Original Article

Second Malignancy of the Oral Cavity after Brachytherapy for Tongue Cancer in Long-term Follow-up Patients

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Introduction: Brachytherapy is as effective as surgery for tumor control, with better functional and cosmetic results. When the primary treatment includes radiation therapy, however, a second malignancy (SM) may develop in the previously irradiated area. The present study investigated the incidence and treatment results of SM in the oral cavity after brachytherapy for tongue cancer.

Study design: A retrospective study was performed using medical records from our institution's database.

Methods and Materials: A retrospective review of 281 patients who had been treated with brachytherapy for stage I or II tongue cancer between 1965 and 2000 was performed. All of the patients had been followed-up for more than 10 years at the Department of Diagnostic Radiology and Oncology, Tokyo Medical and Dental University Hospital.

Results: SM of the oral cavity occurred in 26 (9.3%) of the 281 patients between 8 and 32 years after brachytherapy. Twenty of these patients underwent surgery, and their 4-year overall survival rate was 94.4%. Four patients received a second brachytherapy treatment because of the presence of inoperable and/or unresectable lesions, but all of these treatments failed; 3 of the patients died of SM at a median of 1.8 years after the diagnosis. One patient received laser treatment and another patient received chemotherapy, but both of these patients died of uncontrolled SM at 2 months and 5 months after the diagnosis of SM.

Conclusions: SM can occur in the oral cavity after brachytherapy for tongue cancer during a long-term follow-up period. In such cases, surgery is the only successful salvageable treatment.

Keywords: tongue cancer, treatment results, brachytherapy.

Introduction

As diagnostic and therapeutic techniques for head and neck squamous cell carcinoma continue to improve, the expectation is that the relative survival rates will likely increase.

Brachytherapy has been performed as one of the standard treatments for early-stage tongue cancer. Because brachytherapy delivers a high radiation dose to a limited volume while sparing the surrounding normal tissues, brachytherapy is as effective as surgery for tumor control, with better functional and cosmetic results [1, 2].

Ionizing radiation, including X rays and gamma rays, has long been established as being carcinogenic, in addition to tobacco or alcohol
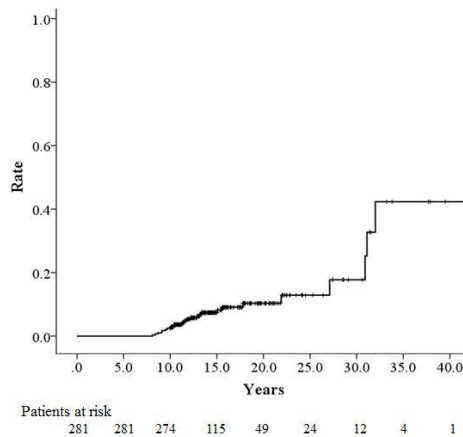
Figure 1: Incidence of second malignancy (SM) in the oral cavity.

exposure [3], and second malignancy (SM) has a reported incidence of 5%-30% following the successful treatment of head and neck tumor and is considered an important negative prognostic maker [4]. However, to our knowledge, SM after brachytherapy for tongue cancer has not been previously reported.

When a primary treatment includes radiation therapy, SM can develop in a previously irradiated area. The treatment of preference in cases of SM in a previously irradiated area is salvage surgery. Although repeat brachytherapy has been reported as being effective for the residual or recurrent cancer in a previously irradiated area with short-term follow-up in our institution [5], there has been no data regarding repeat brachytherapy for SM in the oral cavity with long-term follow-up.

We retrospectively examined the incidence of SM in the oral cavity in the patients who were followed- up for more than 10 years after brachytherapy for tongue cancer and analyzed the treatment results.

