Prognostic factors in mucoepidermoid carcinoma of the minor salivary glands: A single-center retrospective study

Masahiko Terauchi, DDS, PhD,[a] Yasuyuki Michi, DDS, PhD,[b] Hideaki Hirai, DDS, PhD,[c] Kentaro Sugiyama, DDS,[d] Akane Wada, DDS, PhD,[e] Hiroyuki Harada, DDS, PhD,[f] and Tetsuya Yoda, DDS, PhD[g]

Objective. The objective of this study was to investigate the prognostic effects of clinical and histologic findings in patients with mucoepidermoid carcinoma (MEC) of minor salivary glands.

Study Design. This retrospective clinical review included 63 patients (30 males, mean age 52.8 years) with minor salivary gland MEC treated at our hospital from 1994 to 2019. Overall survival (OS) or disease-free survival was determined using the Kaplan-Meier limit method. Correlations between different factors and survival rates were assessed using chi-square tests.

Results. The 10-year OS rate was 91.2%. Low- or intermediate-grade MEC had a good prognosis regardless of the surgical margin, whereas high-grade MEC had a poor 10-year OS rate (64.2%). Ten patients developed recurrence or metastasis after primary surgical resection, of whom 6 were diagnosed with a high-grade tumor. The most frequently affected site was the palate, whereas the mandibular gingiva was the most commonly affected site during recurrence. Of 4 patients who received chemotherapy and/or radiotherapy postsurgery, 2 had local recurrence and/or neck lymph node metastasis and 1 died from MEC.

Conclusion. Patients with low- or intermediate-grade MEC exhibited satisfactory survival after surgery. In patients with high-grade tumors, it has been suggested that survival rates are poor and do not improve following adjuvant therapy. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:209−216)

Salivary gland malignancies are rare in the general population and comprise only 0.5% of all malignancies and <5% of all head and neck malignancies.[1,2] Li et al.[3] investigated 3461 patients with salivary gland tumors and found that the benign-malignant ratio was 1.49:1. Further, authors found that the parotid gland was the most common location with a frequency of 61%, followed by the minor glands in the palate (21%), the submandibular gland (11%), the sublingual gland (1%), and other minor salivary glands. From these results, it appears that the minor salivary glands may be less susceptible to malignant salivary gland tumors compared with major salivary glands.[3]

Mucoepidermoid carcinoma (MEC) comprises approximately 30% of all salivary carcinomas and is the most common malignant salivary gland neoplasm, on par with adenoid cystic carcinoma.[4,5] MEC was first reported in 1945 by Stewart et al.[6] as a mucoepidermoid tumor derived from the salivary gland epithelium, and in 1992 it was classified as carcinoma by the World Health Organization owing to local recurrence and distant metastasis in some cases.[7] MEC is believed to arise from the reserve cells of excretory ducts and can comprise 3 cell types, namely, epidermoid cells, mucous cells, and poorly differentiated intermediate cells.[8] Compared to other salivary gland carcinomas, including adenoid cystic carcinoma, MEC has a favorable prognosis.[9] Therefore, it is often diagnosed clinically as a benign tumor. However, a study reported that MECs have a poor prognosis owing to metastasis or recurrence.[10] For example, Granic et al.[11] reported that 17.2% of patients with MEC developed a recurrence over a 5-year period regardless of whether major or minor salivary glands were affected. It should be noted that approximately 70% of MEC cases occur in a major

Statement of Clinical Relevance

Histologic grade, tumor location, patient age, surgical margin, and lymph node involvement can act as prognostic factors in patients with mucoepidermoid carcinoma of minor salivary glands. Our findings will assist clinicians in planning therapeutic approaches for such patients.

[a]Project Assistant Professor, Department of Maxillofacial Surgery, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University, Tokyo, Japan.
[b]Junior Associate Professor, Department of Oral and Maxillofacial Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.
[c]Assistant Professor, Department of Oral and Maxillofacial Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.
[d]Clinical Fellow, Department of Maxillofacial Surgery, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University, Tokyo, Japan.
[e]Clinical Fellow, Department of Oral Pathology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.
[f]Professor, Department of Oral and Maxillofacial Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.
[g]Professor, Department of Maxillofacial Surgery, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University, Tokyo, Japan.

