Management and outcome of parotid mucoepidermoid carcinoma by histological grade: A 21-year review

Masataka Taniuchi MD | Ryo Kawata MD, PhD | Tetsuya Terada MD, PhD
Masaaki Higashino MD, PhD | Hiromi Nishimura MD
Yoshitaka Kurisu MD, PhD | Hiroko Kuwabara MD, PhD
Yoshinobu Hirose MD, PhD

1Department of Otorhinolaryngology - Head and Neck Surgery, Osaka Medical and Pharmaceutical University, Takatsuki, Japan
2Department of Pathology, Osaka Medical and Pharmaceutical University, Takatsuki, Japan

Abstract
Objective: Mucoepidermoid carcinoma (MEC) is the most common malignancy of the parotid gland, but the outcome depends on the histological grade. Therefore, the aim of this study was to evaluate MEC on the basis of histological grade.

Study Design: Retrospective analysis.

Methods: We performed a retrospective analysis of data from patients whose initial treatment for MEC of the parotid gland was performed at our department between 1999 and 2021. We examined the association between the Armed Forces Institute of Pathology (AFIP) grade and outcome.

Results: The AFIP grades were as follows: low, 26 cases; intermediate, 9 cases; and high, 31 cases. About 50% of cases were correctly diagnosed as malignant, and both grade and histology were accurately determined by fine-needle aspiration cytology in 20% of cases. The 5-year disease-free survival rate was 95.5% and 53.8% in the low-/intermediate- and high-grade cases, respectively. In the high-grade group, cases with recurrence were found to have a higher rate of lymph nodes metastasis than cases without recurrence. Furthermore, in this high-grade group, total sacrifice of the facial nerve did not reduce local recurrence. However, radical resection in the cases without tumor invasion to the nerve has decreased the local recurrence rate. The CRTC1-MAML2 fusion gene was expressed in 42.3% of low-/intermediate- and 14.3% of high-grade cases.

Conclusions: The survival rate in MEC was quite different between the low-/intermediate- and high-grade cases. However, the rate of correct assessment of the grade by fine-needle aspiration cytology was poor. In high-grade cases, total sacrifice of the facial nerve may improve the rate of local recurrence in cases without invasion of the main trunk of the nerve. Expression of the CRTC1-MAML2 fusion gene could be helpful in not only the assessment of grade but the prediction of recurrence.

Level of Evidence: 4
INTRODUCTION

Salivary gland cancer is a rare malignancy and accounts for less than 5% of head and neck cancers; 70% of salivary gland cancers occur in the parotid gland. Among parotid cancers, mucoepidermoid carcinoma (MEC) is the most common subtype, accounting for approximately 50% of cases. Parotid cancer has 23 histological types as recognized by the 2017 WHO classification. Even within the same histological type, the grade can vary from case to case, and MEC is one of the histological types with a wide range of grades. Therefore, for parotid cancer, not only the stage but also the histological type and grade are important for determining treatment.

A diagnosis of MEC is based on the component ratio of three cell types: epidermoid, mucous, and intermediate cells. This component ratio relates to the clinical manifestation, but because of the wide variations in the pathology of MEC, preoperative grading is not easy. A system for correct diagnosis is required, and its correlation with clinical outcome needs to be determined.

Recently, the CRTCl-MAML2 fusion gene was identified. Okumura et al. studied 72 cases with low-grade and 27 cases with high-grade with MEC and reported that the positive rate of the fusion gene was 55.6% and 3.7% in low- and high-grade group, respectively, thus suggesting that it may be a useful tool for grading MEC.

Prognostic factors and survival rate are difficult to determine for parotid cancer because of its low incidence, the wide variety of histological types and grades, and the need for long-term follow-up in low-grade cases. In addition, the basic treatment of parotid cancer, particularly the range of resection and indication for neck dissection, has not been clearly defined.

