Mucoepidermoid Carcinoma of the Parotid Gland

The Mayo Clinic Experience

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Objective: To determine clinical and histopathologic features of mucoepidermoid carcinoma of the parotid gland, specifically, the relation of tumor stage and grade and treatment type with clinical outcome.

Design: Retrospective clinical and histopathologic review.

Setting: Tertiary care medical center.

that includes an intermediate grade. Also, discrepancies exist in defining the high-grade end of the spectrum for MEC. Several authors have recommended that a mucin-containing salivary gland carcinoma be classified as an adenosquamous carcinoma or adenocarcinoma rather than MEC if nuclear anaplasia is pronounced.9-11 Although surgery generally is accepted as the primary treatment for MEC, the extent of parotidectomy and the indications for neck dissection are not clear.8,12,13

We reviewed our experience with 89 cases of MEC occurring in the parotid gland and examined the relation of the histologic factors, including tumor grade and stage, and type of treatment with clinical outcome.

METHODS

The cases of 128 patients with MEC of a major salivary gland diagnosed between 1940 and 1994 were available for study. Of these 128 patients, 89 had the primary carcinoma in the parotid gland and received their first treatment at Mayo Clinic, Rochester, Minn. Patients who previously were treated elsewhere or who presented with recurrent disease were excluded from the study group. The medical and surgical records of these 89 cases were reviewed for the clinical and histopathologic features. One head and neck pathologist (J.E.L.) with vast experience in salivary gland disease independently reviewed all the original slides to confirm the diagnosis and provide uniform tumor grading. Cases were accepted as MEC if the tumor (1) had a combination of mucous, intermediate, and epidermoid cells; (2) had solid and cystic growth patterns; and (3) had no nuclear atypia or had nuclear atypia of mild to moderate degree (similar to that in moderately differentiated squamous cell carcinoma). However, tumors with severe nuclear atypia or marked anaplasia (Broders grade 4) were not classified as MEC. The tumor grades were classified as low, intermediate, or high on the basis of the traditional grading criteria of architectural pattern (cystic vs solid), cell type (mucous vs epidermoid), and nuclear pleomorphism. The presence of a predominant solid growth pattern, prominent epidermoid cells, or mild nuclear atypia was sufficient for the diagnosis of intermediate-grade MEC (Figure 1 and Figure 2). High-grade MEC exhibited moderate nuclear pleomorphism within a predominantly epidermoid cell population (Figure 3). With the use of modern immunostains and histologic review, several cases previously designated as high-grade tumors were reclassified appropriately as intermediate-grade tumors. Likewise, a few high-grade tumors that were misclassified as mucoepidermoid carcinomas were eliminated. The following histopathologic features were compiled for their potential relevance in tumor behavior and prognosis: gross size, gross extent, percentage of mucous cells, percentage of epidermoid cells, cystic component, nuclear pleomorphism, necrosis, neural invasion, vascular invasion, desmoplasia, infiltrative borders, lymphoid component, mitotic count, and status of parotid and neck lymph nodes.

We summarized the clinical and pathological features as mean±SD, median and range, or frequency and percentage. We defined the duration of follow-up as starting from the date of the initial histologic diagnosis. We used the Kaplan-Meier method to estimate the overall and cancer-specific survival and survival free of local and regional recurrence and distant metastasis. This study was approved by the Mayo Foundation Institutional Review Board for research.

RESULTS

CLINICAL FEATURES

The study group included 33 male (37%) and 56 female (63%) patients aged 7 to 78 years (mean±SD, 49±17 years; median age, 51.9 years). Five patients were 18 years or
young. A history of smoking was noted in 35 patients (39%), and previous radiation exposure for a condition unrelated to MEC was reported for 10 patients (11%). Presenting symptoms are listed in the following tabulation:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass in parotid region</td>
<td>87 (98)</td>
</tr>
<tr>
<td>Pain or tenderness</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Facial nerve weakness</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Skin ulceration</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Facial twitching</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cervical mass separate from tumor</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

Some patients presented with more than 1 symptom.