Received for publication Jun 13, 2020; returned for revision Sep 20, 2020; accepted for publication Oct 11, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.10.012

gland and, thus, its occurrence in minor salivary glands is comparatively rare.[11] Hence, not many studies have reported the clinical statistics of MEC in minor salivary glands, especially in cohorts from single institutions. Indeed, although a statistical survey of a combination of patients with major and minor salivary gland MEC at a single center exists,[11,12] one that is focused only on patients with minor salivary gland MEC does not. As such, we considered that the statistical details of the prognosis of patients with minor salivary gland MEC are required. The aim of this retrospective single-institute study was to investigate the clinical and histopathologic features of minor salivary gland MEC to determine the recurrence and prognosis of these tumors. Because surgical resection is the primary therapeutic modality for the treatment of carcinoma,[13] this study also investigated prognosis among those who received adjuvant chemotherapy and radiotherapy after surgical resection of MEC in minor salivary glands in a single-center cohort.

MATERIALS AND METHODS

The present study was approved by the institutional review board of the Faculty of Dentistry at Tokyo Medical and Dental University (approval numbers D2016-003 and D2015-600). All procedures involving the collection of data from human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. The requirement for informed consent was waived owing to the retrospective nature of the study.

This retrospective study included data from patients diagnosed with primary MEC of the minor salivary glands who were treated at our center (Dental Hospital of Tokyo Medical and Dental University) between January 1994 and December 2019. Patients with secondary MEC or those who had not undergone surgical treatment were excluded from this study. The following data were collected: age, sex, anatomic location, histologic grade, tumor stage, nodal status, the histologic status of surgical margins, and follow-up after surgery. MEC was staged according to the seventh edition of the *TNM Classification of Malignant Tumors*, published in affiliation with the International Union Against Cancer (UICC).[14] For histologic analysis, after staining specimens with hematoxylin and eosin, MECs were classified as low-, intermediate-, or high-grade carcinomas according to Goode's classification on the basis of the following data: (1) amount of cystic component, (2) presence of neural invasion, (3) presence of necrosis, (4) number of mitoses per 10 high-power fields, and (5) presence or absence of anaplasia (Figure 1).[14,15] Surgical margins were considered close when the tumor was within 3 mm of the margin of the resected specimen, and these were evaluated as a positive margin.

Statistical analysis

One-way analysis of variance or χ^2 test was used for statistical analysis. The values are expressed as mean ± standard deviation. The Kaplan-Meier limit method was employed to determine overall survival (OS) or disease-free survival (DFS). Follow-up intervals were calculated in months from the date of the first visit to our hospital to the date of the last follow-up or death. Statistical significance was determined using log-rank (Mantel-Cox) tests for the univariate analysis. *P* values <.05 were considered statistically significant. GraphPad Prism 8.02 software (GraphPad Software, San Diego, CA) was used to create survival curves.

RESULTS

Of the 63 patients included in the study, 30 were male (47.6%) and 33 were female (52.4%). Patients' mean age at the first hospital visit was 52.8 (range = 11-84) years. MEC most frequently appeared in the palate (41.3%) and was mostly low grade (60.3%), as determined by the World Health Organization classification of histologic grade, followed by intermediate (19.0%) and high grade (20.6%). The disease stage was I, II, III, and IV in 37, 14, 1, and 11 patients, respectively. Clinicopathologic characteristics of the patients in this cohort are summarized in Table I.

The total 10-year OS and DFS rates for the entire cohort were 91.2% and 94.6%, respectively (Figure 1A). Sex (male, 88.6%; female, 93.3%) was not a statistically significant predictor of OS according to our univariate analysis (Figure 1B). The 10-year survival rate showed that patients with a positive or close margin had an OS rate of 88.9%, whereas those with a negative margin had an OS rate of 91.6%, and the difference was not significant ($P = .325$; Figure 1C). Ten patients developed recurrence and/or metastasis after surgical resection (18.9%; Table II). Regarding histologic grade, the patients had low-, intermediate-, or high-grade MEC (Table III), with 10-year OS rates of 100%, 91.7%, and 64.6%, respectively ($P < .005$; Figure 1D). Regarding the site of MEC, the oral palate, maxillary gingiva, mandibular gingiva, and buccal mucosa were involved in 26, 6, 17, and 11 patients, respectively. The tongue and floor of the mouth were also involved in some patients (Tables I, IV). The 10-year survival rates based on the site of occurrence were 100%, 75%, 80.1%, and 100% for the palate, maxillary gingiva, mandibular gingiva, and buccal mucosa, respectively ($P = .1949$; Figure 1E).

