

Contents lists available at ScienceDirect

## **Oral Oncology**

journal homepage: www.elsevier.com/locate/oraloncology



## Clinical characteristics of multiple primary carcinomas of the oral cavity



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#### ARTICLE INFO

Article history:
Received 11 August 2014
Received in revised form 17 November 2014
Accepted 20 November 2014
Available online 10 December 2014

Keywords:
Multiple primary carcinomas
Oral cavity
Survival rate
The cumulative incidence rate
Squamous cell carcinoma

#### SUMMARY

*Objectives*: This study aimed to clarify the clinical characteristics of multiple primary carcinomas of the oral cavity.

Materials and methods: We retrospectively reviewed the cases of 1015 patients who were treated during follow up for oral cancer at Tokyo Medical and Dental University between March 2001 and December 2012. We compared the clinical characteristics of 961 patients who developed single primary oral squamous cell carcinoma (SCC) during follow up and 54 patients who subsequently developed multiple primary carcinomas in the oral cavity.

Results: Mean age at first diagnosis was significantly higher in patients with multiple primary carcinomas than single primary carcinoma. Multiple primary carcinomas showed a female predilection, were most prevalent in the gingiva, and tended to show earlier tumor and nodal stages than single primary carcinoma. The local recurrence rate was higher for multiple primary carcinomas than single primary carcinoma, and it increased with the number of multiple primary occurrences. The disease-specific survival rate at 10 years for patients with single primary carcinoma was 85.3% and that for patients with multiple primary carcinomas was 79.6%. The cumulative incidence rate for metachronous second multiple primary carcinomas after the onset of first carcinoma at 10 years was 8.0%. The recurrence of multiple primary carcinomas did not decrease the survival rate.

*Conclusion:* Differences were found in the clinical characteristics between patients with single oral SCC and those with multiple primary oral carcinomas. Early diagnosis and treatment as well as close long-term follow up are needed for patients with multiple primary oral carcinomas.

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#### Introduction

Oral cancer, the sixth most prevalent cancer worldwide [1], is difficult to control even after treatment because of the high propensity for multiple primary carcinomas to develop [2–5]. The overall occurrence rate of multiple primary carcinomas in the oral cavity is between 6% and 27% [6–9], and its emergence has shown poor prognosis among patients who have already undergone treatment for early stage oral cancer [3,10,11]. Reducing its mortality and morbidity remains one of the most challenging problems.

While molecular-based explanations of its pathomechanism have been reported, few studies have provided clinical information that is useful for daily practice. Oral and maxillofacial surgeons and head and neck oncologists would clearly benefit from knowing the

Abbreviations: PVL, proliferative verrucous leukoplakia; SCC, squamous cell carcinoma.

characteristics of patients with this disease in order to identify and treat it expeditiously [12,13]. Therefore, this study aimed to examine the specific clinical features of, and discuss the clinical approach to managing, synchronous and metachronous multiple primary oral carcinomas.

#### Materials and methods

We retrospectively reviewed the medical records of patients with primary oral carcinoma who underwent surgical treatment at, and were followed by, the Department of Oral and Maxillofacial Surgery, Tokyo Medical and Dental University Hospital between March 2001 and December 2012. We studied only those patients who gave informed consent to be included in this study. The observation endpoints were set as June 30, 2014. Patients treated at another institute or with no pathology report or inadequate medical records were excluded. The study protocol was approved by our institution and was in accordance with the Declaration of Helsinki.

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#### Definitions of primary oral carcinoma

Single primary carcinoma was defined as carcinoma that developed only once as a single primary lesion during the follow-up period. We limited this to oral squamous cell carcinoma (SCC).