To collect sufficient data to enable accurate conclusions about prognostic factors and outcome in MEC, diagnosis and treatment must be consistently maintained for cases collected over an extended period. Although this approach is difficult, at our department, we have used a consistent policy to diagnose and treat patients with parotid cancer for the past 21 years. Therefore, in this study, to clinically characterize MEC based on its grade, we analyzed our data from 67 patients with MEC on diagnosis and treatment, outcome, expression of the CRTCl-MAML2 fusion gene, and characteristics of high-grade MEC.

MATERIALS AND METHODS

2.1 | Patients

We included 67 patients with MEC who underwent the initial treatment and whose histopathological type was established at the Department of Otorhinolaryngology-Head and Neck Surgery, Osaka Medical and Pharmaceutical University, in the 21 years from September 1999 to August 2021. In this period, 224 cases of parotid cancer were treated at our department. When the MEC cases were graded according to the Armed Forces Institute of Pathology (AFIP) classification, 26, 9, and 32 cases were evaluated as low-, intermediate-, and high-grade, respectively. Table 1 summarizes clinical features for each grade from 67 cases. The study was approved by the ethics committee of Osaka Medical and Pharmaceutical University (approval number #2621). Informed consent was obtained from all individual participants included in the study, including those from parents of minors.

2.2 | Treatment

A total of 65 patients with MEC were treated by surgery, and details of their treatment are shown in Table 2. Whether or not to preserve
the facial nerve was decided according to the following principle. If the tumor had invaded the facial nerve, the facial nerve was sacrificed together with the tumor regardless of the grade; and if the tumor had adhered to the nerve, the nerve was sacrificed in high-grade cases and preserved in low-/intermediate-grade cases. A total neck dissection was used for clinical node-positive (cN⁺) cases, and a selective neck dissection (level I, II, III, and upper level of V) was used for intermediate- and high-grade cases with clinical node negative (cN0). Postoperative radiotherapy was used for cases with high-grade, T4, pathological node-positive (pN⁺), and a histologically positive margin.

2.3 | Signs/symptoms and imaging diagnosis

Signs/symptoms were analyzed in the overall group of patients and according to grade. The evaluated signs/symptoms included pain/tenderness, adhesion to surrounding tissues, and facial nerve palsy. Adhesion to surrounding tissues was classified as movable, restricted, or fixed; cases with restriction or fixation were classified as adhesion positive. Magnetic resonance imaging (MRI) and ultrasonography (US) were used for preoperative imaging, and findings were used to classify tumors into benign, suspicious for malignancy, and malignant. MRI findings of an irregular margin and low intensity at T2 were considered to be malignant, as were US findings of an irregular margin and a low or irregular echo lesion inside. In the case of any inconsistency between MRI findings and US findings, the worse findings were used for analysis.

2.4 | Fine-needle aspiration cytology

The results of fine-needle aspiration cytology (FNAC) obtained preoperatively in 66 patients were analyzed. FNAC was performed with a 22G needle under US guidance, and the results were evaluated according to the Osaka Medical College (OMC) classification used at our institution. The FNAC-based diagnosis was made by three pathologists (co-authors).

2.5 | CRTC1-MAML2 fusion gene

The CRTC1-MAML2 fusion gene was analyzed by reverse transcription polymerase chain reaction (RT-PCR) in 47 cases (17, 9, and 21 cases of low-, intermediate-, and high-grade, respectively). Slices 5 μm in thickness were prepared from formalin-fixed, paraffin-embedded samples, and the tissue slices were deparaffinized, thawed, extracted, and treated with DNase; the obtained total RNA was then purified (Nucleospin® totalRNA FFPE XS; Takara Bio Inc., Shiga, Japan). As an internal control for RNA quality, the ubiquitously expressed ACTB mRNA fragment [135 base pairs (bp)] was amplified. Subsequently, the reverse transcription reaction was performed with a thermocycler at 42°C for 30 min and 95°C for 10 min. The RT-PCR mixture containing the outer primer (CRTC1 TCGCGCTGACAATCAGAAG, MAML2 GGTCGCTTGCTGTTGGCAGG) was added to total RNA, and 35 cycles of the first PCR were performed. The product was diluted to 1:20, and 40 cycles of the second PCR containing the inter primer (CRTC1 GAGGTCATGAAGGACCTGAG, MAML2 TTGCTGTTGGCAGGAGATAG) were performed.