Lymph node status was significantly associated with OS ($P < .0001$). Patients with a negative lymph node status had a survival rate of 95.7%, whereas the 10-year OS

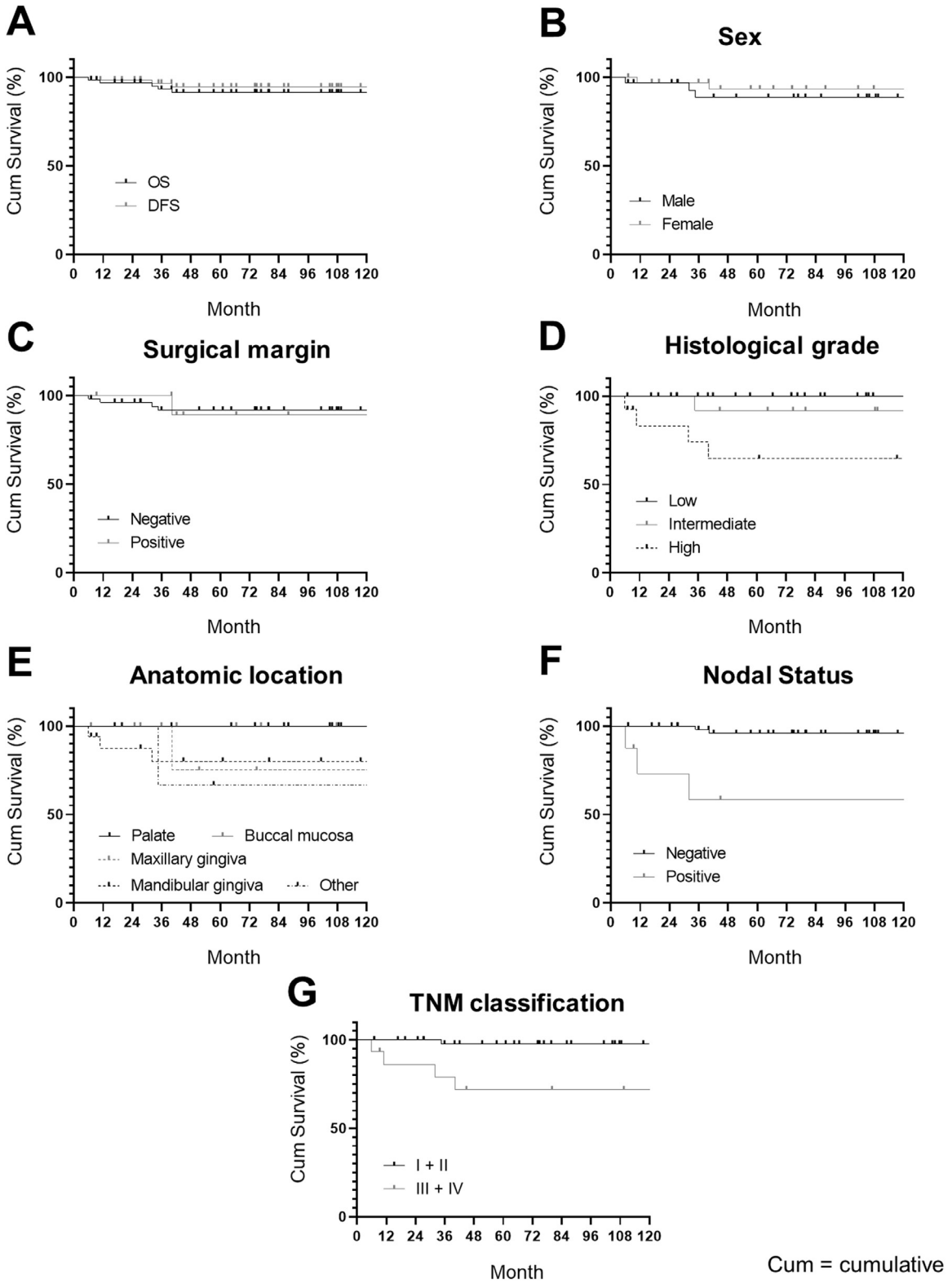

Fig. 1. Kaplan-Meier survival analysis in patients with mucoepidermoid carcinoma. **(A)** The total 10-year overall survival and disease-free survival of patients with mucoepidermoid carcinoma. Overall survival in patients with mucoepidermoid carcinoma according to **(B)** sex, **(C)** surgical margin, **(D)** histologic grade, **(E)** anatomic location, **(F)** lymph node status, and **(G)** TNM classification.