Material and methods

Between 1965 and 2000, 281 patients with stage I or II tongue cancer were treated with interstitial brachytherapy using low-dose-rate sources and, thereafter, were followed-up for more than 10
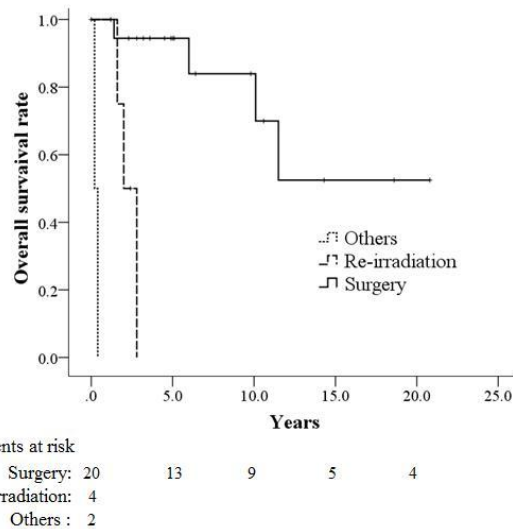
Figure 2: Overall survival rates for patients with second malignancy (SM) according to treatment modality.

years at the Department of Diagnostic Radiology and Oncology, Tokyo Medical and Dental University Hospital. The patients consisted of 114 females and 167 males, and their age ranged from 19 to 82 years, with a median age of 55 years at the time of brachytherapy. According to the UICC TNM Classification of Malignant Tumors seventh edition, 89 patients had stage I (T1N0) disease and 192 patients had stage II (T2N0) disease. The histological diagnosis of all the tongue cancers was squamous cell carcinoma. The brachytherapy sources were Ra-226 needles in 135 patients, Ir-192 pins in 87 patients, Au-198 grains in 27 patients, Rn-222 seeds in 18 patients, Cs-137 needles in 9 patients, and Co-60 needles in 5 patients. The patients underwent brachytherapy alone and were irradiated with 70 Gy over about 7 days with a 5-mm margin around the tumor region [6, 7]. The patients did not undergo chemotherapy. The follow-up period ranged from 10 to 51 years (median, 14.4 years).

We reviewed these tongue cancer patients and investigated the occurrence of SM in the oral cavity as well as the treatment outcome after obtaining the approval from the research ethics board committee. The actuarial curves for the incidence of SM, the overall survival rate, the
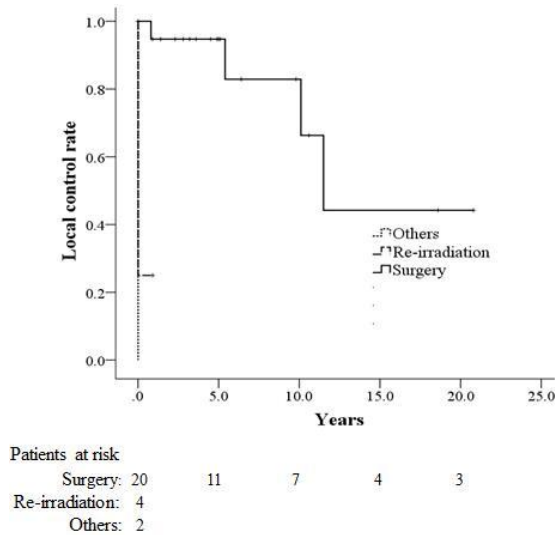
Figure 3: Local control rates for patients with second malignancy (SM) according to treatment modality.

local control rate, and the disease-free survival rate were calculated according to the Kaplan-Meier method. The statistical analyses were performed using SPSS version 19 software, and a univariate analysis was assessed using the log-rank test or chi-square test. A *P*-value less than 0.05 was considered significant.

