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MAIN ARTICLE

Clinicopathological features of mucoepidermoid carcinoma

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Abstract

Objective: We aimed to examine the clinical usefulness of a new World Health Organization classification scheme for salivary gland mucoepidermoid carcinoma, and to identify the factors most strongly associated with prognosis and outcome.

Methods: The clinicopathological features of 45 patients who received treatment for mucoepidermoid carcinoma between 1986 and 2010 were retrospectively investigated.

Results: The overall disease-specific 5-year survival rate was 81.8 per cent. The rate for patients with low-grade tumours (92.5 per cent) was significantly higher than that for patients with intermediate or high-grade tumours (52.2 per cent). Univariate analysis revealed that five factors were significantly associated with five-year survival: age, tumour stage classification, lymph node status, histological grade and treatment method. Four factors were significant in multivariate analysis: age, sex, tumour stage classification and lymph node status.

Conclusion: The new World Health Organization classification was useful in predicting disease progression in patients with mucoepidermoid carcinoma. Patients with high-grade tumours or other prognostic factors positively associated with disease progression should be carefully evaluated and monitored.

Key words: Carcinoma, Mucoepidermoid; World Health Organization; Prognosis

Introduction

Among malignancies of the head and neck, salivary gland carcinomas are particularly diverse in their histological features, and each of the many subtypes has unique pathological characteristics. There have been several attempts at histopathological classification of salivary gland tumours,[1–3] and in 2005 the World Health Organization (WHO) published a new histopathological classification scheme (as part of a revised head and neck tumour classification system).[4]

In the 1972 WHO classification, epidermoid carcinoma was classified as an epidermoid tumour and considered benign. In 1991, the term epidermoid carcinoma was introduced to describe malignant epidermoid tumours.[5] Finally, in 2005 the WHO presented a new classification scheme that included a classification by malignancy grade, based on the histopathological characteristics of these tumours.

We investigated the association of the 2005 WHO classification scheme and other prognostic factors with survival among patients with mucoepidermoid carcinoma who had been registered with the Niigata Prefecture Head and Neck Malignant Tumour Registration Committee since its founding in 1986.

Materials and methods

Fifty cases of mucoepidermoid carcinoma were registered with the Niigata Prefecture Head and Neck Malignant Tumour Registration Committee during the 25-year period from 1986 to 2010. We retrospectively investigated the clinicopathological characteristics of 45 patients who had received treatment and undergone follow-up examination. Duration of follow up ranged from 2 to 249 months (mean, 59.0 months). We classified histological grade according to the 2005 WHO classification scheme (Table I), and we examined the association of histological grade and other clinical and pathological prognostic factors with disease-specific five-year survival.

All analyses were performed with the SPSS software program, version 19 (SPSS Inc, Chicago, Illinois, USA). Survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used to assess differences between groups. Multivariate analysis was done using the Cox proportional hazards model. A p value of less than 0.05 was considered to indicate statistical significance.

The 1997 tumour-node-metastasis (TNM) classification of the Union for International Cancer Control was

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TABLE I
HISTOPATHOLOGICAL FEATURES AND SCORING USED TO GRADE MUCOEPIDERMOID CARCINOMA

Feature	Score
Cystic component <20%	2
Neural invasion	2
Necrosis	3
≥4 mitoses/10 HPF	3
Anaplasia	4
Tumour grade	
– Low	0–4
– Intermediate	5–6
– High	≥7

HPF = high-power fields

used, and histopathological grade was determined in accordance with the 2005 WHO criteria.

Results and analysis

Table II shows the clinicopathological characteristics of the 45 patients. There were 21 men and 24 women, and the average age was 55.5 years (range, 19–87 years). The primary lesion was located in a major salivary gland in 32 patients (involving the parotid gland in 23 patients and the submandibular glands in 9) and in a minor salivary gland in 13 patients (involving the oropharynx in 4 patients, the oral cavity in 4, the epipharynx in 3, the larynx in 1 and the maxillary sinus in 1).