Table I. Clinicopathologic characteristics of patients with minor salivary gland mucoepidermoid carcinoma

Baseline characteristic	*No. of patients (%)*
Mean age (years)	52.8
Sex	
Male	30 (47.6)
Female	33 (52.4)
Tumor subsite	
Palate	26 (41.3)
Maxillary gingiva	6 (9.5)
Mandibular gingiva	17 (27.0)
Buccal mucosa	11 (17.5)
Tongue site	2 (3.2)
Oral floor	1 (1.59)
Histologic grade	
Low	38 (60.3)
Intermediate	12 (19.0)
High	13 (20.6)
Tumor size of TNM	
T1 + 2	51 (81.0)
T3 + 4	12 (19.0)
Lymph Node status	
Negative	55 (87.3)
Positive	8 (12.7)
TNM classification	
I + II	48 (76.2)
III + IV	15 (23.8)
Surgical margin	
Negative	52 (82.5)
Positive	11 (17.5)

decreased to 58.3% when the lymph node status was positive (Figure 1F). Patients with stages I and II MEC according to the TNM classification recovered satisfactorily (97.6%), whereas those with stages III and IV MEC had a decreased OS rate (71.8%; $P < .001$; Figure 1G).

Table IV summarizes the correlation of histologic grade with other clinicopathologic factors. The age of patients with low- or intermediate-grade MEC was 50.3 and 47.8 years, respectively, whereas that of patients with high-grade MEC was 64.8 years. Therefore, high-grade MEC was significantly correlated with age ($P = .0178$). There was no statistical difference between low- and intermediate-grade MEC ($P = .8610$). Similarly, the tumor stage ($P < .0001$), lymph node status ($P < .0001$), and TNM classification ($P < .001$) were significantly worse for high-grade tumors than for low- and intermediate-grade tumors.

Of the 63 patients, 5 underwent neoadjuvant chemotherapy and 58 only underwent surgical treatment. Among them, 1 patient was scheduled to undergo adjuvant radiotherapy; however, it was cancelled because esophageal cancer was found. Four patients underwent reoperation because the margin of the first surgical specimen was positive. Fifty patients survived after receiving only primary surgical treatment (including additional resection because the margin was positive; 79.4%). According to Goode's classification, our cohort presented with high-, intermediate-, and low-

Table II. Demographic and clinicopathologic features of 10 patients with recurrence of mucoepidermoid carcinoma

No	*Age*	*Sex*	*Anatomic location*	*T*	*N*	*Stage*	*Histologic grade*	*Treatment*	*Surgery*	*Margin*	*Recurrence and metastasis*	*Status*	*OS (month)*
1	47	M	Tongue	1	0	I	Intermediate	S	Local excision	–	Neck, Double cancer (stomach)	DOC	35
2	61	M	Maxillary gingiva	2	0	II	High	S	Local excision	+	Neck	AND	142
3	60	F	Mandibular gingiva	4	2b	IV	High	S+C	Hemimandibulectomy + RND	–	Double cancer (esophagus)	DOC	10
4	60	M	Palate	2	2b	IVa	Intermediate	S	Local excision + RND	–	Local	DOC	176
5	81	F	Maxillary gingiva	4a	0	IVa	High	S+R	Total maxillectomy	+	Local	DOD	40
6	39	F	Buccal mucosa	1	0	I	Low	S	Local excision	–	Local	AWD	200
7	63	M	Mandibular gingiva	4a	2b	IVa	High	S	Hemimandibulectomy + RND	–	Local	DOD	32
8	68	F	Mandibular gingiva	4a	0	IVa	High	S+R	Hemimandibulectomy + SOHND	+	Local	AWD	180
9	43	M	Mandibular gingiva	4b	2b	Ivb	High	S+R+C	Hemimandibulectomy + RND	–	Local, Neck	DOD	6
10	35	F	Mandibular gingiva	4a	0	IVa	Intermediate	S	Hemimandibulectomy + SOHND	–	Neck, Lung	AWD	80

T, tumor size according to TNM; *N*, lymph node status; *OS*, overall survival; *M*, male; *DOC*, dead from other causes; *AND*, alive no disease; *F*, female; *S*, surgery; *C*, chemotherapy; *RND*, radical neck dissection; *R*, radiotherapy; *DOD*, dead of disease; *AWD*, alive with disease; *SOHND*, supraomohyoid neck dissection.

Table III. Distribution of histologic grade and point values according to Goode's classification[13,14]

Parameter	*Point value*	*Grade**		
		Low	*Intermediate*	*High*
Intracystic component <20%	+2	10/38 (26.3%)	12/12 (100%)	11/13 (84.6%)
Neural invasion present	+2	3/38 (7.9%)	0/12 (0%)	5/13 (38.5%)
Necrosis present	+3	0/38 (0%)	3/12 (25%)	12/13 (92.3%)
Mitosis (4 or more per 10 HPFs)	+3	1/38 (2.6%)	6/12 (50%)	12/13 (92.3%)
Anaplasia present	+4	0/38 (0%)	3/12 (25%)	2/13 (15.4%)
Total points (average)		0.8	5.3	8.6

HPF, high-power fields.
*Grading criteria based on total points. Low: 0-4, intermediate: 5-6, high: 7-12.

