Effects of Initial Treatment on Disease Outcome for Patients With Submandibular Gland Carcinoma

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Objective: To elucidate the effect on outcome of initial surgical enucleation with or without definitive surgical resection and radiation therapy for patients with submandibular gland carcinoma.

Design: Retrospective clinicopathological review.

Setting: Tertiary referral center.

Patients: Eighty-seven consecutive patients (mean follow-up, 8.7 years) with primary submandibular gland carcinoma.

Main Outcome Measures: Review of proven cases of primary carcinomas of the submandibular gland treated at our institution during a 33-year period to determine the effect of the type of biopsy and subsequent treatment on locoregional disease control, disease-specific survival, and overall survival.

Results: There was no statistically significant difference in locoregional disease control, disease-specific survival, or overall survival between patients undergoing enucleation of the gland vs patients undergoing enucleation of the gland followed by definitive surgical resection before any radiation therapy. There were no locoregional recurrences among 28 patients treated with enucleation and radiation therapy, compared with 3 locoregional recurrences (7%) among 42 patients treated with enucleation followed by definitive surgical resection before any radiation therapy. Twenty-nine (69%) of 42 patients undergoing a second surgical procedure had evidence of residual carcinoma in the final surgical specimen.

Conclusions: En bloc surgical resection followed by radiation therapy remains the standard treatment for patients with submandibular gland carcinoma. Patients without clinical and radiographic evidence of disease after enucleation may be adequately treated with subsequent radiation therapy. Definitive surgical resection remains the treatment of choice for patients with clinical or radiographic evidence of disease after enucleation of the gland.
tors, and effect of different treatment modalities on survival in a prospective manner.\textsuperscript{11-13}

Not uncommonly, patients with a submandibular gland mass undergo initial enucleation biopsy of the gland before establishment of a diagnosis of cancer and referral for definitive treatment. Previous patterns of presentation to tertiary cancer centers demonstrate that about half the referred patients have already undergone prior excision of the submandibular gland on the presumption that the involved process was benign.\textsuperscript{7} How the initial surgical management affects outcome and the benefit of reoperation on local disease control and survival are unclear. Oftentimes, parallels to protocols for parotid carcinoma are used to direct the treatment plan. The aim of this retrospective study was to determine the effect of the initial surgical procedure and subsequent treatment on locoregional disease control and outcome for submandibular gland carcinoma.

**METHODS**

Consecutive patients treated for primary submandibular gland carcinoma at The University of Texas M. D. Anderson Cancer Center, Houston, between January 1970 and December 2003, were eligible for review. Patients were identified through a database maintained in the Department of Head and Neck Surgery. Institutional review board approval was obtained before medical record review.

When initially seen at our institution, all patients were reevaluated by clinical examination and by high-resolution computed tomographic imaging or magnetic resonance imaging. Ultrasonography of the neck is also used to supplement any equivocal radiographic findings. All cases were then reviewed by our multidisciplinary board for treatment recommendations. The type of treatment received depended on any previous therapy and the disease status at the time of referral. Patients without clinical and radiographic evidence of residual primary or nodal disease were referred for definitive radiation therapy. Patients with clinical or radiographic evidence of residual primary or nodal disease underwent definitive surgical resection based on the site of the disease before radiation therapy. In addition, patients with operative notes suggesting piecemeal removal or grossly positive margins underwent definitive surgical resection before radiation therapy.

Criteria for postoperative radiation therapy included histological grade, extraglandular spread, positive surgical margins, perineural invasion, and positive lymph node involvement. Radiation portals were tailored to each individual case and were based on the site and extent of disease. A mean dose of 60 Gy was administered to the tumor bed, with supplemental dosing for patients with poor prognostic factors. When indicated, radiation portals included involved neural pathways to their respective foramina in the skull base.

All pathological data were compiled from the initial medical record review and are reported hereinafter. The cases were then reviewed by one of us (A.K.E.), with the histopathological diagnosis, margin status, presence or absence of perineural invasion, and lymph node status confirmed or reassigned using current histological criteria for salivary gland tumors.\textsuperscript{14} Clinical staging of disease was performed using the 2002 American Joint Committee on Cancer staging system, which considers tumor size, local extension, lymphatic spread, and distant metastases.\textsuperscript{15}

All clinical data were obtained from patient medical records, referring physician correspondence, and autopsy reports.

**RESULTS**

Eighty-seven consecutive patients (50 men and 37 women [mean age, 53.4 years]) with primary submandibular gland carcinoma were included for analysis. The mean follow-up time was 8.7 years. Adenoid cystic carcinoma was the most frequent malignancy encountered (Table 1), and there was a wide range of overall disease stages at the initial presentation (Table 2). Palpable mass (94% [82/87]) and pain (39% [34/87]) were the most common clinical presentations of submandibular gland carcinoma. Only 5 (6%) of 87 patients underwent fine-needle aspiration biopsy before referral to our institution. Based on previously mentioned criteria, 74 (85%) of 87 patients received radiation therapy at our institution in the treatment of their disease. Sixty-two (71%) of 87 patients were alive at 3 years and 53 (61%) of 87 patients were alive at 5 years. At last contact, 43 patients (49%) were living free of disease, 3 (3%) were living with disease, 21 (24%) were dead of disease, 13 (15%) died of other causes free of disease, 3 (3%) died of other causes with disease, and 4 (5%) were dead of unknown causes. Tumor size or T stage had no statistically significant effect on locoregional disease control, disease-specific survival, or overall survival.

