Yonago Acta Medica 2020;63(4):246–254 doi: 10.33160/yam.2020.11.002

Clinical Features of Oral Multiple Primary Carcinomas Compared with Oral Single Primary Carcinoma

Makoto Kawasaki,* Takayuki Tamura,* Yusei Harada,* Nobuyuki Fujii,* Rieko Doi* and Isamu Kodani*
**Division of Oral Maxillofacial Surgery, Department of Sensory and Motor of Organs, School of Medicine, Factory of Medicine, Tottori University, Yonago 683-8503, Japan*

ABSTRACT

Background Owing to the increase in the older population and the increased life span, the number of patients with oral multiple primary carcinomas will increase. Predicting the second and third carcinoma clinically is difficult, and the presence of second or third carcinomas is a factor that determines the prognosis of oral carcinoma. In this study, we examined the clinical features of oral multiple primary carcinomas treated in our department.

Methods We retrospectively reviewed the medical records of patients with oral squamous cell carcinoma who underwent radical treatment at and were followed by the Department of Oral and Maxillofacial Surgery, Tottori University Hospital from January 2003 to October 2017.

Results This study included 261 patients: 241 patients had oral single primary carcinoma and 20 patients had oral multiple primary carcinomas. Oral multiple primary carcinomas showed female predilection and occurred more frequently in the lower gingiva and significantly less frequently in the tongue ($P < 0.01$). Oral multiple primary carcinomas showed a significantly higher recurrence rate ($P < 0.01$). The 5-year overall survival of oral single primary carcinoma patients was 88.0% compared with 95% for oral multiple primary carcinomas, with no significant difference (log rank test, $P = 0.54$). However, the 15-year survival rate dropped to 28.1% in oral multiple primary carcinomas. The cumulative disease incidence rates of metachronous second primary carcinoma from first carcinoma at 5 years and 10 years were 3.45% and 5.36%, respectively.

Conclusion Oral multiple primary carcinomas rarely occur in the tongue. The 5-year survival rate showed no difference between single and multiple carcinoma patients, but over longer observation, the prognosis of multiple carcinoma was poor owing to a high recurrence rate. Because of the high recurrence rate and risk of further metachronous carcinoma in oral multiple primary carcinomas, longer-term follow-up is required.

Key words carcinoma, squamous cell; mouth neoplasms; neoplasms, multiple primary

Oral carcinoma is a major health problem in certain parts of the world. Globally, there are around 270,000 new cases annually and 145,000 deaths related to oral carcinoma.[1] Squamous cell carcinoma is the most frequent type, accounting for at least 90% of all oral carcinomas.[2, 3] Because of the increase in the older population, the increased lifespan and the improvement of treatment results of oral carcinoma, the number of cases with oral multiple primary carcinomas will also increase. Predicting the second and third carcinoma clinically is difficult and the presence of second or third carcinomas is a factor that determines the prognosis of oral carcinoma.[4–9] Also, there is not much literature in Japan comparing the clinical features of oral multiple primary carcinomas with oral single primary carcinoma. In this study, we compared the clinical features of oral multiple primary carcinomas treated in our department with those of oral single primary carcinoma.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients with oral squamous cell carcinoma who underwent radical treatment (including surgical treatment, radiotherapy, and chemotherapy) at, and were followed up by, the Department of Oral and Maxillofacial Surgery, Tottori University Hospital from January 2003 to October 2017. The observation endpoint was set as October 31, 2018 so that the observation period would be one year or longer for all cases including cases of oral single primary carcinoma. Neck dissection was performed for both single and multiple primary carcinoma when cervical lymph node metastasis was clinically suspected.

Patients treated at other facilities, patients who were difficult to evaluate pathologically, or patients who did not provide consent were excluded. The study protocol was approved by our institution and was in accordance with the Declaration of Helsinki (19A128).

Oral single primary carcinoma was defined as

Corresponding author: Makoto Kawasaki, DDS
m-kawasaki@tottori-u.ac.jp
Received 2020 July 27
Accepted 2020 August 26
Online published 2020 September 14

carcinoma that developed only a single lesion during the follow-up period. Oral multiple primary carcinomas were defined according to criteria modified from those of Warren and Gate in 1932 and based on the 'General Rules for Clinical and Pathological Studies on Oral Cancer' edited by the Japan Society for Oral Tumors.[10, 11] Specifically, multiple oral carcinomas were defined as cases in which two or more primary carcinomas were confirmed in the oral cavity and that satisfied the following conditions: (i) the site by Union for International Cancer Control classification was different, (ii) the lesions were recognized on opposite sides in the same site, (iii) if ipsilateral, there was no continuity between the two lesions and they were clinically more than 2.0 cm apart, and (iv) each lesion was histopathologically confirmed to be carcinoma. Multiple primary carcinomas were categorized as synchronous carcinomas, metachronous carcinomas, or synchrony and metachronous carcinomas. Synchronous carcinoma was a carcinoma diagnosed in less than a year after the initial diagnosis, and metachronous carcinoma was diagnosed after a period 1 year or more. If both synchronous and metachronous were present, the case was considered as synchrony and metachronous carcinoma. In the case of synchronous multiple carcinomas, the stage was determined based on the most advanced carcinoma at the time of initial diagnosis.