Table IV. Histopathologic grade and its correlation with other clinicopathologic parameters

Clinical features	*Histologic grade*			*P value*
	Low	*Intermediate*	*High*	
No. of patients	38	12	13	
Mean age (years)	50.3	47.8*	64.2	.0178*
Sex				
Male	15	8	7	.2278†
Female	23	4	6	
Anatomic location				
Palate	17	8	1	
Maxillary gingiva	3	1	2	
Mandibular gingiva	7	2	8	
Buccal mucosa	10	0	1	.00172†
Tongue site	0	1	1	
Oral floor	1	0	0	
Tumor size of TNM				
T1 + 2	35	10	6	
T3 + 4	3	2	7	.0013†
Lymph node status				
Negative	37	10	8	
Positive	1	2	5	.0033†
TNM stage				
I + II	35	8	5	
III + IV	3	4	8	.0003†
Surgical margin				
Negative	33	10	9	
Positive	5	2	4	.3515†

*One-way analysis of variance.
†χ^2 test.

grade tumors in 4/13 (30.8%), 9/12 (75.0%), and 37/38 (97.4%) patients, respectively. Ten patients had MEC recurrence (Table II), most commonly in the mandibular area (5/10 patients). Primary T4 MEC had the highest recurrence (6/10 patients) among the grades. Seven of the 10 patients with stage IV primary MEC had recurrence at the local site, neck, or distant site. Local relapse occurred in 6 patients, neck lymph node metastasis in 4, and distant metastasis to the lung in 1. Two patients diagnosed with esophageal or stomach cancer had double primary cancer. Of the 6 patients who died, MEC was the cause of death in 3 patients (Table II). The average OS after primary surgery was 90.1 months (range = 6-200). Among patients with low-grade MEC, 1 patient had recurrence after the primary excision, which occurred twice; the tumor was resected each time, and the patient survived. Three patients with intermediate-grade MEC had recurrence or neck lymph node metastasis. One of the patients with recurrence at the primary site died. Another patient who had bilateral neck lymph node metastasis underwent bilateral supraomohyoid neck dissection and chemoradiation, after which he died due to stomach cancer. Another patient who had neck lymph node metastasis underwent lymph node dissection and chemotherapy; the patient was later found to have lung cancer and underwent pneumectomy and chemotherapy, which she survived. Of the 13 patients with high-grade MEC, 6 underwent surgical treatment and adjuvant therapy (i.e., chemotherapy, radiotherapy, or chemoradiotherapy). In 4 of these patients, the tumor recurred at the primary site or spread to the lymph nodes, and 1 patient had esophageal cancer. Among them, 3 patients died because of recurrence at the primary site or metastasis in the neck lymph nodes or/and the lung. The other patient died from esophageal cancer.

DISCUSSION

According to the International Union Against Cancer's *TNM Classification of Malignant Tumors* (eighth edition), the treatment of minor salivary gland tumors is equivalent to oral cavity resection, which differs from that of major salivary glands.[16] Hence, in this study, we focused on the data from patients with MEC in the minor salivary glands who underwent surgical treatment. We found that, similar to previous studies,[2,10,12] the most frequent site of primary MEC was the palate (41.3%), followed by the mandibular gingiva (27.0%).

The slight female predominance of minor salivary gland MEC that we observed has been previously reported for both minor and major salivary gland MEC, although the difference was not statistically significant between sexes.[12,17] Granic et al.[11] reported results similar to ours, stating that the difference was not statistically significant. Collectively, such findings suggest that minor salivary gland MEC develops irrespective of sex.