Results

SM in the oral cavity was found in 26 (9.3%) of the 281 patients after brachytherapy for tongue cancer (Table 1). The interval between brachytherapy and the occurrence of SM ranged from 8 to 32 years, with a median of 11.7 years, and the 10-, 20-, and 30-year cumulative incidence rates were 2.5%, 10.3%, and 17.7%, respectively (Fig. 1). No recurrence or metastasis was found in any of the 26 patients at the time of the occurrence of SM. The patient age ranged from 51 to 87 years, with a median of 71 years at the time of the diagnosis of SM. The histological diagnosis was squamous cell carcinoma in 24 patients, granular cell carcinoma in 1 patient, and spindle cell carcinoma in 1 patient. SM occurred in the tongue in 21 patients, the lower gum in 2 patients, the buccal mucosa in 1 patient, the floor of the mouth in 1 patient, and the lip in 1 patient;
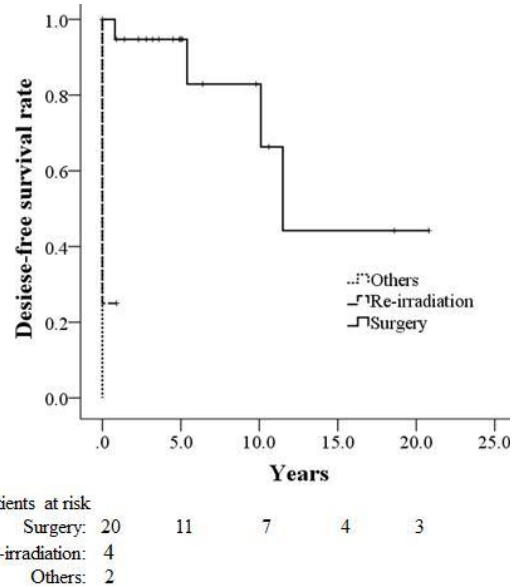

Figure 4: Disease-free survival rates for patients with second malignancy (SM) according to treatment modality.

all the SMs occurred on the side of the initial treatment. No significant differences between the incidence of SM and the characteristics of the initial tongue cancer (disease stage, patient age, sex, or brachytherapy source) were seen (Table 2).

Twenty patients underwent surgery for SM. Because the other 6 patients had inoperable and/or unresectable lesions, brachytherapy was performed again in 4 patients (Au-198, n = 3; Rn-222, n = 1), chemotherapy was performed in 1 patient, and laser treatment of the buccal mucosa was performed in 1 patient. All 6 patients experienced tumor failure between 4 months and 2 years (median, 1.6 years) after the diagnosis of SM, and 5 of them died of SM between 7 months and 2 years (median, 1.8 years) after the diagnosis of SM. Seventeen (85%) of the 20 patients who were treated with surgery were salvaged and are presently alive. One patient died of neck metastasis at 1.4 years after the diagnosis of SM, 1 patient died of pneumonia at 11.5 years, and 1patient was alive with local failure and neck metastasis.

Table 2: Relationship between clinical factors and the incidence of second malignancy (SM)

Variable	10-year incidence of SM [%]	HR	95%CI	P value
Sex				
Male	0.6	1.312	0.603-2.853	0.304
Female	5.3			
UICC staging and TNM classification				
Stage I, T1N0	1.1	1.003	0.442-2.278	0.735
Stage II, T2N0	3.1			
Age				
≤60 y	2.1	1.944	0.812-4.653	0.735
>60 y	3.4			
Low-dose-rate brachytherapy source				
Permanent[*]	4.5	1.272	0.476-3.397	0.303
Temporary[†]	2.3			

Permanent[*]: Au-198, Temporary[†]: Ir-192,Ra-226,Cs-137,Co-60, Rn-222

Abbreviations: HR, Hazard Ratio; CI confidence interval.

The 4-year overall survival rate for the 26 patients was 87.8% after the diagnosis of SM. The 4-year overall survival rate (Figure 2), the local control rate (Figure 3), and the disease-free survival rate (Figure 4) for the patients who underwent surgery were 94.4%, 94.7%, and 90%, respectively, and these values were significantly higher than those of the patients who underwent repeat brachytherapy (0%, 25%, and 25%) or other treatments (0% ,0%, and 0%).

Although oral ulcers were seen in all the patients after repeat brachytherapy, no severe complications occurred in any of the patients who underwent surgery.