TABLE II
PATIENT CHARACTERISTICS

Characteristic	Result
Male/female sex (*n*)	21/24
Age (mean (range); y)	55.5 (19–37)
Primary site (*n*)	
– Parotid gland	23
– Submandibular gland	9
– Oropharynx	4
– Oral cavity	4
– Epipharynx	3
– Larynx	1
– Maxillary sinus	1
Histological grade (*n*)	
– Low	32
– Intermediate	2
– High	11
Tumour size (*n*)	
– T_1	12
– T_2	16
– T_3	8
– T_4	9
Node status (*n*)	
– N_0	36
– N_1	2
– N_2	5
– N_3	2
Stage (*n*)	
– I	12
– II	12
– III	8
– IV	13
Treatment (*n*)	
– Surgery	30
– Surgery + RT	8
– RT*	7

*Two patients also received simultaneous chemotherapy. Y = years; T = tumour; N = node; RT = radiotherapy

On the basis of the 2005 WHO classification scheme, 32 tumours were classified as low grade, 2 as intermediate grade and 11 as high grade. Of patients with high-grade tumours, six lived (one developed pulmonary metastasis), two died of other causes, and three died due to their primary mucoepidermoid carcinoma (the tumour recurred in its original location in all three patients). The two patients with intermediate-grade tumours both died of cancer (pulmonary metastases developed in both patients). Of patients with low-grade tumours, 28 lived, 2 died of other causes and 2 died due to their primary mucoepidermoid carcinoma (1 from cancer recurrence and 1 from pulmonary metastasis).

Regarding patients' TNM classification, tumour size was classified as T_1 in 12 patients, T_2 in 16, T_3 in 8 and T_4 in 9. Node status was N_0 in 36 patients, N_1 in 2, N_2 in 5 and N_3 in 2. No distant metastases were observed. As for staging, 12 patients were stage I, 12 were stage II, 8 were stage III and 13 were stage IV.

Regarding treatment, 30 patients underwent surgery, 8 received surgery and radiotherapy, and 7 underwent radiotherapy (2 of whom also received simultaneous chemotherapy). Reasons for selecting radiotherapy included tumour invasion of the carotid artery, tumour growth into the intracranial area, and patient refusal of surgery.

As for disease progression, the disease-specific 5-year survival rate was 81.8 per cent overall (Figure 1), 92.5 per cent for patients with low-grade tumours, and 52.2 per cent for patients with intermediate- or high-grade tumours (Figure 2).

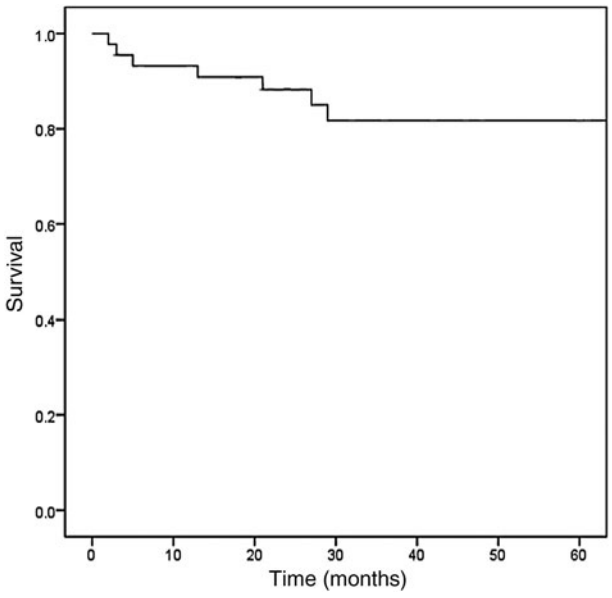

FIG. 1
Kaplan–Meier curves for overall disease-specific survival for the 45 patients with mucoepidermoid carcinoma.

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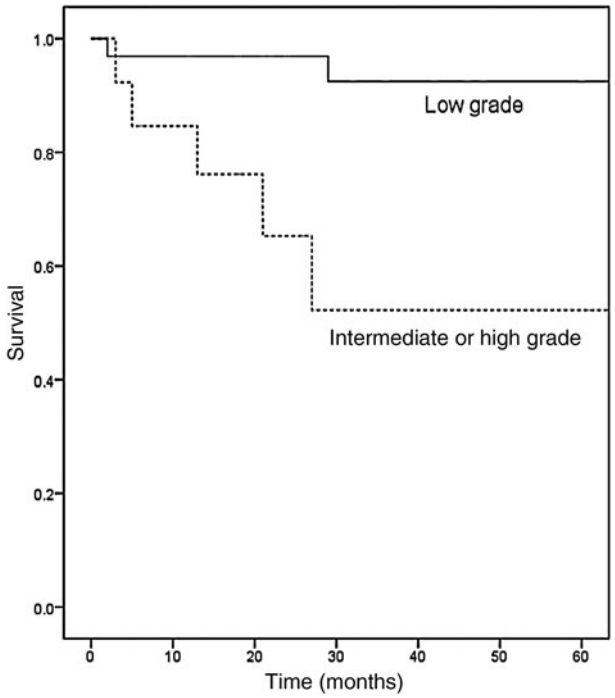

FIG. 2
Kaplan–Meier curves for disease-specific survival by histological tumour grade.