Carcinoma that was not more than 2.0 cm from the first carcinoma or carcinoma that occurred on the same side of the same site was defined as local recurrence. In cases in which it was difficult to judge whether the carcinomas were 2.0 cm apart, the lesion was considered as local recurrence. Carcinoma in situ was also treated as carcinoma in the study. In cases of a metachronous second or third carcinoma treated during the target period and that were treated as oral primary carcinoma at our department before the study period, we considered them as eligible cases.

We compared clinical data such as age, sex, and tumor location, smoking history and drinking habits for oral single and multiple primary carcinomas using the Mann–Whitney *U* test, Chi-square test, or Fisher's exact test.

Prognosis was examined using disease specific survival and overall survival using the Kaplan–Meier curve, and the log rank test was used to evaluate the statistically significant differences. Recurrence rate and cervical lymph node late metastases were also counted. In case of metachronous multiple primary carcinomas, recurrence after secondary carcinoma was also counted

Statistical analysis was performed using SPSS ver.25 software (IBM SPSS, Armonk, NY). $P < 0.05$ was considered statistically significant.

RESULTS

This study enrolled 284 patients with oral squamous cell carcinoma who underwent curative treatment. Among these patients, 13 patients were excluded because they could not be monitored during the observation period, and 10 patients had uncontrolled tumors with initial treatment. Thus, we analyzed 261 patients: 241 patients were single primary carcinoma cases and 20 patients were multiple primary carcinomas cases. The median duration of follow-up was 53 (range, 4–342) months.

Of the 20 cases with oral multiple primary carcinomas, 6 (30%) showed synchronous first multiple primary carcinomas, 7 (35%) had metachronous second multiple primary carcinomas, 1 (5%) showed synchronous second multiple carcinomas, 3 (15%) had metachronous third multiple carcinomas, and 3 (15%) had fourth multiple carcinomas (Fig. 1).

Patient characteristics

The mean age at first diagnosis was 69.5 (range, 42–84) years in the oral single primary carcinoma group and 67.9 (range, 30–93) in the oral multiple primary carcinomas group.

There were 4 men and 16 women in the oral multiple primary carcinomas group and 141 men and 100 women in the oral single primary carcinoma group. Oral multiple primary carcinomas occurred more frequently in women than in men, while single primary carcinoma occurred more frequently in men than in women ($P = 0.041$, chi-square test).

As for drinking habit, for oral single primary carcinoma, 101 had a drinking habit and 123 did not (17 were unknown). With oral multiple primary carcinomas, 5 had a drinking habit and 15 had no drinking habits, there was no significant difference between the two groups ($P = 0.041$, chi-square test).

Regarding smoking history, 127 cases of oral single primary carcinoma had a smoking history and 98 cases had no smoking history (16 cases were unknown). In oral multiple primary carcinomas, 4 had a history of smoking and 16 had no history of smoking. The smoking rate was significantly lower in oral multiple carcinomas ($P = 0.0017$, chi-square test).

Tumor location

The tumor locations are shown in Table 1. The tongue was the most common location in oral single primary carcinoma (113/241, 46.9%), followed by lower gingiva (52/241, 21.6%). In oral multiple primary carcinomas, the most common location was lower gingiva (8/20, 40%), followed by buccal mucosa (6/20, 30%). Normal oral mucosa is classified into three types: masticatory