Discussion

There has been no report concerning SM after brachytherapy for tongue cancer, to our knowledge. However some studies have revealed the incidence of SM after brachytherapy for prostate cancer or uterine cancer. Hinnen et al., [8] analyzed 1187 patients after prostate brachytherapy using I-125 and reported the 10-year incidence of SM in the pelvis as a heavily irradiated area: 1.7% in the colon, 1.1% in the rectum, and 1.5% in the bladder. They compared the incidence of SM after brachytherapy and that after prostatectomy and found no difference. However, their analysis also showed that, after brachytherapy, there was an increased risk of bladder SM during the first 4 years after treatment and in patients aged 60 years or younger. Zelefsky et al., [9] also analyzed 413 patients who had received prostate brachytherapy using I-125, and the SM in the pelvis was observed in 1.6% of the patients at 10 years. They compared the incidence with that of 897 patients with intensity-modulated radiotherapy and found no differences in the incidence of SM (IMRT, 4.9%). Ohno et al., [10] investigated the incidence of SM after brachytherapy and external beam radiation therapy (EBRT) for uterine cervical cancer in 2167 patients and reported that 1.8% of them had SM in the pelvis. They estimated the relative risk (RR) by comparing the results with the expected number from population-based cancer registries in Japan and reported that the RRs of leukemia, corpus, bone and soft tissue, and lung cancer were significantly elevated.

The present study showed that SM in the oral cavity after brachytherapy for tongue cancer was observed in 9.2% of the long-term follow-up tongue cancer patients, and the elevated cumulative risk was 17.7% at 30 years after brachytherapy. Although the incidence of SM in our study was higher than in other reports, one of the limitations of our study was that we were unable to confirm a difference between SM and the local recurrence of tongue cancer because the pathology of almost all the SMs in our study was squamous cell carcinoma. However, a previous report has indicated that local recurrence after brachytherapy for tongue cancer always occurs within 5 years [1], and other studies [6,11] have shown that the 10-year local control rate for early-tongue cancer patients treated with brachytherapy was similar to the 5-year local control rate. As the SMs in our study occurred 8 or more years after brachytherapy (median, 11.7 years), the possibility of a local recurrence, rather than SM, is likely to be low. The small number of patients was also a limitation of this study, but the incidence of tongue cancer is lower than those of other malignancies. An additional limitation is that no information on the tobacco and alcohol consumption of the patients was available. Ohno *et al*., [10] showed the impact of smoking habits on the increased risk of second cancer after cervical cancer treated with radiotherapy, and another report has concluded that tobacco and alcohol consumption are responsible for an estimated 72% of head and neck cancers in the general population [12]. Moreover, it would appear that patients with head and neck cancer continue to have a higher risk of a second cancer even after they stop smoking [13].

The preferable treatment for SM after radiotherapy is surgery, with 5-year survival rates ranging from 16%-36% [14-16]. However, because of the tumor location and extent, medical contraindications, or patient refusal, surgery is often limited and compromised by close or positive margins, and only 20% of patients are able to undergo salvage surgery [14,16]. In this present study, our policy was to perform surgery for patients with operable and resectable tumors and to use repeat brachytherapy for inoperable and/or unresectable cases. The overall survival, local control, and disease-free survival of the patients who underwent surgery were 94.4%, 94.7%, and 90%, respectively, at 4 years, and these values were remarkably superior to those of patients who underwent repeat brachytherapy (0%, 25%, and 25%, respectively). High-dose re-irradiation in inoperable patients is the only treatment option with any potential for a cure. Re-irradiation can be delivered using brachytherapy, stereotactic radiosurgery, intensity-modulated radiotherapy, and so on, with or without chemotherapy and with or without prior debulking surgery. When a SM in a different region other than the treated region occurs, the SM can be treated without considering the toxic effect of re-irradiation [17]. However, for anatomic same-site or sub-adjacent sites of the initial radiotherapy, treatment selection is difficult [18].

Langendijk *et al*., [19] reported the results of a phase II study of re-irradiation for inoperable and/or unresectable SM (n=26) in the head and neck region. They used EBRT (60-66Gy) to re-irradiate sites in the head and neck region, and the 2-year locoregional control rate was 35%. They observed a late swallowing complication of grade III or IV in 24% of the patients, and nasogastric tube feeding was required in 12% of the patients. However, in our study, all the patients who underwent repeat brachytherapy suffered from radiation ulcers, and none of the cases were salvaged. Moreover, Langendijk *et al*., [19] concluded that because most recurrences after re-irradiation developed within the boost volume, there are no reasons to use wider margins surrounding the gross-target volume (GTV). Although brachytherapy can be performed for heavy dose irradiation within the GTV and with a small margin, we felt that the definition of the GTV for SM was too difficult to arrange the repeat brachytherapy sources appropriately. There is a possibility that curative radiotherapy for primary cancer may cause slowly developing radiation fibrosis of the irradiated fields over a

long term, and such fibrosis may cause insufficient blood flow or a decrease in oxygen at the time of the second radiation therapy.