PREOPERATIVE EVALUATION AND CLINICAL STAGING

All patients received a thorough head and neck examination. Fine-needle aspiration was performed preoperatively in 4 patients (4%). The diagnosis of MEC was made in only 2 of the 4 aspirate samples. Magnetic resonance imaging, computed tomography, or both was performed in only 10 patients (11%). For 85 patients, the data were adequate for clinical staging of the tumor according to the 2002 classification of the American Joint Committee on Cancer. The disease stage was T1 in 56 patients, T2 in 13, T3 in 1, T4 in 15, N0 in 85, N1 in 2, and N2 in 2. No patient had N3 or M1 disease. Fifty-three patients (62%) presented with clinical stage I disease, 13 (15%) had stage II disease, 2 (2%) had stage III disease, and 17 (20%) had stage IV disease.

PATHOLOGICAL FEATURES

Gross Features

On gross examination, the tumors varied in size from 0.4 to 7.0 cm (median, 1.5 cm). The tumor extended into the facial nerve in 5 patients (6%). The overlying skin was involved in 3 patients (3%) and the surrounding soft tissue or muscle in 10 (11%).

Microscopic Features

A marked cystic component (ie, occupying >50% of the histologic sections examined) was present in 46 specimens (52%). Mucous cells constituted 2% to 90% of the specimens (mean, 28.5%) and epidermoid cells, 0% to 93% (mean, 24.8%). Fifty specimens (56%) had no or minimal nuclear pleomorphism, and 36 (40%) had mild nuclear pleomorphism. A lymphoid background was present in 79 specimens (89%). A mild to marked desmoplastic stromal reaction was noted in all of the specimens. An infiltrative tumor border was noted in 17 specimens (19%) and neural invasion in 13 (13%). No specimen showed vascular invasion. Tumor necrosis was noted in only 1 case.

Tumor Grade

Of the tumors, 43 (48%) were low, 40 (45%) were intermediate, and 6 (7%) were high grade.

Nodal Status

The status of parotid or periparotid nodes could be determined for 86 patients. Six patients (7%) had positive parotid or periparotid nodes, and 3 (3%) had positive neck nodes at the time of initial treatment. In 4 patients with known positive intraparotid nodes, metastatic lymph nodes were also found after neck dissection.

SURGICAL TREATMENT

Conservative total parotidectomy, defined as total removal of the parotid gland with preservation of the facial nerve, was the most common operation (48 patients [54%]). This was performed with neck dissection in 7 patients (8%) and without neck dissection in 41 (46%). The second most common operation, subtotal parotidectomy, was performed in 32 patients (36%), with neck dissection in 2 (2%) and without neck dissection in 30 (34%). Radical parotidectomy with sacrifice of the facial nerve was performed in 9 patients (10%). In all, neck dissection was performed in 15 patients at the time of the primary operation. The extent of neck dissection was select in 10 patients (11%), modified radical in 3 (3%), and radical in 2 (2%). Of these 15 patients, 3 had positive cervical lymph nodes. In the early years of our study period, 4 patients underwent conservative enucleation of the tumor mass without deliberate identification and exposure of the facial nerve. This conservative local excision was later abandoned. Facial nerve function was intact in 71 patients (80%). In 11 patients (12%), selected branches of the facial nerve were resected and grafted as part of complete treatment of their primary disease. Seven patients (8%) had total facial nerve resection without any nerve grafting.

ADJUVANT RADIOTHERAPY

Seven patients (8%) received postoperative radiotherapy, with doses ranging from 50 to 60 Gy. Most of these patients had an intermediate- or high-grade tumor with clinical stage III or IV disease. One patient with stage I and low-grade disease received adjuvant radiotherapy because of close surgical margins.

OUTCOME AND SURVIVAL

The mean duration from first treatment to latest follow-up was 14.7 years (median, 13.8 years; range, 0-36.9 years). At latest follow-up, 64 patients were alive without disease, 1 was alive with disease, 2 had died of MEC, and 22 had died of other causes.