Multiple primary carcinomas were defined according to criteria modified from those of Warren and Gates in 1932 [14] and based on the 'General Rules for Clinical and Pathological Studies on Oral Cancer' proposed as a draft by the Japan Society for Oral Tumors [15], namely, more than 2 cancerous lesions separated by more than 1.5 cm of clinically non-cancerous epithelium in the oral cavity. As shown in Fig. 1, multiple primary carcinoma occurrence was categorized into synchronous or metachronous type and as first, second, or third multiple primary carcinomas. Synchronous multiple primary carcinomas were defined as more than 2 oral carcinomas separated by more than 1.5 cm of clinically non-cancerous epithelium synchronously or within 6 months of the original lesion. Metachronous multiple primary carcinomas were defined as more than 2 primary lesions that developed metachronously (after more than 6 months of each other) and were second or third occurrences. Local recurrence was defined as a lesion recurring within 1.5 cm of the original lesion. Distance between the lesions was determined by direct measurement from the newly onset lesion to the previous lesion and in reference to the patient's medical records. If it was difficult to judge whether the distance was within 1.5 cm because of postoperative scar formation or irregular anatomy, the lesion was classified as a recurrent lesion. In view of the diagnostic criteria for proliferative verrucous leukoplakia (PVL) proposed by Cerero-Lapiedra et al. [16], we included patients with multiple primary OSCC who previously had PVL.

Although in principle synchronous second and third multiple primary carcinomas are possible, they are rare and no such cases were observed in this study. Furthermore, because synchronous first multiple primary carcinomas greatly influence the survival of patients, we focus in this study on synchronous first multiple primary carcinomas and metachronous second and third primary carcinomas. For a detailed analysis of the features of multiple primary carcinomas, we studied differences in location, the interval between the first and later onsets of multiple primary carcinomas, cumulative incidence of second multiple primary carcinomas,

recurrence, lymph node metastasis, and presence of mucosal changes after the onset of first multiple primary carcinomas.

We compared differences in clinical features (age, sex, tobacco use, tumor location, TN classification, and stage) between the single primary carcinoma and the multiple primary carcinoma groups using the chi-squared or Fisher's exact test for categorical data and we used one-way ANOVA for continuous variables.

The disease-specific survival rates of the types of multiple primary carcinomas (i.e., synchronous first, metachronous, and metachronous third) were estimated by the Kaplan–Meier method. Also, differences in the disease-specific survival rates between patients with local recurrence and those with lymph nodes metastasis from the multiple primary carcinomas were analyzed by the log-rank test.

Statistical analysis was performed using statistical PASW Statistics 18 software for Windows (SPSS Japan Inc., Tokyo, Japan). A *p*-value less than 0.05 was considered statistically significant.

#### Results

We analyzed data for 1015 patients: 961 with single primary carcinoma and 54 with multiple primary carcinomas. The median duration of follow-up was 64 (range, 4–146) months.

Of the 54 patients with multiple primary carcinomas, 10 (20.4%) had synchronous first multiple primary carcinomas, 33 (61.1%) had metachronous second multiple primary carcinomas, and 11 (20.4%) had metachronous third multiple primary carcinomas (Fig. 1). The median interval between onset of first multiple primary carcinomas (regardless of being synchronous or metachronous) and onset of second multiple primary carcinomas was 90 (range, 13–141) months and that between the onset of second and third multiple primary carcinomas (regardless of being synchronous or metachronous) was 63 (range, 28–124) months.

#### Treatment protocols

Of the 961 patients with single primary carcinoma, 843 underwent surgical treatment alone, 26 received brachytherapy (mean dose, 77.1 [range, 57.6–97.0] Gy), 38 received induction chemotherapy plus surgery (cisplatin and 5-FU, 34 cases; other, 4 cases),

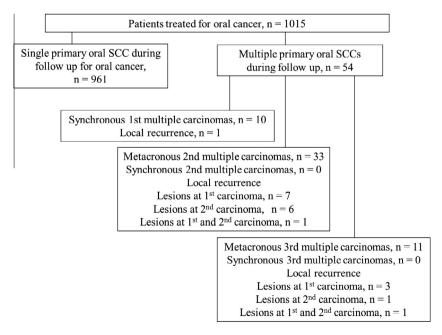


Fig. 1. Flow diagram of patients who developed single primary carcinoma or multiple primary carcinomas during follow up after surgery for an initial occurrence of oral cancer. Number of recurrences are shown. Mean interval between primary tumor resection and recurrence was 22 (range, 2–86) months.

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