To address survival and tumor recurrence based on treatment modality, we identified the following cohorts among 79 of 87 patients: (1) those with enucleation of the gland before referral followed by definitive radiation therapy [32% (28 patients)], (2) those with enucleation of the gland before referral followed by definitive surgical resection and radiation therapy (48% [42 patients]), and (3) those without prior enucleation treated with definitive surgical resection and radiation therapy (10% [9 patients]). Exclusion criteria from the cohorts

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoid cystic</td>
<td>57 (66)</td>
</tr>
<tr>
<td>Mucoepidermoid</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Acinic cell</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Lymphoepithelioma</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Reported recurrences were assigned according to the first site of failure, and any recurrence in the head or neck was considered a locoregional failure. Overall survival, disease-specific survival, and locoregional disease control rates were calculated using the Kaplan-Meier product-limit method.\textsuperscript{16} The log-rank test was used to test differences between actuarial curves.\textsuperscript{17} Survival rates and tumor recurrence data were then used to determine the significance of independent prognostic indicators, as well as the effect of treatment modality against disease-specific survival, overall survival, and locoregional recurrence in the cohorts. The period of analysis was from the date of pathological diagnosis to the date of last follow-up or death, ending in 2003.
Table 2. Submandibular Gland Carcinoma Staging

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>No.</th>
<th>Nodal Stage</th>
<th>No.</th>
<th>Distant Metastasis</th>
<th>No.</th>
<th>Overall Stage</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>24</td>
<td>N0</td>
<td>63</td>
<td>M0</td>
<td>82</td>
<td>I</td>
<td>20</td>
</tr>
<tr>
<td>T2</td>
<td>16</td>
<td>N1</td>
<td>6</td>
<td>M1</td>
<td>5</td>
<td>II</td>
<td>11</td>
</tr>
<tr>
<td>T3</td>
<td>43</td>
<td>N2B</td>
<td>17</td>
<td></td>
<td></td>
<td>III</td>
<td>28</td>
</tr>
<tr>
<td>T4</td>
<td>4</td>
<td>N2C</td>
<td>1</td>
<td></td>
<td></td>
<td>IV</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviation: Ellipses, not applicable.

Figure 1. Effect of N stage (N0 vs N positive [N+]) on overall survival of patients with submandibular gland neoplasms. P<.001 for the difference between the curves.

Figure 2. Effect of specific treatment sequences before radiation therapy (XRT) on disease-specific (A) and overall (B) survival of patients with submandibular gland cancer. A, There was no statistically significant difference between the curves. B, P = .01 for surgery at M. D. Anderson Cancer Center (MDACC), Houston, Tex, before XRT vs surgery outside before XRT. There was no statistically significant difference between the other curves.

COMMENT

Submandibular gland carcinomas often present a challenging dilemma to the head and neck surgeon. Not uncommonly, patients with a submandibular gland mass undergo initial surgical enucleation of the gland before establishment of a cancer diagnosis and referral for definitive treatment. One reason for delay of the cancer diagnosis is that the most common initial symptom for patients with benign and malignant disease is nonspecific and consists only of a palpable mass in the neck. Our data support this clinical finding. The second reason for delay is the overall low incidence of carcinomas in contrast to the high incidence of inflammatory conditions. Therefore, we reviewed our experience with primary car-
cinomas of the submandibular gland treated at our institution to determine the effect of a prior surgical enucleation procedure on locoregional disease control and survival for patients receiving subsequent radiation therapy vs patients undergoing an additional surgical resection before radiation therapy.

Recent trends in the management of malignant submandibular gland tumors suggest that treatment decisions must be based on the tumor extent and the stage of disease. Fewer radical surgical procedures are being performed before radiation therapy. However, the presence of clinically and pathologically detectable disease has been shown to have an adverse effect on the risk of disease recurrence. Prognostic factors for submandibular gland carcinoma also exist, but, to our knowledge, no studies demonstrating the use of initial pathological findings from an enucleation procedure in directing further surgical treatment are available. Several diagnostic tools are available for the workup of submandibular gland carcinomas. The use of magnetic resonance imaging, high-resolution computed tomography, gallium 67 scanning, and ultrasonography has been described in the preoperative management of submandibular gland tumors; in addition, fine-needle aspiration biopsy can assist in tumor diagnosis, thereby aiding surgical planning.

The pattern at our institution is referral after initial enucleation (shell-out) of the gland, with 6% of patients being referred after fine-needle aspiration biopsy. Although fine-needle aspiration biopsies have become more common in diagnosing submandibular gland cancers during the last 20 years, most of our patients continue to be referred with a cancer diagnosis after initial enucleation of the gland, often for presumed benign disease. Fine-needle aspiration biopsies are occasionally performed at our institution to rule out residual disease in the submandibular gland bed after a shell-out procedure performed outside of our institution.