In patients with MEC, Guzzo et al.[10] reported a 10-year OS rate of 51.2% for all salivary glands. The 10-year DFS rates for MEC of the major and minor salivary glands were 72.9% and 66.8%, respectively.[10] In contrast, Granic et al.[11] reported that the 5-year DFS rates for MEC of the parotid gland, submandibular/sublingual gland, and minor salivary gland were 69.7%, 80%, and 95.2%, respectively.[11] The 5-year OS rates of patients with MEC of the parotid, submandibular/sublingual, and minor salivary glands were 63.6%, 30%, and 90.5%, respectively, suggesting that minor salivary gland MECs have a better prognosis than major salivary gland MECs.[11] In our cohort, the 10-year DFS and OS rates after surgical treatment were 94.6% and 91.2%, respectively, which were similar to those reported in the study by Granic et al.[11]

Interestingly, our MEC evaluation based on Goode's classification showed that >80% of high-grade MECs commonly exhibited an intracystic component of <20%, necrosis, and mitosis of ≥4/10 high-power fields. All intermediate-grade MECs also had an intracystic component of <20%. High-grade MEC was strongly associated with the presence of an intracystic tumor component, necrosis, and mitosis based on Goode's classification, whereas both neural invasion and anaplasia hardly influenced the study results. When neural invasion was excluded, the grades changed in 3 of the 8 patients with an MEC grade change from high to intermediate. However, these 8 patients survived. Therefore, Goode's classification was used to predict the prognosis of MEC; the inclusion of neural invasion in the evaluation of histologic grade was not important.

In patients with parotid gland MEC, Zenga et al.[18] reported that those with negative or close surgical margins had satisfactory long-term locoregional control with surgical treatment only, provided that no other high-risk histopathologic factors were present. Caccamese and Ord[19] reported that their patients had no local recurrence of minor salivary MEC, despite the 1- to 2-mm-deep margin (i.e., closed margin). The above findings imply that low- and intermediate-grade MECs can be controlled without adjuvant therapy, as has been observed for MECs of the parotid gland, even if the surgical margin is closed. Conversely, relative to patients with low-grade MEC, those with high-grade MEC tended to have poorer survival rates,[2,13] with higher rates of local recurrence and metastasis.[18] We also observed a similar pattern in patients with high-grade minor salivary gland MEC, where the 10-year OS rate was 60%, which, despite being a higher survival rate than that reported previously, was lower than the survival rates in patients with low- and intermediate-grade minor salivary gland MEC.

Herein, the patients' mean ages were significantly related to the minor salivary gland MEC grade. Indeed, older patients were more likely to be diagnosed with high-grade MEC and worse tumor and disease stages. Therefore, age may predict histologic grade. Furthermore, surgical resection of high-grade minor salivary gland MECs was difficult, resulting in a high rate of positive margins. Thus, histologic diagnosis of salivary gland malignant tumors, status of lymph node metastasis, and distal recurrence may affect patients' prognosis.[20-23] Of the 10 patients with local recurrence or lymph node metastasis in the present study, the most common anatomic site for recurrence was the palate, and patients with mandibular gingiva recurrence had the worst prognosis. Hence, the site of recurrence was a definite prognostic factor. The first-line treatment for MEC is surgery. Although surgical resection is the primary treatment modality for MEC, no correlation between the surgical margin status and OS was observed in this study.

We performed additional resection in 3 patients with positive margins, one of whom also underwent 50-Gy radiotherapy. In 1 patient who did not undergo additional resection for positive margins, cervical lymph node metastasis developed subsequently, which was removed with radical neck dissection. The tumor recurred in the neck and lung, leading to death. None of the 7 patients with closed (negative) margins received any particular postoperative treatment; 1 of these patients developed cervical lymph node metastasis. Thus, we suggest that additional resection should be performed for patients with positive surgical margins, and sufficient follow-up should be planned for patients with negative margins, although additional treatments might not be necessary. Healey et al.[24] recommended aggressive chemoradiotherapy after the surgical resection of MEC with a high histologic grade, strong invasion, and incomplete resection of surgical margins. Sakamoto et al.[25] recommended radiotherapy to control the primary tumor and neck lymph node metastasis and chemotherapy to prevent distant metastasis. Kohno et al.[26] and Eisenberger[27] reported the effectiveness of the cisplatin, adriamycin, and cyclophosphamide chemotherapeutic regimen for treating MECs. However, the effectiveness of chemoradiation as an MEC treatment remains unknown. In this study, 4 patients underwent chemotherapy and/or radiotherapy after surgical resection, of whom 2 had local recurrence and/or neck lymph node metastasis (50%), resulting in death owing to MEC in 1 patient. Nevertheless, surgical treatment is the treatment of choice for MEC, and adjuvant therapy should be considered when the surgical margin is positive, histologic pathology indicates a high-grade tumor, and metastasis or recurrence has occurred. Caccamese et al.[19] and Conley and Tinsley[28] reported that treating MECs solely with radiation was unsuccessful and noted that if