For the 65 patients alive at latest follow-up, the mean ± SD duration from their first treatment to latest follow-up was 14.7 ± 8.7 years (median, 13.8 years; range, 6 months to 36 years). The estimated overall survival for the study group is shown in Figure 4. The estimated overall survival rates at 5, 10, 15, 20, and 25 years after the first treatment were 96.6%, 91.3%, 79.5%, 63.8%, and 54.1%, respectively. The estimated cancer-specific survival rates at 5, 10, 15, 20, and 25 years after the first treatment were 98.8%, 97.4%, 97.4%, 97.4%, and 97.4%, respectively (Figure 5).
In all, disease progression occurred in 5 patients (6%), including 4 local, 4 regional, and 2 distant disease relapses. The histopathologic characteristics of the tumors of these 5 patients did not differ obviously from those of the group as a whole, except for an increased frequency of an infiltrative tumor border (present in 3 of the 5 patients) (Table).

Of these 5, patient 1 presented with clinical stage IVA disease that was treated initially with radical parotidectomy and postoperative radiotherapy. This patient experienced disease relapse in the parotid bed, temporal bone, and ipsilateral neck within 19 months after treatment. Subsequently, the patient underwent excision of the local recurrence, neck dissection, and chemotherapy but died approximately 18 months later. Patient 2 presented with clinical stage II disease that was treated with conservative total parotidectomy. Regional recurrence to the ipsilateral neck occurred 9 months later and a neck dissection was performed. Nearly 12 years later, the patient died of a cause unrelated to MEC. Patient 3 presented with clinical stage IVA disease that was treated with conservative total parotidectomy. However, the disease recurred in the parotid bed and neck 6 months later and was treated with local resection and neck dissection. However, about 41/2 years later, biopsy results confirmed metastasis to the liver. The patient received chemotherapy but died 14 months later. Patient 4 presented with clinical stage I disease that was treated with conservative total parotidectomy; 41/2 years later, recurrent disease in the parotid bed was excised. The patient was alive without evidence of disease 51/2 years later. Patient 5 presented with clinical stage IVA disease that was treated with radical parotidectomy, radical neck dissection, and postoperative radiotherapy. However,

![Figure 4. Overall survival of 89 patients with mucoepidermoid carcinoma.](image)

![Figure 5. Cancer-specific survival of 89 patients with mucoepidermoid carcinoma.](image)

<table>
<thead>
<tr>
<th>Clinical and Pathological Features of 5 Patients With Disease Progression</th>
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<tbody>
<tr>
<td>Patient No. (Age, y/Sex)</td>
</tr>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>Clinical stage</td>
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<tr>
<td>Type of first treatment</td>
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<tr>
<td>Recurrence</td>
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<tr>
<td>Outcome</td>
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<tr>
<td>Pathological T stage</td>
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<tr>
<td>Mayo grade</td>
</tr>
<tr>
<td>Cystic component*</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
</tr>
<tr>
<td>Mucous cells, %</td>
</tr>
<tr>
<td>Epidermoid cells, %</td>
</tr>
<tr>
<td>Neural invasion</td>
</tr>
<tr>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Infiltrative border</td>
</tr>
<tr>
<td>Necrosis</td>
</tr>
<tr>
<td>Mitosis per HPF magnification ×10</td>
</tr>
<tr>
<td>Gross size, cm</td>
</tr>
<tr>
<td>AFP grade, points/grade†</td>
</tr>
<tr>
<td>Brandwein grade, points/grade‡</td>
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</tbody>
</table>

Abbreviations: AFIP, Armed Forces Institute of Pathology; ANED, alive with no evidence of disease; CTP, conservative total parotidectomy; DOC, dead of other cause; DOD, dead of disease; HPF, high-power field; RND, radical neck dissection; RP, radical parotidectomy; RT, radiotherapy.

*Greater than 50% indicates marked; 10% to 20%, mild; and greater than 20% to 50%, moderate.