Patient care is directed by the findings of physical examination, histopathological review, and high-resolution computed tomography or magnetic resonance imaging interpreted by an experienced head and neck radiologist. Patients without clinical or radiographic evidence of residual primary or nodal disease are referred for definitive radiation therapy. Seventy-four (85%) of 87 patients in the present study received radiation therapy during the course of treatment of their disease based on positive surgical margins, extraglandular extension, perineural invasion, lymph node involvement, or high-grade histological features. Patients with clinical or radiographic evidence of residual primary or nodal disease undergo definitive surgical resection based on the extent of the disease before any radiation therapy. Based on this approach, 29 (69%) of 42 patients undergoing a second surgical procedure in the present study had evidence of residual carcinoma in the final surgical specimen.

Surgical management of submandibular gland cancers has historically been conservative. The extent of primary resection is usually determined by tumor burden and includes removal of lymph nodes adjacent to the area of primary resection, as well as any other gross nodal involvement. Elective neck dissection is typically reserved for high-grade or large tumors with a high rate of occult metastases to the neck. However, previous studies have also shown that margin status and incomplete surgical resection notably affect survival. To the best of our knowledge, no studies addressing management of the primary site after a prior enucleation procedure have been reported.

In the present study, there was no statistically significant difference in locoregional disease control, disease-specific survival, or overall survival between those patients undergoing enucleation of the gland vs those patients undergoing enucleation of the gland followed by definitive surgical resection before any radiation therapy. Exceptions to this finding are patients initially seen with advanced (stage IV) disease. Our surgical approach to these tumors is en bloc resection when a preoperative cancer diagnosis is confirmed.

At our institution, en bloc resection includes removal of the submandibular gland (or any residual gland), as well as levels I and IIa lymph nodes. The platysma is resected with the specimen, as well as the anterior belly of the digastric, mylohyoid, and skin in the presence of gross tumor invasion of these structures. When there is tumor involvement adjacent to smaller nerves such as the nerve to the mylohyoid and submandibular gland ganglion, they are resected en bloc if frozen-section analysis reveals perineural invasion. Major nerves such as the marginal mandibular branch of the facial nerve, the lingual nerve, and the hypoglossal nerve are not resected unless they are encased with tumor, analogous to management of the facial nerve with malignant parotid tumor. After an initial enucleation procedure, additional definitive surgical resection is reserved for patients with clinical or radiographic evidence of disease followed by radiation therapy. Patients lacking clinical and radiographic evidence of disease after enucleation may be adequately treated with subsequent radiation therapy and no additional surgical intervention.

Although many studies indicate a general benefit from postoperative radiation therapy for patients with submandibular gland malignancy, few data exist regarding selection of individual patient subgroups that may benefit from such treatment. Excellent locoregional disease control rates have been previously reported using surgery combined with radiation therapy; these results include patients who have tumors with soft tissue extension, as well as patients with residual disease. Furthermore, significant survival advantage and enhanced locoregional disease control has been demonstrated for patients with stage III/IV disease. All patients in the 3 cohorts in this study received postoperative radiation therapy, and we routinely use this treatment modality as an adjunct to surgical resection when indicated.

The American Joint Committee on Cancer staging system for these tumors has been shown to correlate well with survival and is probably the single most important prognostic factor for carcinomas of the submandibular gland. Tumor staging has also been implicated as a major predictor of poor outcome in patients with adverse histological findings and lymph node metastasis, factors independent of tumor size. Conversely, it has been demonstrated that tumors less than 4 cm do well regardless of histological type and have a distinct sur-
vival advantage vs tumors 4 cm or larger. The present study demonstrated that factors adversely affecting survival outcomes in all treatment groups included lymph node metastasis and advanced disease stage at presentation. Tumor size or T stage displayed no statistically significant difference in locoregional disease control, disease-specific survival, or overall survival.

**CONCLUSIONS**

En bloc surgical resection followed by radiation therapy remains the standard treatment for patients with submandibular gland carcinoma. Patients without clinical and radiographic evidence of disease after enucleation may be adequately treated with subsequent radiation therapy. Definitive surgical resection remains the treatment of choice for patients with clinical or radiographic evidence of disease after enucleation of the gland followed by radiation therapy.

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Author Contributions: Drs Kaszuba, Zafereo, El-Naggar, and Weber had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kaszuba, Zafereo, and Weber. Acquisition of data: Kaszuba and Zafereo. Analysis and interpretation of data: Kaszuba, Zafereo, Rosenthal, El-Naggar, and Weber. Drafting of the manuscript: Kaszuba, Zafereo, Rosenthal, and Weber. Critical revision of the manuscript for important intellectual content: Kaszuba, Zafereo, Rosenthal, El-Naggar, and Weber. Administrative, technical, and material support: Rosenthal and El-Naggar. Study supervision: Rosenthal and Weber.

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**REFERENCES**