasonographic tumor thickness measurements corresponded well with those of the histopathological sections [15]. IUS is a reliable method for objectively evaluating tumor thickness and surgical margin clearance [16]. The use of IUS to identify the extent of lesions and the position of implanted ^{198}Au grains is effective and probably improves the local control rate.

In previous reports on ^{198}Au brachytherapy for tongue cancer, the two-year CSS rate was 73%, the three-year CSS rate was 73% with T1 and T2, and the five-year CSS rates were 71% and 75% for patients with oral cancer [2, 5, 19]. The three-year OS rate was 57%, and the five-year OS rates were 51% and 52% for patients with oral cancer [2, 5]. These numbers are lower than those reported in the current study. Lymph node metastasis is a known prognostic factor. In our study, 14 out of 45 patients developed cervical lymph node metastases (seven T1 and seven T2 cases). Four of the 14 patients died due to uncontrolled cervical lymph node metastasis. There have been some reports that the

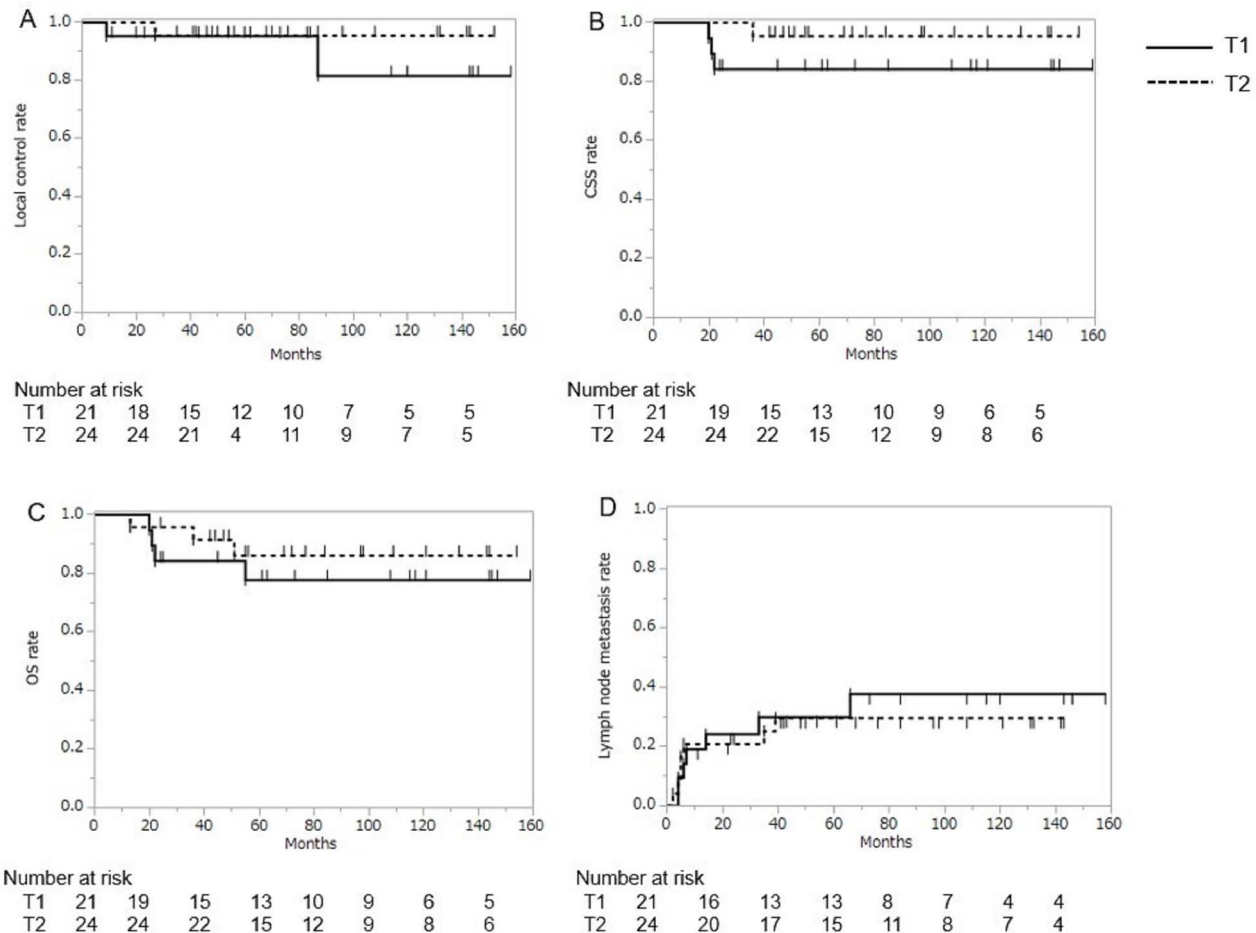


Fig. 2. Local control, CSS, OS, and occurrence of lymph node metastasis rates with ^{198}Au grain brachytherapy for T1 and T2 tongue cancer patients. (A) Local control rates with ^{198}Au for T1 and T2 tongue cancer patients. There were no statistically significant differences between T1 and T2 tongue cancer patients ($P = 0.39$). (B) CSS rates and OS rates with ^{198}Au for T1 and T2 tongue cancer. There were no significant differences between T1 and T2 tongue cancer patients ($P = 0.19$). (C) OS rates with ^{198}Au for T1 and T2 tongue cancer. There were no significant differences between T1 and T2 tongue cancer patients ($P = 0.46$). (D) Occurrence rate of lymph node metastasis treated with ^{198}Au for T1 and T2 tongue cancer patients. There were no significant differences between T1 and T2 tongue cancer patients ($P = 0.75$).

occurrence of lymph node metastasis is associated with the thickness of the lesion. Matsuura *et al.* reported that treatment for patients with a maximum tumor thickness > 8 mm was more likely to fail for tumors in the neck. In addition, they suggested that prophylactic EBRT to the upper neck at 30 Gy would reduce the risk of subsequent cervical lymph node metastases [20]. In other reports, a critical boundary of 5-mm tongue tumor depth was proposed, in which cervical metastasis was more likely. They suggested that elective neck therapy was strongly indicated for tumors exceeding 5-mm invasion [21]. In our study, the combination therapy with EBRT and/or chemotherapy, and ^{198}Au grain brachytherapy was used for the infiltrative type and thick lesions. Comparing the tumor thickness between the group without EBRT and/or chemotherapy and the group with EBRT and/or chemotherapy, the tumor thickness was significantly greater in the EBRT and/or chemotherapy group. The mean tumor thickness was 6.2 mm in the

