Mucoepidermoid Carcinoma of the Parotid Gland Treated by Surgery and Postoperative Radiation Therapy: Clinicopathologic Correlates of Outcome

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**Objectives/Hypothesis:** To determine clinical and pathological correlates of outcome among patients treated by surgery and postoperative radiation therapy for mucoepidermoid carcinoma of the parotid gland.

**Study Design:** Retrospective review.

**Methods:** The medical records of 61 patients treated by surgery and postoperative radiation therapy for localized mucoepidermoid carcinoma of the parotid gland were retrospectively reviewed in an attempt to identify clinicopathologic correlates of overall survival. Secondary endpoints included local-regional control, distant metastasis-free survival, and complications.

**Results:** The 3- and 5-year estimates of overall survival were 85% and 79%, respectively. Multivariate analysis identified high tumor grade (hazard ratio [HR] = 7.92) and T4 disease (HR = 3.35) as independent predictors of decreased survival, with the former also predicting for distant metastasis and the latter predicting for local-regional recurrence. The 5-year estimate of overall survival was 83% for patients with non-high-grade tumors, compared to 52% for those with high-grade histology ($P = 0.001$). Late complications included trismus (2 patients), osteoradionecrosis (1 patient), and hearing loss (1 patient).

**Conclusion:** Patients with high-grade tumors and T4 disease are at increased risk for treatment failure after surgery and postoperative radiation therapy for mucoepidermoid carcinoma of the parotid gland. Investigative strategies to improve outcome should be considered for these particular patients in the future.

**Key Words:** Mucoepidermoid carcinoma, radiation, salivary gland cancer, parotid gland.

**Level of Evidence:** 4.

**INTRODUCTION**

Initially described by Stewart et al. in 1945 and named for its classic histological appearance consisting of a mixed pattern of epidermoid and mucus-producing cell types, mucoepidermoid carcinoma represents the most common malignant tumor of the parotid gland.1–3 Although once classified as a benign tumor, mucoepidermoid carcinoma of the head and neck is in fact characterized by its widely diverse biologic behavior. For nearly all patients surgery forms the mainstay of treatment.

While some prognostic factors predicting for disease recurrence, including advanced T stage, high histological tumor grade, positive surgical margins, and lymph node metastasis have been identified for patients treated by resection, there is limited data analyzing clinicopathologic correlates of outcome among patients treated by surgery followed by postoperative radiation therapy.4–6 This is particularly pertinent because the use of a combined modality approach for carcinomas of the salivary glands has become increasingly accepted with the publication of several single-institutional series in the 1970s demonstrating improved rates of local-regional control among selected patients with the addition of postoperative radiation therapy.7–9 This study was undertaken to determine clinical and pathological characteristics predictive of outcome for patients treated by surgery and postoperative radiation therapy for mucoepidermoid carcinoma of the head and neck.

**MATERIALS AND METHODS**

**Patient Population**

This study was approved by the Institutional Review Boards at the University of California, Davis, prior to the collection of all patient information. A retrospective review of patient records identified 75 adult patients with a histological diagnosis of mucoepidermoid carcinoma of the parotid gland who were treated with radiation therapy from 1998 to 2008 at the University of California, Davis, School of Medicine. Nine patients treated with radiation therapy alone for surgically or medically inoperable disease; and five patients were treated with radiation therapy for gross residual disease after subtotal resection.
were excluded. The remaining 61 patients who had gross total tumor resection and underwent postoperative radiation therapy for newly diagnosed mucoepidermoid carcinoma of the parotid gland comprised the primary population of this study. No patient had evidence of distant metastatic disease at diagnosis. The median age was 60 years (range, 30–94 years). Thirty-six patients (56%) were male.

Computed tomography (CT) of the head and neck was performed in all patients. Fifteen patients (25%) underwent magnetic resonance imaging (MRI) of the head and neck. Tumors were staged in accordance with the 2009 American Joint Committee on Cancer (AJCC) staging system for major salivary glands. As outlined in Table I, the Armed Forces Institute of Pathology (AFIP) system for mucoepidermoid carcinoma, as defined by Goode et al.,10 was the grading scheme utilized during the period of this study. Other pathological characteristics such as pathological T stage, margins, bone invasion, and muscle invasion were also extracted from the pathology reports at the time of initial treatment. The most common reasons for T4 disease were facial nerve involvement, skull base invasion, extension to the auditory canal, and skin involvement, with most patients having multiple adverse risk features.

