High Incidence of Lymph Node Metastasis in Major Salivary Gland Cancer

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Objective: To analyze the incidence and risk factors for clinically apparent and occult lymph node metastases in patients with major salivary gland cancers.

Design: Cohort of patients with a median follow-up of 46 months (range, 1-174 months).

Setting: University-based referral center.

Patients: A total of 160 consecutive patients with complete clinical and pathologic data.

Intervention: Neck dissection was performed in all cases. Patients were treated with surgery alone (55%); surgery and radiation therapy (43%); or a combination of surgery, radiation, and chemotherapy (2%).

Main Outcome Measure: Incidence of apparent and occult lymph node metastases. Univariate and multivariate analyses were used to evaluate the significance of clinical and pathologic data.

Results: Histologically confirmed positive neck was found in 53% of all cases. Histologic diagnosis was significantly related to the incidence of lymph node metastasis: 89% (16/18) for undifferentiated carcinomas. However, so-called low-risk tumors had incidence rates of 22% to 47%. Twenty-one patients (13%) presented with clinically apparent cervical lymph node metastasis. Of the 139 patients with clinical N0 neck, 45% had occult neck metastasis. Neck metastasis was found in 29% (10/34) of T1, 54% (38/70) of T2, 65% (20/31) of T3, and 54% (16/25) of T4 tumors. Assessment of survival according to nodal status revealed significant correlations for overall ($P<.001$) and disease-free survival ($P<.001$).

Conclusions: We found a high incidence of lymph node metastasis from major salivary gland cancers. Neck dissections should be considered as an integral part of the surgical approach in patients with major salivary gland cancer, especially if no postoperative radiation therapy is planned.


The Treatment of Salivary Gland Cancers is Challenging because of their Infrequent Incidence and their Varied Biologic Behavior.

In addition, prognostic estimates are more difficult, owing to their prolonged risk for recurrence. The standard treatment of primary salivary gland cancers is surgical resection. Postoperative radiation therapy is believed to be indicated for most patients following initial surgery. However, there is no agreement on the management of the neck. Some authors recommend elective neck dissection (ND) only for specific histologic entities that are associated with the highest risk for lymph node metastasis. In line with this is a recent comment that ND be considered in the clinically uninvolved neck only in primary squamous cell carcinoma, undifferentiated carcinoma, adenosquamous carcinoma, salivary duct carcinoma malignant mixed tumors, and high-grade mucoepidermoid carcinoma. The overall incidence of clinically obvious lymph node metastasis is reported to range from 14% to 20%. The reported incidence of occult lymph node metastasis varies from 12% to 48%. However, since current thinking is that elective ND is rarely (if ever) indicated, most of these estimates are based on small numbers of patients in whom elective ND has permitted for histologic assessment of lymph node metastasis. In most of the studies, irradiation was the preferred treatment of potential metastatic deposits in the lymph nodes and irradiation of the neck is believed to treat the N0 neck adequately.

In contrast to most reports in the literature, our policy is to perform ND of the involved side in all major salivary gland cancers independent of T stage and histologic type. This enables us to analyze the true incidence of occult nodal metastasis based on the results of histologic workup of these ND specimens. To address this issue, we reviewed the cases treated at our institution in the last 14 years.
METHODS

From 1987 to 2001, 1151 patients were treated surgically for salivary gland tumors at the Department of Otorhinolaryngology, Head and Neck Surgery, of the University of Cologne. Of these cases, 230 (22%) were malignant tumors. Sixty-one cases were metastatic tumors from other primary sites or malignant lymphomas. Twenty-nine cases were not available for review because of incomplete clinical or pathologic data and were excluded from further analysis. The remaining 160 patients with primary salivary gland cancer were fully evaluable and constitute the subject of this report. The study population consists of 83 males (52%) and 77 females (48%). Their data were accumulated in a database and analyzed retrospectively. Age at time of diagnosis ranged from 7 to 93 years (median, 58 years). All medical charts were reviewed for leading symptoms in the medical history, pretherapeutic staging, surgical procedure, histologic diagnosis, pathologic staging, and radiation and chemotherapeutic treatment. Pretherapeutic staging was at least based on clinical examination and imaging, usually computed tomographic or magnetic resonance imaging scans. Tumor staging was performed according to the 1997 American Joint Committee on Cancer staging criteria.¹⁰ One hundred forty-nine primary cancers were located in the parotid gland, and 11 in the submandibular gland. The incidence of the histologic tumor types are given in Table 1. Fifteen percent (24/160) of the patients had stage I disease; 20% (32/160), stage II; 28% (28/160), stage III; and 38% (60/160), stage IV. Patients were treated with surgery alone (35%), surgery and radiation therapy (43%), or a combination of surgery and postoperative concomitant chemoradiation (2%). All patients underwent ND of the involved side. A selective supraomohyoidal ND was performed in 39% of patients and a modified radiation therapy (43%), or a combination of surgery and postoperative concomitant chemoradiation (2%).