†Described by Goode et al.5

‡Described by Brandwein et al.8
disease recurred in the parotid bed and neck at 9 and 16 months, respectively. Also, results of a biopsy confirmed distant metastases to the skin of the lower back. All sites of recurrence were widely excised and the patient was alive with no evidence of disease after more than 20 years of follow-up. Thus, only 2 of these 5 patients died of mucoepidermoid carcinoma, and both of them had locoregional recurrence of disease.

The Kaplan-Meier estimated rates of survival free of local recurrence rate at 5, 10, 15, and 25 years after the first treatment were 96.6%, 95.2%, 95.2%, and 95.2%, respectively (Figure 6). The estimated rates of survival free of regional recurrence at 5, 10, 15, and 25 years after the first treatment were 95.4%, 94.1%, 94.1%, and 94.1%, respectively (Figure 7). The estimated rate of survival free of distant metastases at 5, 10, 15, and 25 years after the first treatment was 97.6% (Figure 8).

Survival analysis for individual clinical and pathological features (age, sex, grade, clinical stage, nodal status, and type of surgical treatment) was not possible because of the small number of adverse events. None of the 6 patients who had high-grade MEC experienced disease progression.

**COMMENT**

Mucoepidermoid carcinoma is the most frequently diagnosed malignancy of the salivary gland. Among the major salivary glands, the parotid gland is most commonly involved. Our study has documented the Mayo Clinic experience with 89 cases of MEC occurring in the parotid gland. We sought to examine the relation of tumor grade and stage and type of treatment with clinical outcome. However, even with prolonged follow-up, disease progression occurred in only 5 patients, resulting in 2 deaths.

Consistent with other reports, MEC occurred most frequently between the third and fifth decades of life (mean age, 49 years) in our patients. Our youngest patient was 7 years. Similar to other series that have shown a slight female preponderance, female patients were affected 1.7 times more often than male patients in our series.

Specific etiologic factors for MEC were not evident in our study. Several reports have implicated exposure to ionizing radiation, with latency periods ranging from 7 to 32 years. Ten patients in our series had previous radiation to the head and neck as part of the treatment for unrelated diseases such as acne and thyroid disease. Unlike squamous cell carcinoma of the oropharynx, in which smoking has been implicated as a strong risk factor, smoking has not been shown to be strongly associated with MEC. In our series, there was a predominance of nonsmokers compared with current or previous smokers (44 vs 33 patients). Mucoepidermoid carcinomas of the parotid gland characteristically present as a painless mass 2 to 3 cm in diameter at initial discovery. With high-grade lesions, pain and rapid growth can be prominent. Without pain or facial weakness, pleomorphic adenoma is usually the first clinical impression. This may result in undertreatment when one is not guided by pathological findings of frozen-section analysis. In our series, all of the patients presented with a 0.4- to 7.0-cm mass in the parotid gland. Only 15% of patients had pain or tenderness, and only 1 had palpable cervical adenopathy at initial presentation. Marked cystic features constituting more than 50% of the histologic section were encoun-
tered in more than half of the tumors. Thus, cystic lesions identified in the parotid gland during physical examination or on ultrasonography should not be dismissed as benign lesions. Preoperative fine-needle aspiration may yield a diagnosis of malignancy and facilitate preoperative surgical planning. Nevertheless, fine-needle aspiration is not required in all cases and was performed in only 4 of our patients. The routine use of imaging studies is debated, and magnetic resonance imaging or computed tomography was performed in only 10% of our patients. We find that imaging studies are useful when the full extent of the tumor cannot be palpated, when tumor infiltration into adjacent structures is suspected clinically, or when the likelihood of regional lymph node spread is high.

Since MEC was first described, various grading schemes have been proposed. Some pathologists have classified MEC into low- and high-grade types, but more recently most have used a 3-tiered grading system that includes an intermediate grade. Even so, tumor grade is dependent on the interpretation of the pathologist, and, as pointed out recently, uniform interpretation is lacking when different pathologists grade MEC. Also, disagreement remains about the appropriate upper boundary of nuclear anaplasia acceptable for diagnosis of MEC.

