Clinical Course of Multiple Primary Oral Cancer:
Three of 13 Cases with Second Primary Tumor

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Abstract

Of 124 patients with oral squamous cell carcinomas treated during the past 14 years, 13 developed second primary cancers with clinical symptoms in the same tissues or in organs different from those of the initial lesions during follow-up. The second primary tumors also appeared in the oral cavity in 3 of the patients, the hypopharynx in 1, the esophagus in 2, the stomach in 2, the colon in 1, the thyroid gland in 2 and the lung in 2. Of the 3 patients with second tumors in the oral cavity, 1 underwent surgery after chemo- and radiotherapy and 2 underwent laser surgery or chemo- and radiotherapy only. The second primary cancers appeared on the contralateral or ipsilateral side, completely separate from the sites of the primary lesions during a period of 1 to 3 years. One patient with triple cancers involving the oral cavity, esophagus and hypopharynx is still alive after 15 years. The other two patients died of cervical or lung metastases after 3 years.

Introduction

In the treatment of oral squamous cell carcinoma, increasingly successful prognoses have been achieved as a result of surgery with or without irradiation and administration of antitumor agents. Furthermore, the number of patients in whom follow-up can be continued over a long period of time is gradually increasing.

In 1932, WARREN and GATES[1] proposed criteria for the diagnosis of multiple primary malignant tumors. Some modifications of these criteria for multiple primary malignant tumors. Some modifications of these criteria for multiple primary malignant tumors.
primary tumors\cite{2,3} and second primary tumors\cite{4,5} were later reported. Malignant transformation from leukoplakia and erythroplakia\cite{6-8} as a result of alcohol intake or smoking\cite{9} has been noted as a cause of multiple primary tumors appearing in the oral cavity.

This paper describes the clinical courses of 3 patients with multiple primary oral cancers in different regions of the oral cavity and the incidence of second primary tumors following oral squamous cell carcinomas in 13 patients.

### Second Primary Tumors in 13 Patients

During a 14-year period from 1975 to 1988, 124 patients with oral squamous cell carcinomas were referred to the Dental Clinic of Iwate Medical University. Second primary malignant tumors with clinical symptoms were found by histological diagnosis of biopsy samples in 10 cases or by autopsy in 3. The tumors involved the same tissues or different organs from those affected by the initial lesions in 13 (10.5%) cases, the upper aerodigestive tract in 10 (8.0%) and other regions of the oral cavity in 3 (2.4%) (Table 1). The TNM classification of the UICC\cite{10} (1987) was used for diagnosis.

As the sites of tumor involvement, the oral cavity was affected in 3 cases, the hypopharynx in 1, the esophagus in 2, the stomach in 2, the colon in 1, the thyroid gland in 2 and the lung in 2. The tumors were synchronous (occurring within a period of 6 months) in 5 of the 13 patients, and metachronous (occurring after 6 months) in the remaining 7\cite{4}.

### Table 1 Multiple primary tumors with oral squamous carcinoma during the period 1975-1988

<table>
<thead>
<tr>
<th>Tumor sites</th>
<th>Number of patients</th>
<th>Second primary cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All sites</td>
</tr>
<tr>
<td>Tongue</td>
<td>41</td>
<td>4 (9.8%)</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>15</td>
<td>3 (20.0%)</td>
</tr>
<tr>
<td>Upper gingiva</td>
<td>17</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Lower gingiva</td>
<td>33</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>18</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>13 (10.5%)</td>
</tr>
</tbody>
</table>

### Multiple Primary Oral Cancers in 3 Patients

Case 1: A 61-year-old woman with a painful tumor and swelling in the submandibular region was referred to our clinic on January 12, 1984. A biopsy specimen was taken from the lesion on the upper gingiva over the lower buccal mucosa on the right side, and this revealed well differentiated squamous cell carcinoma. The tumor, showing resorption of the upper alveolar bone and a metastatic nodule over 6 cm in diameter in the submandibular lymph nodes, was classified as T4N3M0. Two other erosions of the frenulum of the upper lip and hard palate in the region of the contralateral upper molars were also identified to be squamous cell carcinoma (T1) and a synchronous primary tumor, respectively. A white lesion in the region of the buccogingival sulcus of the above molars
escaped detection and was not histologically evaluated by biopsy (Fig. 1-A, D). The patient’s mouth was sore due to ill-fitting upper and lower dentures at the time of the first examination.