2.6 | Disease-free survival

The disease-free survival rate was calculated by the Kaplan–Meier method in those 60 patients whose outcome was documented (30 low-/intermediate-grade and 30 high-grade cases). The observation period ranged from 6 months to 21 years.

2.7 | Characteristics of high-grade MEC

Among the 32 high-grade cases, we analyzed the 30 cases where the cause of death or recurrence type was known. Background, treatment, and outcome were compared in 11 cases with recurrence and 19 cases without recurrence. Twenty-eight cases treated by surgery were analyzed according to the treatment of the facial nerve (9 cases with preservation/partial sacrifice and 19 cases with total sacrifice).

2.8 | Statistical analysis

Fisher’s exact test was used for comparisons based on sex, tumor location, T stage, N stage, stage, expression of CRTC1-MAML2, signs/symptoms, imaging findings, treatment, recurrence, and outcome. Mann–Whitney U test was used for comparisons based on age at initial treatment, tumor diameter, and disease duration; the log rank test was used for analysis of disease-free survival. JMP Pro software (version 14) (SAS Institute Inc., Cary, North Carolina) was used for
statistical analysis. For each test, \( P < .05 \) was considered to show a statistically significant difference.

3 | RESULTS

3.1 | Patient demographics and clinical features

Patient demographics and clinical features were analyzed by tumor grade. The percentage of high-grade malignancy was significantly higher in men \( (P = .0013) \), and age was significantly higher in high-grade cases and lower in low-/intermediate-grade cases \( (P < .001) \). Moreover, tumor diameter was significantly larger in high-grade cases \( (P < .001) \), and incidence of advanced T (T3 and T4) was significantly higher in high-grade cases than in low-/intermediate-grade cases \( (P < .001) \). Incidence of node metastasis was significantly lower in low-/intermediate-grade cases \( (P < .001) \), and the percentage of patients with stage IV MEC was significantly higher in high-grade cases \( (P < .001) \). Expression of the CRTC1-MAML2 fusion gene was found in 11 out of 26 low-/intermediate-grade cases, and 3 out of 21 high-grade cases \( (P = .555; \text{Table 1}) \).

3.2 | Signs/symptoms and imaging diagnosis

Evaluation of signs/symptoms in the total 67 cases showed that 33 (49.3%) had spontaneous pain/tenderness, 44 (65.7%) had adhesion to the surrounding tissue, and 8 (11.9%) had facial nerve palsy. In signs/symptoms, adhesion to surrounding tissue showed a significant difference in incidence between low-/intermediate- and high-grade cases \( (P < .001) \).

MRI/US imaging showed a significant difference in the percentage of malignancy between the low- and high-grade cases: 6 out of 26 (23.1%) low-grade cases and 27 out of 32 (84.4%) high-grade cases were evaluated as malignant. Among the low-grade cases, 6 out of 26 cases (23.1%) were diagnosed as benign \( (P < .001; \text{Table 3}) \).

3.3 | Fine-needle aspiration cytology

FNAC results classified according to the OMC classification showed malignancy \( (\text{category 6-1 to 6-4}) \) in 8 (30.8%), 3 (33.3%), and 19 (61.3%) cases of low-, intermediate-, and high-grade MEC, respectively. Seven cases were evaluated as benign \( (\text{OMC category 4}) \), and among these, four were low-grade cases. Grade was confirmed correctly in three of four malignant cases \( (\text{OMC category 6-3}) \); the remaining case was rated as an intermediate-grade case but evaluated by FNAC as a high-grade case. Grade and histological type \( (\text{OMC category 6-4}) \) could be confirmed in 13 of 19 cases. Among the remaining six cases, the histological type was wrong in three cases, the grading was wrong in one case, and both histological type and grading were wrong in two cases (\text{Table 4}).