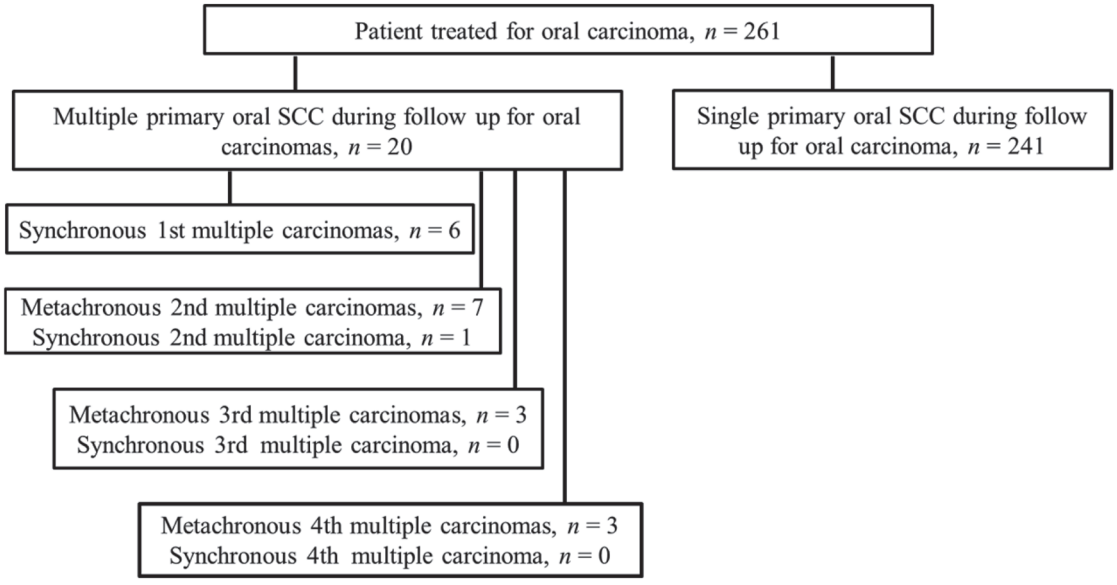

Fig. 1. Flow chart of patients with single or multiple primary oral carcinomas. Multiple primary carcinomas were categorized by the number of carcinomas, and synchronous or metachronous. SCC, squamous cell carcinoma.

Table 1. Primary site of oral single primary carcinoma and oral multiple primary carcinomas at the first occurrence

	Single primary SCC, $n = 241$	Multiple primary SCC at the first occurrence, $n = 20$
Lower gingiva	52	6
Lower gingiva+ Buccal mucosa	0	1
Lower gingiva+ Tongue	0	1
Buccal mucosa	19	3
Buccal mucosa+ Upper gingiva	0	1
Buccal mucosa+ Tongue	0	1
Buccal mucosa+ Hard palate	0	1
Upper gingiva	23	3
Floor of month	28	2
Tongue	113	0
Tongue+ Hard palate	0	1
Hard palate	6	0

SCC, squamous cell carcinoma.

mucosa (lower gingiva, upper gingiva, hard palate), coated mucosa (buccal mucosa, floor of mouth), and special mucosa (tongue),[12] and the sites of occurrence were divided into groups according to their classification. (Table 2). In multiple primary carcinomas, a significant number of cases occurred in the lower gingiva, upper gingiva, and hard palate compared with other groups ($P = 0.041$, chi-square test; in cases of simultaneous multiple cancers, each site was recorded). In addition, when buccal mucosa and floor of the mouth were compared with other groups, buccal mucosa and floor of the mouth had significantly higher incidence of oral multiple primary carcinomas ($P = 0.025$, Fisher's exact test). Furthermore, compared with other parts of the tongue, the tongue had a significantly lower incidence of oral multiple primary carcinomas ($P < 0.01$, chi-square test).

T and N classification

T and N classifications are shown in Table 3. In oral single primary carcinoma, the frequency of Tis and T1–2 cases were 76.3% (184/241) and T3–4 cases were 23.7% (57/241). In oral multiple primary carcinomas, the frequency of Tis and T1–2 cases were 50.0% (10/20) and T3–4 were also 50.0% (10/20). The rate of advanced carcinoma was higher in oral multiple primary carcinomas than oral single primary carcinoma, but the Mann–Whitney *U* test did not show significant differences between oral single primary carcinoma and oral multiple primary carcinomas in T classification ($P =$

Table 2. Comparison of sites in single primary carcinoma and multiple primary carcinomas (synchronous multiple primary carcinomas were included for each site)

	Single primary SCC, $n = 241$	Multiple primary SCC at the first occurrence, $n = 26$	P value
Lower gingiva, Upper gingiva, Hard plate (Masticatory mucosa)	81	14	$P = 0.041$
Buccal mucosa, Floor of mouth, Tongue	160	12	
Buccal mucosa, Floor of mouth (Coated mucosa)	47	9	$P = 0.025$
Lower gingiva, Upper gingiva, Hard plate, Tongue	194	17	
Tongue (Special mucosa)	113	3	$P < 0.001$
Lower gingiva, Buccal mucosa, Upper gingiva, Floor of mouth, Hard palate	228	21	

SCC, squamous cell carcinoma.