### Treatment

All patients underwent definitive resection followed by postoperative radiation therapy. The operative procedure was dependent on the location of the cancer, extent of disease, and the discretion of the surgeon. Procedures included superficial parotidectomy (35 patients), total parotidectomy (20 patients), and local excision (6 patients). Gross total tumor resection was the goal of surgery in all cases, with careful consideration given to cosmetic and functional outcome. Frozen-section analysis was routinely obtained, and all attempts were made to achieve microscopically negative margins. Resection of adjacent muscle and bone was indicated when the tumor extended into these structures. Cancers that involved the skull base and/or deep lobe of the parotid gland with extension into the parapharyngeal space often required skull base procedures. Lateral temporal bone resection was performed in 17 patients (28%). The use of a prosthetic obturator or microvascular free-tissue transfer to close a surgical defect occurred in 10 cases (16%). Although the facial nerve was preserved whenever possible, resection occurred in 11 patients (18%) when the nerve was grossly encased or involved with cancer. Reconstructive techniques using nerve grafts were attempted in five cases (8%).

No definite policy existed regarding adjuvant therapy, but in general patients were referred for radiation therapy in the presence of high-risk pathological features such as lymph node involvement, soft tissue extension, and perineural or lymphovascular space invasion—or when there was uncertainty about the completeness or adequacy of the excision based on intraoperative and pathological findings. The majority of patients were presented before a multidisciplinary head and neck tumor board held weekly at our institution. The interval between surgery and the start of radiation therapy ranged from 5 to 65 days (median, 29 days). All patients were irradiated with megavoltage equipment using photons or mixed photons and electrons. Radiation therapy techniques included wedged-pair fields (21 patients), mixed photon-electron appositional fields (11 patients), and 3-field isocentric treatments (6 patients). Intensity-modulated radiation therapy (IMRT) was used for 23 patients. Median dose was 60 Gy (range, 50–70 Gy).

Three patients (5%) presented with palpable lymphadenopathy (all upper jugular). All of these patients underwent neck dissection followed by postoperative radiation for pathologically confirmed tumor. Prophylactic neck dissection of the clinically negative (N0) neck was performed for 39 patients, with eight of these patients having evidence of occult histological disease. An additional 19 patients with clinically N0 necks were treated with elective neck irradiation (ENI) to a median dose of 50 Gy (range, 45–60 Gy). Among the entire population, 11 patients (18%) had pathological lymph node metastasis.

### Endpoints and Statistical Analysis

Median follow-up was 45 months (range, 6 to 101 months). Tests of association for categorical variables were performed using a chi-square statistic. Three- and 5-year estimates of the probability of overall survival, local-regional control, and distant metastasis-free survival were calculated using the Kaplan-Meier method, with comparisons among groups performed with two-sided log-rank tests. A Cox proportional hazards model was used to identify independent predictors of mortality. A stepwise forward method was carried out, and the likelihood ratio test (LLR) was used to identify significant independent predictors of outcome. Hazard ratio parameters were determined using the Wald test. All tests were two-tailed, with a probability value of less than 0.05 considered statistically significant.

### RESULTS

#### Overall Survival

Disease characteristics for the primary population are outlined in Table II. Overall survival at 3 and 5 years was 85% and 79%, respectively. Univariate analysis of the clinical and pathological variables analyzed revealed that high tumor grade, T4 disease, and pathological lymph-node metastasis predicted for decreased survival. The 5-year estimates of overall survival for patients with low, intermediate, and high-grade tumors were 84%, 80%, and 52%, respectively ($P = 0.08$). When this analysis was repeated for non-high-grade versus high-grade disease, a statistically significant difference was observed (83% vs. 52%, $P = 0.001$). When patients with T1–T3 disease were compared to those with T4 disease, a statistically significant difference was detected (78% vs. 63%, $P = 0.01$). Additionally, the subset of patients with pathological lymph node metastasis at diagnosis had inferior survival, with 55% alive at 5 years compared to 77% for those without lymph node involvement ($P = 0.01$).
Although lymph node involvement appeared to predict strongly for decreased survival on univariate analysis, this feature was highly associated with patients having T4 disease (7 of 11 patients, $P = 0.004$) and high-grade tumors (9 of 11 patients, $P = 0.001$). None of the other variables analyzed predicted for overall survival.