The rates of correct diagnosis by FNAC relative to final pathology are summarized in \text{Table 5}. The rate of correct diagnosis of malignancy was 45.5% in the total MEC cases, and the rate of correct diagnosis of grade, histology, and grade/histology was 28.8%, 21.2%, and 19.7%, respectively, thus indicating a higher rate in high-grade cases than in low- and intermediate-grade cases.

3.4 | Disease-free survival

The 5-year disease-free survival rate was 95.5% in the low-/intermediate-grade cases \( (n = 30) \) and 53.8% in the high-grade cases \( (n = 30) \), respectively. Regarding the type of recurrence, 11 patients had local recurrence, two had lymph node metastasis, and one had distant metastasis. Among the low-/intermediate-grade cases, only one patient experienced recurrence (lymph node metastasis) (\text{Figure 1}).

3.5 | Characteristics of high-grade MEC

Among the 11 high-grade cases with recurrence, 10 patients had local recurrence, and one had lymph node metastasis; 3 patients survived, but 8 died from the underlying disease. Among the 19 high-grade cases without recurrence, one patient died from another disease and
the remaining 18 patients survived. We found no significant difference between cases with and without recurrence, except that the percentage of node metastasis was significantly higher in the cases with recurrence ($P = .016$). Of note, no case with recurrence showed expression of the CRTC1-MAML2 fusion gene. As well, no significant differences were found in treatment methods between cases with and without recurrence (Table 6).

Among the 28 high-grade cases that were analyzed according to the treatment of the facial nerve during surgery, 19 cases of them were treated by total sacrifice and, of these, 7 cases had tumor invasion into the main trunk of the facial nerve and 12 cases had no such invasion. We found no significant difference in the percentage of cases with T4 or pN+ between the total sacrifice group and the preservation/partial sacrifice group. The extent of resection was

| OMC classification                   | Total cases, $N = 66$ | Low grade, $n = 26$ | Intermediate grade, $n = 9$ | High grade, $n = 31$ |
|-------------------------------------|----------------------|---------------------|-----------------------------|----------------------|
| 1-1 Inadequate, $n$                 | 10                   | 4                   | 3                           | 3                    |
| 1-2 Cyst contents, $n$              | 2                    | 2                   | 0                           | 0                    |
| 2 Non-neoplastic, $n$               | 3                    | 2                   | 0                           | 1                    |
| 3 Atypia of undetermined significance, $n$ | 3                    | 2                   | 1                           | 0                    |
| 4-1 Benign, histology confirmed, $n$ | 3                    | 1                   | 0                           | 2                    |
| 4-2 Benign, histology unconfirmed, $n$ | 4                    | 3                   | 1                           | 0                    |
| 5 Uncertain malignant potential, $n$ | 11                   | 4                   | 1                           | 6                    |
| 6-1 Suspicious for malignancy, $n$  | 4                    | 2                   | 1                           | 1                    |
| 6-2 Malignant, grade/histology unconfirmed, $n$ | 3                    | 1                   | 0                           | 2                    |
| 6-3 Malignant, $n$ (grade confirmed, $n$) | 4 (3)                | 1 (1)               | 1 (0)                       | 2 (2)                |
| 6-4 Malignant, $n$ (grade/histology confirmed, $n$) | 19 (13)              | 4 (3)               | 1 (0)                       | 14 (10)              |

*Numbers shown as “total cases (number of cases with a correct diagnosis).”