Table 3. Tumor staging of oral single primary carcinoma and oral multiple primary carcinomas

	Single primary SCC, $n = 241$	Multiple primary SCC at the first occurrence, $n = 20$
Tis	24	2
T1	57	2
T2	203	6
T3	20	5
T4	37	5
N (–)	198	19
N1	18	0
N2	25	1
N3	0	0

SCC, squamous cell carcinoma.

0.054).

Only 5.0% (1/20) of oral multiple primary carcinomas showed cervical lymph node metastasis compared with 17.9% (43/241) in oral single primary carcinoma. There was no significant difference between the groups ($P = 0.33$, Fisher's exact test).

Local recurrence and postoperative cervical lymph node metastasis

Local recurrence was observed in 80.0% (16/20) of patients with oral multiple primary carcinomas, compared with 17.0% (41/241) of patients with oral single primary carcinoma. The rate of local recurrence was significantly higher in oral multiple primary carcinomas than in oral single primary carcinoma ($p < 0.01$, Fisher's exact test) (Fig. 2). Postoperative cervical lymph node metastasis was observed in 25.0% (5/20) of patients with oral multiple primary carcinomas compared with 18.3% (44/241) of patients with oral single primary carcinoma. There was no significant difference between them ($P = 0.55$, Fisher's exact test) (Fig. 3).

Disease specific survival and Overall survival

The disease specific survival of patients with single primary carcinoma at 5 years and 10 years was 90.2% and 86.3%, respectively, while the overall survival of patients with multiple primary carcinomas at 5 years and 10 years was 95.0% and 74.8%, respectively. There was no significant difference in disease free survival between the two groups (log rank test, $P = 0.103$) (Fig. 4).

The overall survival of patients with single primary carcinoma at 5 years and 10 years was 88.0% and 85.1%, respectively, while the overall survival of patients with multiple primary carcinomas at 5 years and 10 years was 95.0% and 74.8%, respectively. There was no significant difference in overall survival between the two groups (log rank test, $P = 0.54$) (Fig. 5).

However, the 15-year survival rate dropped to 28.1% in patients with oral multiple primary carcinomas in disease specific survival and overall survival.

Cumulative disease incidence rate of metachronous second multiple primary carcinomas

The cumulative disease incidence rates of metachronous second primary carcinoma from first carcinoma at 5 years and 10 years were 3.45% and 5.36% (Fig. 6).

DISCUSSION

The mechanism underlying the onset of oral multiple primary carcinomas is unknown, but some hypotheses have been reported. One of the most common hypotheses is the concept of "field cancerization," introduced by Slaughter et al in 1953.[13] The concept is that carcinoma develops in multiple locations owing to long-term

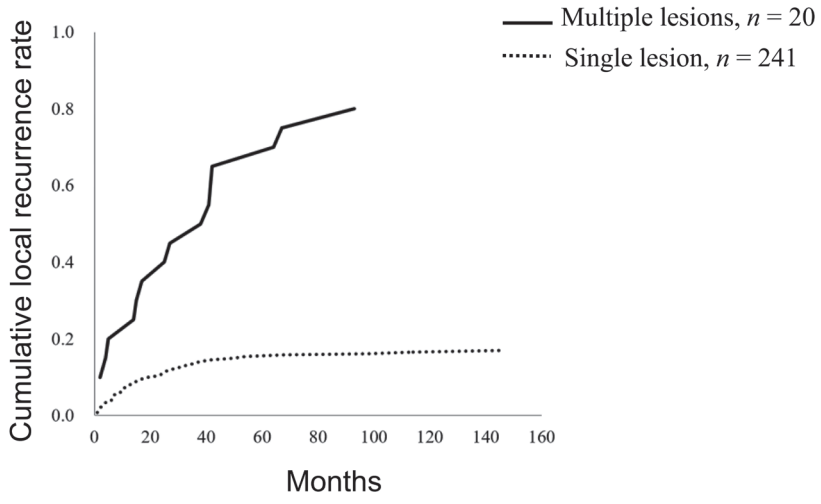

Fig. 2. Cumulative local recurrence rates in patients with oral single primary carcinoma and those with oral multiple primary carcinomas. The rate of local recurrence was significantly higher in oral multiple primary carcinomas than in oral single primary carcinoma ($P < 0.01$, Fisher's exact test).