residual disease is present at the surgical margins and reoperation is not possible, radiotherapy is beneficial as adjuvant therapy. On the other hand, Guzzo et al.[10] reported that patients who were considered unsuitable for surgery despite recurrence received only radiation as symptomatic treatment; however, none of the patients were ever rendered free of the disease.[10] In our study, only 1 of the patients with high-grade minor salivary gland MEC underwent radiotherapy before surgical treatment; nevertheless, she died because of this disease. Four patients underwent adjuvant radiotherapy postoperatively, of whom 2 (1 low-grade and 1 high-grade) had DFS without recurrence. In contrast, 2 patients with high-grade minor salivary gland MEC had recurrence at the primary site despite undergoing adjuvant radiotherapy. Such findings suggest that the addition of adjuvant therapy to surgical treatment is minimally effective in the treatment of patients with high-grade MEC. Therefore, the effects of radiotherapy for MEC remain unknown.

Shinohara et al. suggested that organ metastasis was confirmed in the lungs, brain, and lumbar spine.[9] Metastatic lesions were also found in the liver and skin according to other previous reports.[15,20,21,29,30] These reports suggest that MECs are different from the adenoid cystic carcinoma that often occurs in the lung, and it tends to metastasize to various organs in the body. Therefore, it should be noted in the postoperative examination. Evans[12] reported that distant metastases occurred only in patients with high-grade MECs, with the most common site of distant metastasis being the soft tissue and skin and the second most common site being the lungs. In this study, 6 patients experienced metastasis and 4 had recurrence after surgery. Confirmed cases of metastasis involved the lung in 1 patient and both the esophagus and stomach in another patient. Therefore, screening of the entire upper gastrointestinal tract, not only the primary site and neck, is important during follow-up.

In conclusion, we retrospectively analyzed the data from 63 patients diagnosed with MEC of the minor salivary glands in our department during a 25-year period. The 10-year OS rate was 91.2%, which was better than that reported previously.[10] Low- or intermediate-grade MEC had a good prognosis irrespective of other factors. Patients with high-grade MECs presented with high local recurrence and/or neck lymph node metastasis and had a poor prognosis. The effects of postoperative chemoradiotherapy remain inconclusive. Except for patients with high-grade tumors, the OS of patients with minor salivary gland MEC is generally satisfactory. However, further studies are needed to delineate the influence of treatment factors on the survival of patients with high-grade MEC.

ACKNOWLEDGMENTS

We are grateful to Satoshi Yamaguchi, Misaki Yokokawa, Yu Oikawa, Toshimitsu Ohsako, Yumi Mochizuki, Kae Tanaka, Hirofumi Tomioka, Hiroaki Shimamoto, and Kou Kayamori from Tokyo Medical and Dental University for research assistance.

FUNDING

This work was supported by a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science (JSPS KAKENHI Grant Number JP17 K11827 to YM).

REFERENCES

1. Kokemueller H, Brueggemann N, Swennen G, Eckardt A. Mucoepidermoid carcinoma of the salivary glands—clinical review of 42 cases. *Oral Oncol*. 2005;41:3-10.
2. Liu S, Ow A, Ruan M, Yang W, Zhang CP, Wang L. Prognostic factors in primary salivary gland mucoepidermoid carcinoma: an analysis of 376 cases in an eastern Chinese population. *Int J Oral Maxillofac Surg*. 2014;43:667-673.
3. Li L-j, Li Y, Wen Y-m, Zhao H-w. Clinical analysis of salivary gland tumor cases in West China in past 50 years. *Oral Oncol*. 2008;44:187-192.
4. Auclair L, Èllis GL. Mucoepidermoid carcinoma. In: Èllis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*, Philadelphia, PA: W.B. Saunders; 1991:269-298.
5. Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. *Int J Oral Maxillofac Surg*. 2010;39:235-242.
6. Stewart FW, Foote FW, Becker WF. Muco-epidermoid tumors of salivary glands. *Ann Surg*. 1945;122:820-844.
7. Tamaki S, Yamanaka Y, Shimomura H, et al. Mucoepidermoid carcinoma of the salivary gland: a clinicopathological study. *J Jpn Soc Oral Oncol*. 2012;24:137-145. [in Japanese].
8. Ozawa H, Tomita T, Sakamoto K, et al. Mucoepidermoid carcinoma of the head and neck: clinical analysis of 43 patients. *Jpn J Clin Oncol*. 2008;38:414-418.
9. Shinohara M, Shimada M, Nakamura S, et al. Clinicopathological study of salivary gland carcinomas. Cervical lymph node and distant metastases. *Jpn J Oral Maxillofac Surg*. 1993;39:573-582.
10. Guzzo M, Andreola S, Sirizzotti G, Cantu G. Mucoepidermoid carcinoma of the salivary glands: clinicopathologic review of 108 patients treated at the National Cancer Institute of Milan. *Ann Surg Oncol*. 2002;9:688-695.
11. Granic M, Suton P, Mueller D, Cvrljevic I, Luksic I. Prognostic factors in head and neck mucoepidermoid carcinoma: experience at a single institution based on 64 consecutive patients over a 28-year period. *Int J Oral Maxillofac Surg*. 2018;47:283-288.
12. Evans HL. Mucoepidermoid carcinoma of salivary glands: a study of 69 cases with special attention to histologic grading. *Am J Clin Pathol*. 1984;81:696-701.
13. Rapidis AD, Givalos N, Gakiopoulou H, et al. Mucoepidermoid carcinoma of the salivary glands. Review of the literature and clinicopathological analysis of 18 patients. *Oral Oncol*. 2007;43:130-136.
14. Goode RK, El-Naggar AK. Mucoepidermoid carcinoma. In: Barnes L, Evason JW, Richart P, Sidransky D, eds. *World Health Organization Classification of Tumors: Pathology & Genetics—Head and Neck Tumours*, Lyon, France: International Agency for Research on Cancer Press; 2005:219-220.