| Table 4 Cytopathology results according to the Osaka Medical College (OMC) classification system after fine-needle aspiration cytology. |
|---------------------------------------------------------------------------------------------------------------|
| OMC classification | Total cases, $N = 66$ | Low grade, $n = 26$ | Intermediate grade, $n = 9$ | High grade, $n = 31$ |
|---------------------|-----------------------|---------------------|-----------------------------|----------------------|
| Malignancy correct, $n$ (%) | 30 (45.5)            | 8 (30.8)            | 3 (33.3)                    | 19 (61.3)            |
| Grade correct, $n$ (%)       | 19 (28.8)            | 5 (19.2)            | 1 (11.1)                    | 13 (41.9)            |
| Histology correct, $n$ (%)  | 14 (21.2)            | 3 (11.5)            | 0 (0.0)                     | 11 (35.4)            |
| Grade and histology correct, $n$ (%) | 13 (19.7)       | 3 (11.5)            | 0 (0.0)                     | 10 (32.3)            |

**FIGURE 1** Kaplan-Meier curve of 5-year disease-free survival for low-/intermediate- ($n = 30$) and high-grade ($n = 30$) mucoepidermoid carcinoma. MEC, mucoepidermoid carcinoma.
significantly larger in the total sacrifice group \( (P = .0062) \), but the percentage of local recurrence showed no significant difference between the two groups. All of the nine patients with local recurrence died from the underlying disease. Among the 19 cases treated by total sacrifice of the facial nerve, recurrence was seen in 4 of the 7 cases (57%) with tumor invasion for the nerve and 2 of the 12 cases (17%) without such invasion. On the other hand, three of the nine cases (33%) treated by preservation/partial sacrifice experienced recurrence (Table 7).

Among the 26 low-grade cases, the facial nerve was preserved in 20 cases, partially sacrificed in 6 cases, and totally sacrificed in zero cases. Among the nine intermediate-grade cases, it was preserved in three cases, partially sacrificed in five cases, and totally sacrificed in one case.

### 4 | DISCUSSION

The importance of histological grade as a prognostic factor for the parotid MEC is well known.\(^9\) A database study of 2400 cases of MEC revealed that the 5-year cancer-specific survival rates were 99%, 97%, and 67% for low-, intermediate-, and high-grade cases, respectively.\(^{10}\) In the National Cancer Database study, 5-year overall survival rates were 92%, 86%, and 49% for low-, intermediate-, and high-grade cases, respectively.\(^{11}\) In our analysis, 5-year disease-free survival rates were 95.5% and 53.8% in low-/intermediate-grade and high-grade cases, respectively, which is consistent with the results obtained from the above studies. The percentage of high-grade tumors among MEC is reported to be 21%–31%,\(^{10-13}\) but our analysis found a higher rate (48%). In a database study, some cases of high-grade MEC might have been diagnosed as squamous cell carcinoma.\(^{14}\) At our institution, only 9 out of 224 cases with parotid cancer were diagnosed as squamous cell carcinoma, which may be one reason for the higher percentage of MEC cases in our study.

Several histological grading systems have been suggested that classify MEC into two or three categories.\(^5,15\) The AFIP classification was suggested by Goode et al.\(^5\) in 1998. This system classifies MEC into the three categories of low-, intermediate-, and high-grade, according to the scores of five parameters: the cystic component, the presence or absence of glandular differentiation, the degree of keratinization, the mitotic rate, and the necrosis.