Conclusion

SM within a prior brachytherapy area in the oral cavity was found after a long interval (≥8 years) in about 1 out of 10 tongue cancer patients treated with brachytherapy, and surgery was a unique salvageable treatment for such cases.

Conflict of Interests

The authors declare that there are no conflicts of interests

Author's contribution

EO: performed the literature search and prepared the draft manuscript.

HS: conceived and designed the study and edited the final manuscript.

KN,KA and NH: participated in the study design and helped in the preparation of the manuscript.

All the authors have read and approved the final manuscript.

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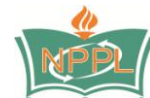
Case number	Stage	Age at diagnosis (years)	Sex	Type of irradiation	Latency in years and months	Site of the second malignancies	Histopathological diagnosis of the second malignancies	Modality of treatment for the second malignancies
							Table 1: Summary of 26 patients with a second malignancy (SM)	
1	T1	81	Male	Ra-226	27y1m	Tongue	Squamous cell carcinoma	Au-198
2	T1	74	Female	Rn-222	31y1m	Tongue	Squamous cell carcinoma	Surgery
3	T1	63	Female	Ra-226	32y0m	lower gum	Squamous cell carcinoma	Surgery
4	T1	84	Male	Ir-192	13y2m	Tongue	Squamous cell carcinoma	Au-198
5	T1	80	Male	Ir-192	21y10m	Tongue	Squamous cell carcinoma	Surgery
6	T1	51	Male	Au-198	11y3m	Tongue	Squamous cell carcinoma	Surgery
7	T1	79	Female	Ir-192	8y0m	Floor of mouth	Squamous cell carcinoma	Surgery
8	T1	71	Male	Au-198	10y5m	Tongue	Squamous cell carcinoma	Surgery
9	T1	64	Male	Ra-226	13y4m	Lip	Granular cell carcinoma	Surgery
10	T2	59	Female	Rn-222	9y1m	Tongue	Squamous cell carcinoma	Rn-222
11	T2	85	Male	Co-60	15y7m	Buccal mucosa	Squamous cell carcinoma	Laser treatment
12	T2	64	Female	Rn-222	8y4m	Tongue	Squamous cell carcinoma	Surgery
13	T2	78	Male	Rn-222	30y11m	Tongue	Squamous cell carcinoma	Chemotherapy
14	T2	58	Female	Ra-226	11y4m	Tongue	Squamous cell carcinoma	Surgery
15	T2	71	Male	Ir-192	15y1m	Tongue	Squamous cell carcinoma	Surgery
16	T2	61	Male	Ir-192	10y5m	Lower gum	Squamous cell carcinoma	Surgery
17	T2	76	Female	Ra-226	9y8m	Tongue	Squamous cell carcinoma	Surgery
18	T2	55	Female	Ra-226	17y10m	Tongue	Squamous cell carcinoma	Surgery
19	T2	74	Female	Ra-226	10y0m	Tongue	Squamous cell carcinoma	Surgery
20	T2	74	Female	Ra-226	11y9m	Tongue	Squamous cell carcinoma	Surgery
21	T2	63	Male	Ra-226	11y7m	Tongue	Spindle cell carcinoma	Surgery
22	T2	58	Male	Ra-226	9y0m	Tongue	Squamous cell carcinoma	Surgery
23	T2	68	Female	Ra-226	8y8m	Tongue	Squamous cell carcinoma	Surgery
24	T2	87	Female	Ir-192	12y10m	Tongue	Squamous cell carcinoma	Au-198
25	T2	66	Male	Ra-226	12y2m	Tongue	Squamous cell carcinoma	Surgery
26	T2	76	Female	Ra-226	9y5m	Tongue	Squamous cell carcinoma	Surgery