After intravenous injection of 67.5 mg of peplomycin (PEP) with external irradiation of 54 Gy of telecobalt (60Co) to the primary tumor and 30 Gy of electron-beam (EB) irradiation to the submandibular lymph node metastasis, a partial maxillectomy including the buccal mucosa and total neck dissection were performed for the initial primary tumor. However, the two small tumors and the white lesion on the contralateral side were not excised at surgery, because they had already disappeared after the chemo- and radiotherapy (Fig. 1-B). The patient then wore an upper full denture for cosmetic purposes, but not for functional restoration.

At 2 years and 1 month after surgery, a second primary cancer (T1N1M0) appeared in a region corresponding to that of the previous white lesion on the contralateral side (Fig. 1-C, D). After intravenous injection of 67.5 mg of PEP and external irradiation 30 Gy of (60Co) to the second primary tumor, partial resection of the maxilla and total neck dissection were carried out. At 3 years and 8 months, the patient died of uncontrollable metastases to the para-pharyngeal lymph nodes in spite of postoperative chemo- and radiotherapy.

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Fig. 1 Case 1. A: Synchronous and multifocal primary cancers of the oral cavity at the first examination. There is ulceration of the upper right alveolgingiva, 2 erosions of the upper frenulum of the superior lip (arrow) and left hard palate (arrow), and a white lesion (arrow) in the left alveolobuccal sulcus. B: Disappearance of the cancers and white lesion (arrow) after chemo- and radiotherapy. C: Malignant transformation of the white lesion with ulceration (arrow). D: Histopathological findings of biopsy specimens, showing squamous cell carcinoma (left; A, right; C).
Case 2: An 83-year-old man with well differentiated squamous cell carcinoma of the lower gingiva on the left side was referred to our clinic on January 12, 1984. The tumor, showing erosion, was classified as T1N0M0 (Fig. 2-A, D). In the regions of the anterior gingiva and labial angle, white patches were seen. The mouth was sore due to an ill-fitting lower full denture at the time of the first examination. Though surgical excision was planned for the initial primary cancer, this was rejected by the patient in view of his age. Laser surgery was therefore performed at another hospital. The white patch in the labial angle found at the first examination developed into leukoplakia after 1 year (Fig. 2-B, D).

At 2 years and 9 months, he was referred to our clinic again, complaining of growth of a second primary tumor with metastasis to the submandibular lymph nodes. The tumor appeared in a region corresponding to the site of the white lesion found previously in the labial angle (T2N1M0) (Fig. 2-C, D). The patient had used his previous denture without improvement of oral hygiene. After intravenous injection of 30 mg of PEP with 90 Gy of Mold irradiation to the primary tumor and 30 Gy of EB for the metastasis, resection of the lower lip was carried out with the entire cheek and total neck dissection. Reconstruction of the defect was carried out using a rotation flap from the upper lip. At 3 years and 10 months, the patient died of multiple lung metastases.

Case 3: A 42-year-old man was referred to our clinic in May 15, 1976,
complaining of pain in the dorsal tongue slightly to the right of the mid line. Biopsy revealed well differentiated squamous cell carcinoma (T2N1M0). Although the patient also had a small ulcer on the contralateral side of the dorsal tongue, it escaped detection and was not histologically examined (Fig. 3-A). After intraarterial infusion of 60 mg of bleomycin (BLM) and 4850 mg of 5-fluorouracil (5-FU), external irradiation with 54 Gy of (60Co) and internal irradiation with 30 Gy of needle radium (Ra) bilaterally, both the tumor and ulcer disappeared. However, severe stomatitis caused by the chemo- and radiotherapy occurred contralaterally at the lateral margin of the tongue, and this persisted for approximately 2 weeks. Thereafter, total neck dissection was carried out for the management of metastasis to the superior internal jugular lymph nodes. The biopsy specimen showed no evidence of residual tumor cells. The patient then inserted his upper and lower partial dentures.