Table III shows the results of univariate analyses (log-rank test) comparing survival rates by age, sex, location of primary lesion, T classification, N classification, histological grade and treatment. Patients aged 55 years or younger ($n = 23$) had a survival rate of 95.7 per cent, which was significantly higher ($p = 0.032$) than the rate for those older than 55 years (66.8 per cent; $n = 22$). The difference in survival between men (71.2 per cent; $n = 21$) and women (90.2 per cent; $n = 24$) was not significant ($p = 0.083$). Also, no significant difference in survival ($p = 0.406$) was observed between patients with a primary lesion in the major salivary glands (84.8 per cent; $n = 32$) and those with a primary lesion in the minor salivary glands (74.6 per cent; $n = 13$).

There was a significant difference in survival ($p = 0.001$) between patients with T_1 or T_2 cancer (96.2 per cent; $n = 28$) and those with T_3 or T_4 cancer (49.9 per cent; $n = 17$). A significant difference in survival ($p = 0.003$) was also seen between N_0 patients (92.8 per cent; $n = 36$) and patients who were N_1, N_2 or N_3 (44.4 per cent; $n = 9$). There was also a significant difference ($p = 0.003$) between the survival rate of patients with low-grade tumours (92.5 per cent; $n = 32$) and those with intermediate- or high-grade tumours (52.5 per cent; $n = 13$). The survival rate was 86.7 per cent for patients who underwent surgery ($n = 30$), 100 per cent for those who received both surgery and radiotherapy ($n = 8$), and 38.7 per cent for those receiving radiochemotherapy ($n = 7$) ($p = 0.0001$ for the comparison among the 3 groups).

Multivariate analysis using the above variables revealed significant differences in survival with respect to age ($p = 0.049$; hazard ratio = 0.090), sex ($p = 0.013$; hazard ratio = 51.776), T classification ($p = 0.008$; hazard ratio = 0.10) and N classification ($p = 0.012$, hazard ratio = 0.027) (Table IV).

TABLE III
UNIVARIATE ANALYSIS RESULTS

Factor	Pts (*n*)	DSS (%)	*p*
Age			
– ≤55 y	23	95.7	0.032
– >55 y	22	66.8	
Sex			
– Male	21	71.2	0.083
– Female	24	90.2	
Primary site			
– Major SG	32	84.8	0.406
– Minor SG	13	74.6	
Tumour size			
– T_1 or T_2	28	96.2	0.001
– T_3 or T_4	17	49.9	
Node status			
– N_0	36	92.8	0.003
– N_1 or N_2 or N_3	9	44.4	
Histological grade			
– Low	32	92.5	0.003
– Int or high	13		
Treatment			
– Surgery	30	86.7	<0.0001
– Surgery + RT	8	100	
– RT*	7	38.7	

*Two patients also received simultaneous chemotherapy. Pts = patients; DSS = 5-year disease-specific survival; y = years; SG = salivary gland; T = tumour; N = node; Int = intermediate; RT = radiotherapy

TABLE IV
SIGNIFICANT MULTIVARIATE ANALYSIS RESULTS*

Factor	Category	HR	95% CI	*p*
Age	≤55 y	0.090	0.008–0.984	0.049
Sex	Male	51.776	2.295–1168.246	0.013
T	T_1 or T_2	0.10	0.000–0.3000	0.008
N	N_0	0.027	0.002–0.452	0.012

*For variables associated with 5-year disease-specific survival. HR = hazard ratio; CI = confidence interval; y = years; T = tumour; N = node

Discussion

When first described in 1945, the tumour later termed mucoepidermoid carcinoma was designated as a benign salivary gland tumour containing both epidermoid and mucous cells, and was named mucoepidermoid tumour. However, metastases were reported in some patients, and these tumours came to be regarded as borderline lesions, i.e. between benign and malignant.[1–3] A previous WHO classification scheme categorised these lesions as benign mucoepidermoid tumours; however, in 1992 the term mucoepidermoid carcinoma was used as the new designation for malignant tumours,[5] and this designation was maintained in the 2005 WHO classification.