15. Auclair PL, Goode RK, Ellis GL. Mucoepidermoid carcinoma of intraoral salivary glands. Evaluation and application of grading criteria in 143 cases. *Cancer*. 1992;69:2021-2030.
16. Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 8th ed., Chichester, UK: Wiley-Blackwell; 2017.
17. Triantafillidou K, Dimitrakopulos J, Iordanidis F, Koufogiannis D. Mucoepidermoid carcinoma of minor salivary glands: a clinical study of 16 cases and review of the literature. *Oral Dis*. 2006;12:364-370.
18. Zenga J, Yu Z, Parikh A, et al. Mucoepidermoid carcinoma of the parotid: very close margins and adjuvant radiotherapy. *ORL J Otorhinolaryngol Relat Spec*. 2019;81:55-61.
19. Caccamese J.F. Jr, Ord RA. Paediatric mucoepidermoid carcinoma of the palate. *Int J Oral Maxillofac Surg*. 2002;31:136-139.
20. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO international histological classification of tumours. Tentative histological classification of salivary gland tumours. *Pathol Res Pract*. 1990;186:555-581.
21. Levitt SH, McHugh RB, Gómez-Marin O, et al. Clinical staging system for cancer of the salivary gland: a retrospective study. *Cancer*. 1981;47:2712-2724.
22. Spiro RH, Huvos AG, Strong EW. Cancer of the parotid gland. A clinicopathologic study of 288 primary cases. *Am J Surg*. 1975;130:452-459.
23. Batsakis JG. Pathology consultation. Metastatic patterns of salivary gland neoplasm. *Ann Otol Rhinol Laryngol*. 1982;91:465-466.
24. Healey WV, Perzin KH, Smish L. Mucoepidermoid carcinoma of salivary gland origin. Classification, clinical-pathologic correlation, and results of treatment. *Cancer*. 1970;26:368-388.
25. Sakamoto K, Izumaru S, Kurita T, Miyajima Y, Nakashima T. Clinical review of mucoepidermoid carcinomas. *Nippon Jibiinkoka Kaiho (Tokyo)*. 2005;108:142-149.
26. Kohno N, Kitahara S, Kawaida M, Nakazawa E, Ichikawa G. The role of radiotherapy and/or chemotherapy for mucoepidermoid carcinoma. *Nihon Koku Intoka Gakkai*. 1999;11:269-276.
27. Eisenberger MA. Supporting evidence for an active treatment program for advanced salivary gland carcinomas. *Cancer Treat Rep*. 1985;69:319-321.
28. Conley J, Tinsley PP. Treatment and prognosis of mucoepidermoid carcinoma in the pediatric age group. *Arch Otolaryngol*. 1985;111:322-324.
29. Byun YS, Fayos JV, Kim YH. Management of malignant salivary gland tumors. *Laryngoscope*. 1980;90:1052-1060.
30. Komori A, Takagi M, Ishikawa G. Distant metastasis of oral carcinoma part II. Relationship between histologic types and distant metastasis. *Kokubyou*. 1979;46:158-165.

Reprint requests:

Yasuyuki Michi
Junior Associate Professor
Department of Oral and Maxillofacial Surgery
Graduate School of Medical and Dental Science
Tokyo Medical and Dental University
1-5-45 Yushima
Bunkyo-ku
Tokyo 113-8510
Japan.
Y-mic.mfs@tmd.ac.jp