In our study, we classified tumors as low, intermediate, or high grade on the basis of traditional grading criteria. We specifically excluded fully anaplastic tumors (severe or marked nuclear atypia [Mayo grade 4]) that others might have classified as high-grade MEC. Most of our cases were low- or intermediate-grade MEC, and only 7% were high-grade lesions, which is lower than the percentage reported in other series. The inclusion of anaplastic carcinomas in the category of high-grade MEC in other studies may have affected the statistical relation between grade and survival. We were unable to confirm statistically a multitude of histologic variables that have been regarded as potentially important in grading and clinical outcome. This is at variance with what others have reported. We attempted to apply histlogic grades as recommended by Goode et al and Brandwein et al to cases of MEC that had disease progression, but because of the low number of adverse events, we could not statistically compare the predictive value of these grading schemes. Many studies that examined the relation between MEC histologic grade and clinical outcome included major and minor tumors of the salivary gland. However, the clinical behavior of MEC may vary by site. Certainly, the treatment of MEC and the ability to obtain tumor-free margins vary by site, as does the distribution of tumor grade and stage. Minor salivary glands are more likely to have higher-grade MECs and more advanced stage tumors, and a minor salivary gland site itself may be associated with worse survival. Therefore, comparison of high- and low-grade lesions may show worse survival for the former because of a greater proportion of minor salivary gland sites with high-grade lesions. For these reasons, when analyzing the clinical behavior and outcome of patients with MEC, the data must be analyzed independently by site.

Several studies have shown that staging parotid gland lesions, including MEC, according to the American Joint Committee on Cancer is predictive of survival. However, in a review of MEC of major and minor salivary glands, Spiro et al found a preponderance of low-grade tumors in patients with lower-stage disease. Therefore, the finding of better survival for patients with lower-grade lesions may be a case of confounding variables, whereby lower-grade lesions are associated with better survival only because they are associated with less advanced disease stage.

In our series, only 5 patients had disease progression. We examined the clinical and histopathologic features of this group, checking for characteristics that might distinguish them (Table). All 5 patients (3 women and 2 men) ranged in age from 42 to 53 years. In the study of malignant salivary tumors by O’Brien et al, patients younger than 60 years fared better than older ones. In addition, they found no significant difference between male and female patients. Their study, however, included major and minor tumors of the salivary gland from all sites and all histologic subtypes. We were not able to perform survival analysis for age and sex because of the limited number of adverse outcomes in our series. Of interest, all 5 patients with disease progression had intermediate-grade (grade 2) lesions. The histologic features in various grading systems include the degree of nuclear pleomorphism, proportion of the cystic component, mitotic rate, presence or absence of necrosis, neural invasion, vascular invasion, and infiltrative tumor borders. Although the numbers are small, we could not discern a significant difference between this group of 5 patients and the rest of the study group except for a tendency toward more infiltrative tumor borders (3 of the 5 tumors). However, an assessment for the presence or absence of infiltrative tumor borders, as suggested by Brandwein et al, may be important; the tumor in 3 (60%) of the 5 patients with disease progression exhibited this feature, in contrast to 14 (17%) of the 84 patients without disease progression.

Among the 5 patients with disease progression, 3 had stage IVA, 1 had stage II, and 1 had stage I disease. The 2 patients who died of MEC presented with clinical stage IV disease. Survival analysis for tumor grade and disease stage was not possible because of the small number of adverse events.

Further analysis of the recurrences showed that most were locoregional, with distant recurrence occurring in only 2 patients (Table). Others have found a greater proportion of distant recurrences, but even in those studies most of the patients with distant recurrence also had concomitant locoregional recurrence or had experienced multiple locoregional recurrences. Thus, our small number of distant recurrences may be related to the lower number of locoregional recurrences.