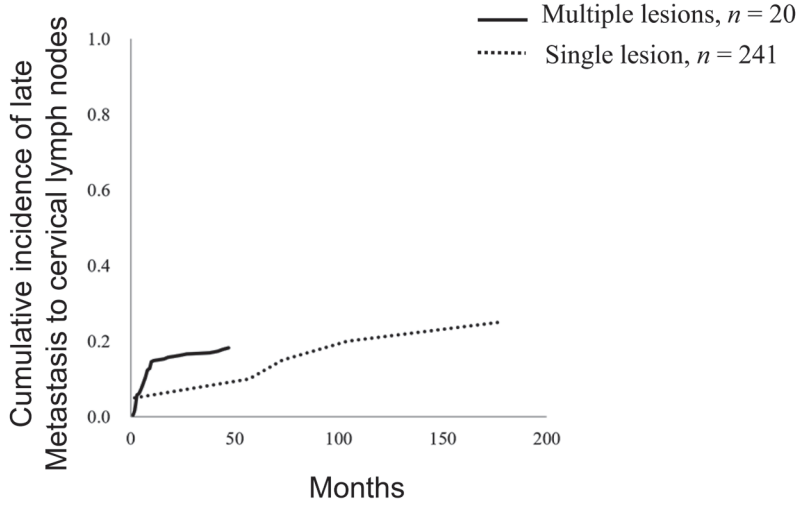

Fig. 3. Cumulative incidence of late metastasis to cervical lymph nodes with oral single primary carcinoma and those with oral multiple primary carcinomas. There was no significant difference between single primary carcinoma and oral multiple primary carcinomas ($P = 0.55$, Fisher's exact test).

exposure to a common cancer-inducing factors. Several researchers have reported the relationship between genes and multiple head and neck carcinomas based on this concept.[14, 15] For example, Tabor et al reported that the first primary tumor and second primary tumor develop from a single contiguous genetically altered field and thus have a common clonal origin.[15] However, oral multiple primary carcinomas are thought to occur due to multiple factors including environmental factors as well as the above-mentioned genetic factors.[3–7] For example, tobacco, which is an important risk factor for oral carcinoma,[16, 17] did not affect the occurrence of oral secondary carcinomas. Tomek et al reported that the frequency of secondary carcinoma in head and neck carcinoma that occurred in patients who continued smoking after the diagnosis of primary carcinoma did not differ from those in the group of patients who quit smoking, indicating no association between the occurrence of secondary carcinoma and tobacco.[18] Because there are many unclear points about oral multiple

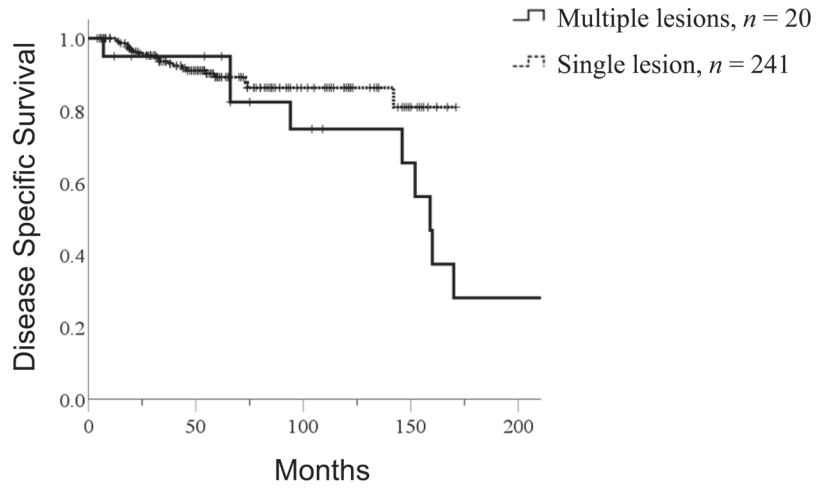

Fig. 4. Disease specific survival of patients with oral single primary carcinoma and those with oral multiple primary carcinomas. There was no significant difference between single primary carcinoma and oral multiple primary carcinomas (P = 0.103, log rank test).

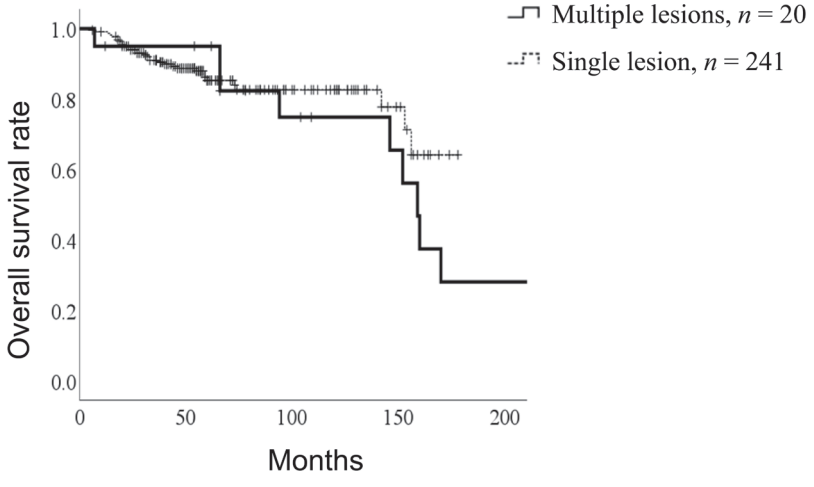

Fig.5. Overall survival rates of patients with oral single primary carcinoma and those with oral multiple primary carcinomas. There was no significant difference between single primary carcinoma and oral multiple primary carcinomas (P = 0.54, log rank test).