Six months later, an erythroplakia-like lesion developed in the region of contact between the contralateral dorsal tongue and the upper first molar. At biopsy, 1 year and 7 months after surgery, the lesion was diagnosed as well differentiated squamous cell carcinoma (T1N0M0), as in the initial primary tumor (Fig. 3-B). The patient initially refused surgical excision of the second primary tumor because of the absence of subjective symptoms. However, the tumor gradually enlarged, and partial resection (T2N0M0) was carried out in the 5th year following careful observation. After excision of the second primary cancer, the patient did not use his dentures.

In the 8th year, a third primary cancer (T3N1M0) appeared in the esophagus. Esophagectomy, cervical esophago-gastrostomy to the posterior mediastinum and postoperative irradiation of the tumor with 30 Gy of (60Co) were performed. In the

Fig. 3 Case 3. A: An initial primary cancer of the dorsal tongue on the right side (arrow) and small ulcer on the left side (arrow) at the first examination. B: A second primary cancer on the left side 1 year and 7 months after surgery.
13th year, the patient underwent chemo- and radiotherapies for a fourth primary cancer of the hypopharynx (T3N2cM0), and is still alive after 15 years despite metastases to the bilateral cervical lymph nodes.

**Discussion**

The incidence of second primary malignant tumors appearing in the upper aerodigestive tract of the oral cavity, oropharynx, and lip is high, whereas the incidence of esophageal tumors is low\[3,4\]. However, in the present retrospective follow-up investigation of 13 patients with second and/or third primary malignant tumors, the incidence (5 cases) of those involving the esophagus or stomach following the initial primary oral cancers was high. If the upper gastrointestinal tract is examined routinely at the time of treatment for oral primary cancers, second primary malignant tumors might be detected more frequently, in view of the relatively high incidence of gastric cancers in Japan.

The three patients with second primary cancers occurring in different regions from or contralaterally to the sites of the initial primary cancers within 1-3 years after treatment of the initial primary oral cancers has a higher risk of malignancy because of metastases to regional lymph nodes. Furthermore, since all three patients had ulcers or white lesions in regions entirely different from the sites of the initial primary cancers, it was considered that the lesions were already cancerous or precancerous, or that they had later undergone malignant transformation. The white lesion and small ulcer found on the contralateral side in cases 1 and 3 had escaped detection at the time of initial treatment. After preoperative chemo- and radiotherapy, these disappeared, and therefore were not excised. The second primary or recurrent cancers, however, appeared in the same tissues as that of the initial lesions 1 to 2 years later. This is consistent with the report of TASHIRO et al., who described that tumors recurred at 1-4 years after chemo- and radiotherapy without surgery for oral cancers, and that such patients might be at risk of latent malignancy due to residual epithelial dysplasia or microcancer. In the patient in case 2, who was not treated preoperatively by chemo- and radiotherapy, the white patch changed to leukoplakia after 1 year and underwent malignant transformation after 2 years.

In spite of their small size, these cancers were at an advanced stage with metastases to the regional lymph nodes in 2 of the 3 patients at the time of the first examination. The degree of histological differentiation of the initial and second primary cancers showed no marked differences. However, the second primary cancers tended to metastasize to regional lymph nodes. Two of the patients died as a result of this. In the other patient, multiple metastases to the lung occurred. The patient in case 3 with metachronous triple-organ cancers of the tongue, esophagus and hypopharynx is still alive after more than 15 years in spite of cervical metastases. This suggests that detection and excision of a subsequent cancer as early as possible, and careful observation of the clinical course following treatment are very important\[12,13\]. All of the 3 patients underwent regular follow-up examinations for 2 years. The patient in case 2 refused initial treatment at our clinic, and was referred again after the second primary tumor had developed.
Additionally, deterioration of the immunological and physiological conditions, sore mucosa beneath the plate denture and stimulation of the oral mucosa by the teeth were suspected to have promoted the development of the second oral tumors. Especially, in 2 of the 3 patients, the cancers occurred in the lower oral cavity. Treatment by surgery or irradiation might result in insufficient oral hygiene due to a decrease in salivary secretion. The two men had both drunk alcohol and smoked for a long time, and did not give up these habits even after therapy. The woman had no such habits. It was considered that there was a relationship between these habits, the irritation and the tumors.

**Conclusion**

Any white lesion found to exist in the oral mucosa should be excised if detected at initial examination, even if it disappears after preoperative chemo- and radiotherapy, since it presents a risk of malignant transformation in patients with oral cancers.

**References**