A multivariate analysis of the entire patient sample was performed using a Cox proportional hazard model considering T stage (T1–T3 vs. T4), histological grade (high-grade vs. non-high grade), and pathological lymph node metastasis as possible predictors of decreased survival. High tumor grade and T4 disease were identified as independent predictors of decreased survival in that order (LLR test: $P = 0.0001$ and 0.02, respectively). The hazard ratios for mortality among those treated with high-grade tumors and with T4 disease were 7.92 (95% confidence interval: 4.73–14.80) and 3.35 (95% confidence interval: 1.72–8.33), respectively. Figures 1 and 2 depict overall survival for the patient population according to tumor grade and T stage, respectively.

Local-Regional Control

For the entire patient population, the 3- and 5-year estimates of local-regional control were 89% and 84%, respectively. The median time to local-regional recurrence was 26 months (range, 6 to 75 months) with all but one of the local-regional recurrences occurring within 5 years from diagnosis.

On univariate analysis, T4 disease was predictive of local-regional recurrence. The 5-year rates of local-regional control for patients with T1, T2, T3, and T4 tumors were 92%, 83%, 83%, and 64%, respectively ($P = 0.09$). When this analysis was repeated for T1–T3 versus T4 disease, a statistically significant difference was observed. As illustrated in Figure 3, the 5-year estimate of local-regional control was 88% for patients with T1–T3 tumors versus 64% for those with T4 tumors ($P = 0.001$). The 5-year estimates of local-regional control were 85% for patients with low-grade tumors, 84% for patients with intermediate-grade tumors, and 79% for patients with high-grade tumors, respectively ($P = 0.24$). None of the other clinical or disease characteristics analyzed predicted for local-regional control ($P > 0.05$, for all).

### TABLE II. Disease Characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Patients (%)</th>
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<tbody>
<tr>
<td>Pathological T-stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>14 (23)</td>
</tr>
<tr>
<td>T2</td>
<td>14 (23)</td>
</tr>
<tr>
<td>T3</td>
<td>14 (23)</td>
</tr>
<tr>
<td>T4</td>
<td>19 (31)</td>
</tr>
<tr>
<td>Margins</td>
<td></td>
</tr>
<tr>
<td>Positive or close (&lt;1mm)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Negative</td>
<td>52 (85)</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>33 (54)</td>
</tr>
<tr>
<td>Negative</td>
<td>28 (46)</td>
</tr>
<tr>
<td>Bone invasion</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Negative</td>
<td>55 (90)</td>
</tr>
<tr>
<td>Muscle invasion</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Negative</td>
<td>51 (84)</td>
</tr>
<tr>
<td>Pathological lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (16)</td>
</tr>
<tr>
<td>No/unknown</td>
<td>51 (84)</td>
</tr>
<tr>
<td>Histological tumor grade</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>19 (31)</td>
</tr>
<tr>
<td>High</td>
<td>24 (40)</td>
</tr>
</tbody>
</table>

Although lymph node involvement appeared to predict strongly for decreased survival on univariate analysis, this feature was highly associated with patients having T4 disease (7 of 11 patients, $P = 0.004$) and high-grade tumors (9 of 11 patients, $P = 0.001$). None of the other variables analyzed predicted for overall survival.