primary carcinomas, we performed a comparative study of oral multiple primary carcinomas based on clinical data, and the characteristics were investigated.

In our report, females were significantly more frequently present than males in the oral multiple primary carcinoma group. Some previous studies reported that oral multiple primary carcinomas developed in males only,[4, 5] while others showed they were more common in females.[6–8] Although our data showed a significantly increased frequency among females, it is not possible to conclude that there is a sex difference in oral multiple primary carcinomas because the sex difference varies greatly from report to report.

The mean patient age at first diagnosis was 67.9 (range, 42–84) years for patients with oral multiple primary carcinomas, which is younger than 69.5 (range, 30–93) years for patients with oral single primary carcinoma. Other studies reported the mean age of patients with oral multiple primary carcinomas as 52.2–68.3 years.[4, 6–8] Mochizuki et al reported that the age of patients with oral multiple primary carcinomas was significantly higher than that of patients with oral single

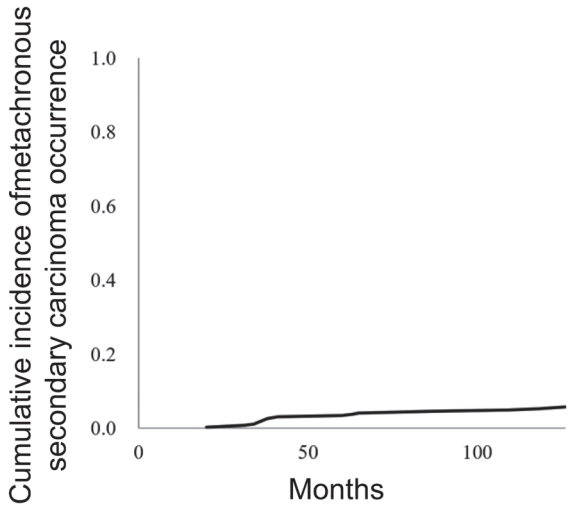

Fig. 6. Cumulative incidence of metachronous secondary carcinoma occurrence. The incidence rates were 3.45% and 5.36% at 5 and 10 years from first carcinoma, respectively.

primary carcinoma (68.3 vs. 61.6 years),[6] which was not consistent with our data. Thus, patient age on diagnosis appears to vary depending on the report. According to our study and other reports, the peak age of onset of oral multiple primary carcinomas was about the same as the peak age of onset of oral single primary carcinoma.

Regarding drinking habits, there was no significant difference between oral single primary carcinoma and oral multiple primary carcinomas, and it seems that there was no correlation between the drinking habits and the appearance of multiple primary carcinomas.

Smoking history was significantly lower in oral multiple primary carcinomas. Although it is unlikely that smoking has a preventive effect on oral multiple primary carcinomas, at least it was not possible to conclude that smoking induces oral multiple primary carcinomas, which was consistent with previous literature.[17]

In our report, the most common site of oral multiple primary carcinomas was lower gingiva, followed by the buccal mucosa. We found significantly fewer cases in the tongue in oral multiple primary carcinomas. In other studies, oral multiple primary carcinomas tended to be less frequent in the tongue compared with oral single primary carcinoma, while oral multiple primary carcinomas were more common in the gingiva and buccal mucosa,[5, 6, 8] which is consistent with our report. The cervical lymph node metastasis rate was lower in oral multiple primary carcinomas than in oral single primary carcinoma. The reason for the location of oral multiple primary carcinomas differing from the location of oral single primary carcinoma is unclear. However, this may explain the low proportion of cervical lymph nodes in oral multiple primary carcinomas. Carcinoma that develops in the special mucosa or coated mucosa tends to metastasize to cervical lymph nodes.[6] In our report, in oral multiple primary carcinomas, the gingiva and hard palate covered by masticatory mucosa were significantly more numerous than other sites. The difference in the incidence of cervical lymph node metastasis between oral multiple primary carcinomas and oral single primary carcinoma may be due to the difference in the site where the primary carcinoma occurs.