The other important variable affecting survival is adequacy of surgical excision margins. Patients with positive margins are more likely to have locoregional recurrence, regardless of tumor grade, than those with negative resection margins. Nonetheless, the relation between the type of surgical treatment for MEC and survival has not been clearly examined. However, a higher proportion of patients in our study appear to have had total parotidectomy than occurred in other studies. For instance, in the series of 63 cases of parotid MEC re-
ported by Jakobsson et al, only 5 patients underwent what could be termed parotidectomy. The study of Healey et al included 42 patients with parotid MEC, only 11 of whom underwent total parotidectomy, and as many as 12 underwent less than a superficial parotidectomy. In the series of Spiro et al, 48 patients underwent enucleation alone and 82 underwent subtotal parotidectomy that spared the facial nerve. Other types of operations have been performed less often.

In contrast to these reports, most patients treated at Mayo Clinic underwent conservative total parotidectomy, whereby all parotid tissue was removed and the facial nerve was preserved. This was the procedure of choice for high-grade tumors. Partial or total facial nerve resection was performed when there were intraoperative findings of gross nerve involvement. In addition, conservative total parotidectomy was performed for low- and intermediate-grade tumors when frozen-section evidence indicated involvement of intraparotid nodes. In patients with clinical N0 disease, selective nodal dissection addressing high and midjugular nodes was performed for high-grade tumors and other tumors with positive intraparotid nodes. We believe that this type of aggressive treatment may well account for the few treatment failures in our series. This approach allows complete removal of the primary tumor and all possible metastatic foci to intraparotid nodes. Moreover, the functional status of the facial nerve was completely preserved in 80% and partially preserved in 12%. Two cases illustrate this treatment approach. First, an 11-year-old boy presented with a slowly growing parotid mass noted during the course of 5 years. He was completely asymptomatic and had clinical N0 neck findings. Superficial parotidectomy completely removed the parotid tumor. Results of frozen-section analysis showed a low- to intermediate-grade mucoepidermoid carcinoma with 1 positive intraparotid node. A conservative total parotidectomy with selective neck dissection addressing high and midjugular nodes was then completed. This revealed a positive intraparotid node in the deep lobe. The neck nodes were all negative. In the second case, a 67-year-old woman presented with a 2-cm parotid mass completely excised with a superficial lobe parotidectomy. Results of frozen-section analysis revealed an intermediate-grade lesion with 1 positive intraparotid node. A conservative total parotidectomy was then completed, but no additional positive intraparotid nodes were identified. A selective neck dissection was then performed and yielded 2 metastatic nodes.

The small number of treatment failures in our series limits our power to detect differences in survival according to grade, tumor stage, type of surgical treatment, and other variables. It suggests that if MEC is treated aggressively with conservative total parotidectomy, tumor grade and stage become less important for predicting survival because of uniformly excellent disease control. Furthermore, most recurrences in our series were in the parotid bed, which attests to the need for adequate control at the initial operation. Generally, patients who die of MEC have distant metastases, but they also usually have associated locoregional recurrence. In our study, only 4 patients had clinically positive nodes. Nonetheless, 15 underwent neck dissection (mostly selective neck dissection). There were no cases of contralateral nodal metastases at initial presentation, and all regional recurrences were in the ipsilateral neck. The rate of nodal metastases in MEC varies depending on the series, but it appears to be a predictor of survival. Not unexpectedly, the inclusion of tumors with anaplastic features as high-grade MEC would lead to the finding of more patients with cervical lymph node metastases.

There appears to be a further decrease in survival as patients are followed up beyond 5 years. This has been pointed out by others and stresses the importance of adequate follow-up.

CONCLUSIONS

For low- and intermediate-grade parotid MEC with a primary lesion adequately excised by means of subtotal parotidectomy, if the intraparotid nodes in the superficial lobe are negative, then the deep lobe and neck nodes do not need further treatment. If any intraparotid node is positive, the deep lobe should be addressed with a conservative total parotidectomy along with a selective neck dissection. Also, a dissection of regional lymph node basins should be performed in cases of suspicious adenopathy and in those with more advanced-stage and high-grade lesions. When treated in this fashion, parotid MEC appears to be a highly curable disease. Nonetheless, follow-up should continue for an extended time to rule out late recurrence.

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