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**Fig. 1.** Overall survival according to histological tumor grade. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Distant Metastasis

Distant metastases developed in 20 patients, 14 of which were isolated events. Initial sites of distant failure were: 16 lung, three bone, and one liver. Median time to the development of distant metastasis was 20 months (range, 6–70). The 3- and 5-year estimates of distant metastasis-free survival were 78% and 70%, respectively. High histologic grade and pathological lymph node metastasis was associated with a significantly greater occurrence of distant metastases. As illustrated in Figure 4, the 5-year distant metastasis-free survival was 87% for patients, with non-high grade tumors compared to 47% for those with high-grade tumors ($P = 0.001$). The 5-year estimate of distant metastasis-free survival for patients with and without pathological lymph node metastasis was 57% and 80%, respectively ($P = 0.03$).

Complications

One patient treated by superficial parotidectomy and postoperative radiation therapy to 70 Gy using wedged-pair fields experienced osteoradionecrosis at approximately 2 years after treatment and was referred for hyperbaric oxygen, but ultimately required surgical debridement. Two additional patients with parotid gland cancers developed varying degrees of trismus at 3 and 6 months after treatment, respectively. These patients were treated by total parotidectomy with lateral
temporal bone resection for T4 tumors, followed by 66 Gy using mixed photon-electron fields. Both were managed with conservative measures including physical therapy and experienced subjective improvement of symptoms.

**DISCUSSION**

The observed rates of disease control are relatively encouraging despite the fact that this study of patients, treated by surgery and postoperative radiation therapy for mucoepidermoid carcinoma of the parotid gland, includes a heterogeneous group with respect to clinical and pathological characteristics. Although we did not include patients treated by surgery alone in this retrospective report, and thus could not specifically compare the outcome of those treated with and without postoperative radiation therapy, others have shown that the addition of adjuvant radiation therapy results in significant improvements in local-regional control and/or overall survival in select patients with salivary gland carcinomas.13–15 Attempts to compare the outcomes of patients treated by surgery and postoperative radiation therapy to those treated by surgery alone for salivary gland cancers are inherently confounded by selection bias. This is such because patients treated with postoperative radiation therapy tend to have more advanced tumors and a higher incidence of positive margins, unfavorable histology, and lymph node metastasis—features that have generally been accepted as predicting for disease failure after definitive treatment. In the present series, the incidence of T3–T4 disease, positive or close margins, high tumor grade, and lymph node metastasis was 54%, 15%, 40%, and 18%, respectively. Of note, these percentages are substantially higher than those reported by series limited to patients treated by surgery without postoperative radiation therapy.16–19 Despite the obvious selection bias toward more adverse prognostic features among patients treated by a combined modality approach for mucoepidermoid carcinoma of the parotid gland, our results demonstrating a 5-year local-regional control rate of 84% compare favorably to those of series detailing the outcomes of patients treated by surgery alone. For instance, investigators from the University of California, San Francisco, previously reported 5- and 10-year local-regional control rates of 86% and 74% among 207 patients with salivary gland carcinomas, including 67 with mucoepidermoid histology treated by surgery alone.18 In that study, patients with T3–T4 disease, positive margins, high tumor grade, or positive lymph nodes had significantly inferior disease control with the presence of any one of these factors, resulting in 10-year local-regional control rates of only 37% to 63%. In the only series that has compared surgery versus surgery and postoperative radiation therapy, Hosokawa et al. demonstrated that none of the patients with positive margins after surgery alone for mucoepidermoid carcinoma achieved local control, compared to 63% among those treated with postoperative radiation therapy.19

The literature reporting on clinical outcomes after surgery and postoperative radiation therapy for patients with mucoepidermoid carcinoma of the head and neck is relatively sparse and complicated by the fact that most published series have not analyzed this disease as a separate entity, preferring instead to group this histology with all salivary gland cancer subtypes. Although Mendenhall et al. reported a 10-year local-regional control rate of 81% among a large series of salivary gland cancer patients treated with surgery and postoperative radiation therapy, only about a quarter of this population had mucoepidermoid histology.20 Garden et al. also reported a 10-year local control rate of 90% among 166 salivary gland carcinoma patients, 46 of whom had mucoepidermoid carcinomas, treated by surgery and

![Fig. 4. Distant metastasis-free survival according to tumor grade.](image-url)
postoperative radiation therapy. In another analysis of 27 patients with mucoepidermoid carcinoma of the head and neck treated at the University of California, San Francisco, 23 of 27 patients (85%) achieved disease control, including seven of seven patients (100%) treated by surgery and postoperative radiation therapy. However, it must be recognized that this report, initially published by Fu et al. in 1977, was based almost entirely on patients with what are now considered low-risk disease characteristics, as made evident by the documented 10-year overall survival of 96%. For instance, the vast majority of patients in that series presented with T1–T2 cancers, and only four of the 27 patients had high-grade tumors.