Although there was no significant difference in T and N classification between single and multiple carcinomas, patients with oral multiple primary carcinomas had a significantly higher recurrence rate than those with oral single primary carcinoma. Oral multiple primary carcinomas have been reported to be related to leukoplakia, lichen planus, and oral epithelial dysplasia,[8, 19] and it is possible that the dysmorphic cells remained after resection and recurrence occurred. For other reason, by definition, if the distance between the site of the first lesion and the site of the next lesion is not more than 2 cm or if they are on the same side and have the same name, the secondary lesion is considered a recurrence. Carcinoma, that do not originate from atypical cells or cancer cells that remain after surgery, and that are formed after surgery based on "field cancerization" are also considered to be recurrent if it is close to the first carcinoma or in the same name and site on the same side as the first carcinoma.

Kao et al. reported that there are no special treatments for oral multiple primary carcinomas.[4] Surgery is the standard treatment for single primary oral carcinoma in resectable cases,[20] and the same is true for oral multiple primary carcinomas. Although a large margin of resection increases the severity of dysfunction, it is very important to have a sufficient margin because local recurrence in oral squamous cell carcinomas is related poor prognosis.[4] To avoid secondary or tertiary primary carcinoma, secure resection is desirable.

Radiation therapy is not recommended for resectable oral carcinoma. Hashibe et al. reported that radiation therapy for a first oral carcinoma was a risk factor of second primary carcinoma.[21] The reason for this is that although the carcinoma of patients who underwent radiation treatment was at an advanced stage, the recurrence rate of these patients was high. In addition, no report has examined the effect of radiation therapy on preventing the appearance of secondary and tertiary carcinomas. Therapeutic radiotherapy of resectable oral carcinoma or prophylactic radiotherapy of secondary carcinoma is not recommended and may cause carcinoma in other sites. Radiation therapy should

be done when the tumor is unresectable or at high risk of recurrence, such as when the margin is positive and upon multiple lymph node metastases after surgery, and should be carefully considered when the recurrence risk is not high.

Previous studies reported no significant difference in overall survival between patients with oral multiple primary carcinomas and oral single primary carcinoma.[21] Similar to other reports,[4, 6] the 5-year survival rate for patients with oral multiple primary carcinomas in this study was not low, but the 15-year survival rate of patients with multiple primary carcinomas dropped to 28.1%. Although there is a limitation that there were few long-term observation cases in oral single primary carcinoma compared with oral multiple primary carcinomas, we consider that the long-term prognosis of oral multiple primary carcinomas was poor for the following reasons. As described above, the recurrence rate is high in oral multiple primary carcinomas. Local recurrence of oral carcinoma is often not fatal if it is resectable, but dysphagia due to additional resection for local recurrence may lead to pneumonia, and a long-term cancer-bearing state at the primary site due to recurrence makes metastasis to cervical lymph nodes and distant organs more likely, leading to poor prognosis. Other reasons for the low 15-year survival rate may be that these patients do not receive treatment at confirmation of recurrence or appearance of multiple carcinomas due to the older age of patients or the onset of dementia.

The cumulative disease incidence of metachronous secondary carcinomas at 5 years and 10 years after the initial cancer was 3.45% and 5.36%, respectively, and a proportion of metachronous carcinomas was observed. Even if the progress of the primary site is good, oral carcinoma is at risk for developing multiple primary carcinomas, and long-term follow-up is considered useful for early detection of oral multiple primary carcinomas.

In conclusion, oral multiple primary carcinomas frequently occur in the lower gingiva and buccal mucosa and occur less frequently in the tongue. Although the 5-year survival rate of oral multiple primary carcinomas was not lower than that of single carcinoma, over longer periods of time, the recurrence rate was significantly higher in oral multiple primary carcinomas and the prognosis was worse over the longer term. Oral multiple primary carcinomas have a high recurrence rate, and there is a risk of further metachronous carcinomas occurring with oral multiple primary carcinomas. Oral metachronous multiple primary carcinomas can occur 5 or 10 years after the initial treatment of oral carcinoma treatment, so long-term follow-up of oral carcinoma helps early detection of oral multiple primary carcinomas.

Acknowledgments: We thank Gabrielle White Wolf, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

The authors declare no conflict of interest.