combination therapy group. Late cervical lymph node metastasis was observed in only one of seven patients in the EBRT and/or chemotherapy group. Combination therapy for thick lesions with a high risk of late cervical nodes may have reduced the incidence of late cervical node metastasis. In contrast, six of the 38 patients in the group without EBRT and/or chemotherapy developed late cervical lymph node metastasis. However, for the early detection of late cervical lymph node metastasis, examinations by doctors from multiple departments and examinations by ultrasonography and/or CT were performed every month for at least one year after treatment, which may have led to the favorable CSS rate.

Our study has several limitations. The patients were treated with ^{198}Au brachytherapy; therefore, we were not able to compare the IUS and histopathology images concerning the extent, shape, margin and border of the disease. Furthermore, because IUS was performed in

all ^{198}Au brachytherapy patients at our institution, it was not possible to divide patients into groups, such as with and without IUS, in the present study. Future studies should corroborate our assumption that the use of IUS significantly contributes to an accurate estimation of the tumor area, and therefore, to optimal placement of the ^{198}Au grains and significant improvement of the local control rate. IUS after ^{198}Au grain implantation is considered to be effective for checking the appropriate placement; however, the increased exposure of the examiner is a problem. In the future, we plan to investigate the exposure dose and study methods to reduce it. Regarding the evaluation of dose distribution, in many cases of our study, a dose distribution map has been created based on 2D X-ray images. In the future, we will take into consideration the creation of a radiation dose distribution map using CT images and the DVH. Additionally, three-dimensional dose assessment using IUS images and hybrid images combining IUS and CT will also be considered.

CONCLUSION

In conclusion, our study reported several treatment outcomes of ^{198}Au brachytherapy for primary tongue squamous cell carcinoma. Our findings suggest that IUS should be considered along with visual inspection and palpation when determining the appropriate strategy to treat T1 and T2 primary tongue cancer patients. We believe that the use of IUS during ^{198}Au grain implantation can contribute to the improvement of the local control rate because it ensures more appropriate placement.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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