### Table 6 Recurrence and nonrecurrence among cases of high-grade mucoepidermoid carcinoma.

|                  | Recurrence, \( n = 11 \) | No recurrence, \( n = 19 \) | \( P \) value |
|------------------|--------------------------|---------------------------|--------------|
| Age, median, y   | 63.8                     | 63.5                      | .78          |
| Sex, \( n \), male:female | 9:2                   | 13:6                      | .67          |
| T4, \( n \)      | 6                        | 7                         | .45          |
| Pathological node, \( n \), negative:positive | 1:9                  | 11:7                      | .016         |
| Tumor location, \( n \), superficial:deep:lower pole | 7:1:3              | 13:3:3                    | 1.0          |
| CRTCL1-MAML2, \( n \), positive:negative | 0:7                  | 3:11                      | .52          |
| Local resection, \( n \), (partial) parotidectomy:subtotal parotidectomy:total parotidectomy | 0:4:6              | 4:8:6                     | .24          |
| Facial nerve, \( n \), preservation:partial sacrifice:total sacrifice | 0:3:7          | 3:3:12                    | 1.0          |
| Neck dissection, \( n \), none:selective:total | 0:2:8             | 4:7:7                     | .055         |
| Postoperative radiotherapy, (No) recurrent cases:total cases\(^a\) | 8/10             | 13/18                     | 1.0          |
| Recurrence, \( n \), local:node | 10:1                | 0                         | –           |
| Outcome, \( n \), alive:dead | 3:8             | 18:1                      | <.001        |

\(^a\)In total cases, surgery was performed in 10 of the patients with later recurrence and in 18 of those without later recurrence.

### Table 7 Facial nerve preservation/sacrifice among cases of high-grade mucoepidermoid carcinoma.

|                  | Preservation/partial sacrifice, \( n = 9 \) | Total sacrifice, \( n = 19 \) | \( P \) value |
|------------------|------------------------------------------|-------------------------------|--------------|
| Preoperative facial paralysis, \( n \) | 1                          | 4                             | 1.0          |
| T4, \( n \)     | 4                        | 7                             | .70          |
| Pathological node positive, \( n \) | 6                          | 10                            | .69          |
| (Sub)total parotidectomy, \( n \) | 5                        | 19                            | .0062        |
| Nerve reconstruction, \( n \) | 1                          | 9                             | .098         |
| Postoperative radiotherapy, \( n \) | 5                          | 16                            | .17          |
| Local recurrence, \( n \) | 3                          | 6                             | 1.0          |
| Node recurrence, \( n \) | 0                          | 1                             | 1.0          |
| Outcome, \( n \), alive:dead | 6:3                      | 12:7                         | 1.0          |
perineural invasion, necrosis, mitoses, and anaplasia. In 2001, Brandwein et al.\(^2\) argued that the AFIP system tends to downgrade malignancy and suggested evaluating tumors on the basis of eight parameters. The WHO classification version 4 (2017) did not systematize grading and described only typical histological manifestations of three categories.\(^7\) When we evaluated our 67 cases according to the AFIP classification, 26, 9, and 32 cases were classified as low-, intermediate-, and high-grade, respectively. In contrast, when they were evaluated according to the Brandwein system, the respective numbers were 9, 16, and 42, confirming that the malignancy grade tends to be downgraded when it is classified according to the AFIP system. Nevertheless, we believe that the AFIP classification is superior to the Brandwein classification in terms of identifying cases with a poor prognosis as high-grade cases\(^17\) because, in our study, only one of the low-/intermediate-grade cases showed recurrence.

At our institution, we use FNAC not only to evaluate whether the carcinoma is benign or malignant but also to determine as accurately as possible the histological type and grade for malignant cases. The overall rate of correct diagnosis of malignancy in MEC is 45.5%, and we found rates of 31.4% and 61.3% in our low-/intermediate-grade and high-grade cases, respectively. Klijianenko et al.\(^18\) examined 50 cases of MEC and reported that 19 cases (38%) were correctly diagnosed as MEC by FNAC; they concluded that the rate of correct diagnosis is poor for low-grade cases. Iftikhar et al.\(^19\) reported that only 7 of 16 MEC cases were correctly diagnosed as malignant. We suggest that low-grade MEC is difficult to diagnose because it has a large cystic component that interferes with the collection of cells and has less cellular atypism.\(^20\) In terms of grading in our study, only 17.1% in the low-/intermediate-cases were correctly diagnosed, thus demonstrating the limitation of FNAC in correctly diagnosing low-/intermediate-grade cases. Because MRI/US imaging showed a significant difference in the percentage of malignancy between the low- and high-grade cases, it can be a complement to FNAC for grade diagnosis.