REFERENCES

1 Masamatti SS, Gosavi AV. Histopathological Study of Malignant Oral tumors: A Five-Year Study. Int J Sci Stud. 2016;4:30-4. DOI: 10.17354/ijss/2016/312
2 Beenken SW, Urist MM. Head and neck tumors. In: Way LW, Doherty GM, editors. Current surgical diagnosis and treatment. 11th ed. New York: Lange Medical Books/McGraw-Hill; 2003. p. 282-97.
3 Coleman JJ, Sultan MR. Tumors of the head and neck. In: Schwartz SI, editor. Principles of surgery. 7th ed. New York: McGraw-Hill; 1999. p. 601-65.
4 Kao HK, Abdelrahman M, Huang Y, Tsai CH, Barrera MJ, Tsang NM, et al. Multiple concomitant oral cavity cancers: Incidence, management, and outcomes. J Surg Oncol. 2017;115:835-41. DOI: 10.1002/jso.24600, PMID: 28320044
5 Liao CT, Kang CJ, Chang JTC, Wang HM, Ng SH, Hsueh C, et al. Survival of second and multiple primary tumors in patients with oral cavity squamous cell carcinoma in the betel quid chewing area. Oral Oncol. 2007;43:811-9. DOI: 10.1016/j.oraloncology.2006.10.003, PMID: 17174143
6 Mochizuki Y, Harada H, Ikuta M, Shimamoto H, Tomioka H, Tanaka K, et al. Clinical characteristics of multiple primary carcinomas of the oral cavity. Oral Oncol. 2015;51:182-9. DOI: 10.1016/j.oraloncology.2014.11.013, PMID: 25498922
7 Ashikaga Y, Kuribayashi K, Ohiro Y, Ono M, Tei K. Clinical study of multiple primary oral cancer. Hokkaido J Dent Sci. 2016;37:20-4.
8 Qaisi M, Vorrasi J, Lubek J, Ord R. Multiple primary squamous cell carcinomas of the oral cavity. J Oral Maxillofac Surg. 2014;72:1511-6. DOI: 10.1016/j.joms.2014.03.012, PMID: 24813779
9 González-García R, Naval-Gías L, Román-Romero L, Sastre-Pérez J, Rodríguez-Campo FJ. Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: A retrospective analytic study of 500 patients. Head Neck. 2009;31:1168-80. DOI: 10.1002/hed.21088, PMID: 19408289
10 Warren S, Gate O. Multiple primary malignant tumors: a survey of the literature and a statistical study. Am J Cancer. 1932;16:1358-414.
11 Ota K, Noguchi T, Nagatsuka H, Ariji E, Ueda M, Uzawa N, et al., eds. General rules for clinical and pathological studies on oral cancer. 2nd ed. Japan: Japanese Society of Oral Oncology; 2019.
12 Gartner LP. Oral anatomy and tissue types. Semin Dermatol. 1994;13:68-73. PMID: 8060828
13 Slaughter DP, Southwick HW, Smejkal W. "Field cancerization" in oral stratified squamous epithelium. Clinical implications of multicentric origin. Cancer. 1953;6:963-8. DOI: 10.1002/1097-0142(195309)6:5<963::AID-CNCR2820060515>3.0.CO;2-Q, PMID: 13094644
14 Bedi GC, Westra WH, Gabrielson E, Koch W, Sidransky D. Multiple head and neck tumors: evidence for a common clonal origin. Cancer Res. 1996;56:2484-7. PMID: 8653681

15 Tabor MP, Brakenhoff RH, Ruijter-Schippers HJ, van der Wal JE, Snow GB, Leemans CR, et al. Multiple head and neck tumors frequently originate from a single preneoplastic lesion. Am J Pathol. 2002;161:1051-60. DOI: 10.1016/S0002-9440(10)64266-6, PMID: 12213734
16 Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chronic Dis. 1972;25:711-6. DOI: 10.1016/0021-9681(72)90006-9, PMID: 4648515
17 More Y, D'Cruz AK. Oral cancer: review of current management strategies. Natl Med J India. 2013;26:152-8. PMID: 24476162
18 Tomek MS, McGuirt WF. Second head and neck cancers and tobacco usage. Am J Otolaryngol. 2003;24:24-7. DOI: 10.1053/ajot.2003.12, PMID: 12579479
19 Wright A, Shear M. Epithelial dysplasia immediately adjacent to oral squamous cell carcinomas. J Oral Pathol Med. 1985;14:559-64. DOI: 10.1111/j.1600-0714.1985.tb00529.x, PMID: 3928850
20 Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 2.2017. J Natl Compr Canc Netw. 2017;15:761-70. DOI: 10.6004/jnccn.2017.0101, PMID: 28596256
21 Hashibe M, Ritz B, Le AD, Li G, Sankaranarayanan R, Zhang ZF. Radiotherapy for oral cancer as a risk factor for second primary cancers. Cancer Lett. 2005;220:185-95. DOI: 10.1016/j.canlet.2004.10.023, PMID: 15766594