On multivariate analysis, we identified high tumor grade and T4 disease as predictive of decreased survival among patients treated by surgery and postoperative radiation for mucoepidermoid carcinoma. This finding is in accordance with the results of others. Bhattacharyya et al. similarly showed that tumor grade and extraglandular extension were the most important predictors of survival among 367 patients treated for mucoepidermoid carcinoma of the parotid gland. Pires et al. reviewed the records of 173 patients surgically treated for mucoepidermoid carcinoma, half of who received postoperative radiation therapy, and also identified T stage and histological grade as significant prognostic variables. The 10-year overall survival was 73% and 37% for patients with T1–T2 tumors and T3–T4 tumors, respectively. For low, intermediate, and high grade tumors, the respective overall survival rates were 88%, 66%, and 23%. The profound influence of grade on survival among patients with mucoepidermoid carcinoma was further illustrated by two recently published studies. Suzuki et al. reported a 5-year survival of 100% among patients with low or intermediate grade tumors compared to 0% for those with high grade tumors. Kokenmueller et al. also reported 10-year survival rates of 82% and 0% for patients with high and low grade mucoepidermoid carcinomas, respectively.

The incidence of occult lymph node involvement in the present series is consistent with those reported by others for mucoepidermoid carcinoma of the head and neck. Although the relatively small number of patients who were treated with elective neck dissection or ENI makes it difficult to draw definitive conclusions, our finding that 89% of the regional relapses occurred among those with high-grade tumors and clinically N0 necks treated without ENI suggests that these patients may benefit from neck treatment. Hicks et al. also reported that 75% of patients with high-grade mucoepidermoid carcinoma had pathological lymph node metastasis. Our current policy regarding elective neck treatment is to evaluate each case on an individual basis, considering the grade and extensiveness of the primary tumor.

Lastly, considerable controversy exists regarding the histological grading of mucoepidermoid carcinomas. Although the various schemes that have been proposed are all based primarily on the prevalence of cell types and cystic areas and on the features of cellular atypia, a substantial amount of subjectivity exists. The AFIP criteria used in the present series relies on numerical scores given to histological features such as cystic component (<25%), mitosis per 10 high-power fields (>4), tumor necrosis, neural invasion, and nuclear/cellular atypia—and attempts to classify tumors into low, intermediate, and high grade cases based on the presence or absence of these characteristics. It is essential to recognize that even though this system has been validated by some investigators to possess prognostic significance for those treated by surgery alone, others have not confirmed its utility. Consequently, several classification schemes have been proposed and are currently used in the grading of mucoepidermoid carcinoma. To complicate matters further, the grading guidelines endorsed by the World Health Organization (WHO) stratify tumors into only two grades, eliminating the intermediate designation used by the AFIP. Historically, some have also suggested that high-grade mucoepidermoid carcinoma be reclassified as squamous cell carcinoma. Regardless of these dilemmas, the current study is notable because to our knowledge it is the first to demonstrate the utility of the AFIP system in predicting prognosis for patients treated with a combined modality approach using surgery and postoperative radiation therapy for mucoepidermoid carcinoma.

CONCLUSION

While subject to the usual limitations of any retrospective study, the present series identified high-grade histology and T4 disease as adverse prognostic indicators after treatment by surgery and postoperative radiation therapy for mucoepidermoid carcinoma of the parotid gland. Strategies to improve outcome should focus on patients with these features in the future. In particular, the potential role of radiation dose-escalation, possibly in conjunction with the use of biological and chemical modifiers, remains to be determined. The high incidence of distant metastases, especially among those with high-grade tumors, underscores the need for effective systemic therapies.

BIBLIOGRAPHY