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Mucoepidermoid carcinomas are composed of squamoid cells, mucus-producing cells and intermediate cells, and comprise a wide variety of histological types. Because of this histological variation, there have been a number of attempts to categorise malignancy grade.[1–3] In the 2005 WHO classification, malignancy grade was assigned based on the cystic component of the tumour (≤20 per cent *vs* more), presence and extent of neural invasion, tumour necrosis, mitoses (≥4/10 high-power fields *vs* fewer), and anaplasia. The total score from these five categories is used to identify low-, intermediate-, and high-grade tumours.[4] In the present study, we used this 2005 WHO classification in our clinicopathological analysis.

Of the 45 patients analysed in the present study, 32 had low-grade tumours, 2 had intermediate-grade tumours, and 11 had high-grade tumours. The overall disease-specific 5-year survival rate was 81.8 per cent, similar to rates reported in some previous studies[6,7] and slightly worse than results from another previous study.[8] This discrepancy may be due to the fact that 21 (46 per cent) of our patients had stage III or IV disease.

Patients with low-grade tumours had a disease-specific 5-year survival rate of 92.5 per cent, which was significantly higher than the 52.5 per cent rate among those with intermediate- or high-grade tumours. This finding indicates that the 2005 WHO classification has clinical value in determining prognosis.

Pre-operative histological diagnosis of salivary gland tumours is difficult.[9–11] Because malignancy grade cannot be accurately determined before surgery, it is sometimes necessary to develop a treatment plan based on clinical prognostic factors other than malignancy grade. Factors putatively associated with mucoepidermoid carcinoma prognosis include age, disease stage and histopathological malignancy grade.[12–14] The present univariate analysis showed that disease outcome was significantly associated with age, tumour size classification, lymph node status, histological grade and treatment method.

Tumour size classification was strongly associated with resection margin status and, in patients with parotid gland carcinoma, facial paralysis. Furthermore, patients with high-grade tumours were more likely to have a high T stage.[15] Metastasis to cervical lymph nodes is common among patients with high-grade tumours.[16] In the present study, among nine patients with metastases to lymph nodes, four had high-grade tumours. Furthermore, among the 11 patients with high-grade tumours, 4 developed metastases to neck lymph nodes. In addition, multivariate analysis revealed that age, sex, tumour size classification and lymph node metastasis were significantly associated with outcome.

Surgery is the standard first-line treatment for mucoepidermoid carcinoma of the salivary glands.[6–8] In the present study, outcomes were generally successful among patients who underwent surgery, which suggests the importance of surgical treatment as a prognostic factor. However, it is often difficult to diagnose mucoepidermoid carcinoma by means of biopsy or fine needle aspiration, and there are numerous reports of tumours initially diagnosed as benign which were found to be mucoepidermoid carcinomas upon post-operative pathological inspection.[9–11] Such misdiagnosis could easily lead to inadequate surgical margins during resection. We did not investigate the association between resection margin and disease outcome, partly due to the limited number of patients; however, in cases of adjacency to the resection margin or margin positivity, a second operation would probably be required.

- **Salivary gland carcinomas have diverse histology and many subtypes**
- **This study tested the new (2005) World Health Organization classification for mucoepidermoid carcinoma**
- **The classification was useful for predicting disease progression**
- **Patients with high-grade tumours, older age, male sex, larger tumours and/or lymphadenopathy should be carefully evaluated and monitored**

In general, it is difficult to achieve local control of mucoepidermoid carcinoma with radiotherapy alone,[17] but there are reports of post-operative radiotherapy being successfully used for local control in patients with positive margins.[7,18] In the present study, patients who underwent surgery (with or without post-operative radiotherapy) had more successful outcomes, while those receiving radiotherapy alone had worse outcomes. This again suggests the importance of surgery, including resection with adequate margins. Nonetheless, patients receiving post-operative radiotherapy had much better outcomes than those receiving radiotherapy alone, which suggests that post-operative radiotherapy should be considered in patients with high-grade tumours or inadequate surgical margins.

At present, an effective chemotherapy regimen has not been clinically established, and among regimens that have been attempted, the success rate has been quite low.[19] Thus, additional research and development of new pharmaceuticals (including molecularly targeted drugs) will be required to achieve satisfactory rates of local control and to improve survival.

Conclusion

Mucoepidermoid carcinoma displays considerable cytological variation and diverse histomorphological characteristics. There have been several investigations of the clinicopathological progression of the disease. Our results highlight the usefulness of the 2005 WHO malignancy classification system and confirm

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the prognostic importance of patient age, sex, tumour size classification and lymph node status.

In the treatment of mucoepidermoid carcinoma of the salivary glands, adequate surgical margins are important in patients with an unfavourable prognosis. Post-operatively, after determining malignancy grade and evaluating the resection margins, other treatments – including radiotherapy and additional surgery – can be given as required.

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