The relation of the CRTC1-MAML2 fusion gene to MEC was first reported by Nordkvist et al.\(^21\) and subsequently characterized by Toron et al.\(^22\) Expression of the CRTC1-MAML2 fusion gene is known to be a favorable prognostic factor in MEC.\(^23,24\) In our analysis, the CRTC1-MAML2 fusion gene was found in 11 of 26 low-/intermediate-grade cases (42.3%) and 3 of 21 high-grade cases (14.3%). Furthermore, no recurrence occurred in three high-grade cases that were CRTC1-MAML2 positive, and all cases with recurrence were CRTC1-MAML2 negative. To examine the fusion gene by using the surgical specimen may be useful not only for grading but also for predicting recurrence in high-grade cases.

In parotid tumors, preservation of the facial nerve is the standard approach, provided that there is no tumor invasion to the nerve.\(^25\) However, whether this approach is also applicable in high-grade cases is controversial. In the high-grade cases in this study, there was no significant difference in the recurrence rate when patients were compared on the basis of radical resection, sacrifice of facial nerve, or postoperative radiotherapy. Also, there was no significant difference in the incidence of local recurrence or death from underlying disease when patients were compared according to the treatment of the facial nerve. Thus, radical resection with nerve sacrifice does not appear to improve prognoses in high-grade cases. However, radical resection in the cases without tumor invasion to the main trunk may have decreased the local recurrence rate. Renehan et al.\(^26\) reported that the 10-year survival rate was 74% in patients whose facial nerve was preserved and 45% in those whose facial nerve was not preserved and argued that sacrifice of the facial nerve does not improve prognoses. Of note is that this study evaluated 103 cases of parotid gland tumors, but only 39 of the cases were high-grade. Furthermore, only one of the 39 high-grade cases was MEC. Magnano et al.\(^27\) also maintained that the survival rate is the same regardless of preservation of the facial nerve (52% with preservation vs. 43% without preservation), but this analysis did not include T4 cases. Further studies are warranted to elucidate whether total sacrifice of the facial nerve can decrease local recurrence in high-grade cases without tumor invasion to the facial nerve.

One limitation of our study is the small sample size (n = 67). Database analyses and multicenter studies can enroll larger numbers of patients, but these study designs have the inherent problem of inconsistencies in diagnosis or treatment, which may thus compromise the quality of the results.

5 | CONCLUSION

When the MEC cases were graded by the AFIP classification, 26, 9, and 32 cases were evaluated as low-, intermediate-, and high-grade, respectively. The rate of correct diagnosis by FNAC was about 50% for malignancy and 20% for grade/histology, and the respective rates were higher in high-grade cases. The 5-year disease-free survival rate was 95.5% in low-/intermediate-grade and 53.8% in high-grade cases. The incidence of local recurrence showed no significant difference between the group with total sacrifice and the group with preservation/partial sacrifice of the facial nerve. However, radical resection in those cases without tumor invasion to the nerve may have decreased the local recurrence rate. Expression of the CRTC1-MAML2 fusion gene may be useful not only for grading but also as a predictor of recurrence.

AUTHOR CONTRIBUTIONS

Ryo Kawata designed and supervised the study, Masataka Taniuchi, Tetsuya Terada and Ryo Kawata wrote the manuscript. Masaaki Higashino, Hiromi Nishimura and Tetsuya Terada acquired all clinical data. Yoshitaka Kurisu, Hiroko Kuwabara, and Yoshinobu Hirose assisted in the pathological analyses. All authors performed data analysis and interpretation, and approved the manuscript.

CONFLICT OF INTEREST

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