RESULTS

Thirteen percent (21/160) of the patients presented with clinically apparent cervical lymph node metastasis. The overall incidence of pathologically confirmed lymph node metastasis was 53% (84/160). The incidence of positive nodes for different histologic diagnoses is given in Table 1. The highest incidence was found in patients with undifferentiated carcinomas (89% [16/18]); the lowest incidence was found in patients with a carcinoma ex pleomorphic adenoma (2% [1/59]). Contra-lateral lymph node metastasis was not found in any of the patients.

Of the 139 patients who presented clinically with a N0 neck, 45% had positive lymph nodes in their neck specimen. High rates of occult metastasis were found in undifferentiated (75%), lymphoepithelial (60%), squamous cell (64%), and adenocarcinomas (58%). The incidence of occult metastasis in histologic entities expected to have a lower risk for nodal metastasis were as follows: acinic cell carcinoma, 44%; adenoid cystic carcinomas, 36%; mucoepidermoid carcinoma, 30%; and carcinoma ex pleomorphic adenoma, 20%.

The influence of primary tumor stage on the risk for overall positive lymph nodes was also assessed (Table 2). Lymph node metastases were found in 29% of all T1 lesions (10/34), in 54% of T2 lesions (38/70), in 65% of T3 lesions (20/31), and in 54% of T4 carcinomas (16/23). As expected, statistical analysis showed an increasing risk for positive nodes with increasing tumor size. T2 tumors had a significantly higher risk for lymph node metastasis than T1 tumors ($P$ < .002; odds ratio, 0.35; 95% confidence interval, 0.15–0.84). From T2 to T3 and from T3 to T4 the differences were not statistically significant. Data on the extension of the neck disease are given in Table 2.

The overall survival rate for all patients at 5 years and 10 years was 59% and 56%, respectively. The 5-year and 10-year disease-free survival rates for all patients were 62% and 32%, respectively. The overall and the disease-free survival rates decreased with positive node status from 84%
to 43% and from 83% to 47%, respectively. When the influence of the nodal status is analyzed using the Cox proportional hazard model adjusting for the effects of T stage, it was shown that nodal status is an independent predictor for overall ($P = .03$) and disease-free survival ($P = .001$).

**COMMENT**

There is an agreement in the literature that ND is indicated in cases of apparent neck involvement in salivary gland cancers. Additional, postoperative radiation therapy is invariably recommended in these cases. In contrast, the indications of ND for the N0 neck in salivary gland cancer are not well defined. Ferlito et al recommend to base the decision for elective ND mainly on the histologic type of the primary tumor. They recommend elective ND for 6 "high-risk" histologic types: high-grade mucoepidermoid carcinomas, malignant mixed tumors, salivary duct carcinomas, squamous cell carcinomas, undifferentiated carcinomas, and adenosquamous carcinomas. Medina has reviewed the literature regarding recommendations for the treatment of the neck in salivary gland cancers. He summarizes that some authors have recommended resection of the first echelon node for all tumors, others for high-risk tumors, and some for T3 and T4 tumors. Further, instead of elective ND, elective irradiation has been recommended as adequate treatment of the clinically N0 neck in patients with high-risk tumors. In most of the studies reporting on incidences of pathologically positive nodes, elective ND was performed in only some of the patients. Armstrong et al reported a 12% overall rate of occult metastasis; however, they state that this might be underestimated because elective ND was performed only in 19% of the N0 cases. Evaluating only patients undergoing elective ND in their series would result in a 38% rate of occult metastasis. Kelley and Spiro reported occult metastasis in 10 (48%) of 21 elective NDs. They recommend elective ND for histologic subtypes that carry the highest risk for nodal metastasis.

In our study we found an overall incidence of histologically proven lymph node metastasis in 53% of patients, regardless of histologic type of the tumor and size of the primary tumor. Thirteen percent had clinically apparent lymph node metastases, and 43% had occult metastases. Our rate of occult metastasis is comparable to the data of Kelley and Spiro (48%) and of Regis et al (37%), but higher than reported in other studies. The incidence of positive nodes of high-grade tumors in our study population is comparable to that of prior reports. Taking into account the limitations of a retrospective study design, there was no evidence in the medical records that the cases with squamous cell and basal cell carcinomas presented metastatic tumors. However, a bias cannot be definitively excluded in these cases.

In contrast, we found higher rates of lymph node metastasis for tumors traditionally associated with a lower risk for nodal metastasis. For acinic cell carcinoma, the reported
overall rate for positive nodes ranges from 7% to 23%,\textsuperscript{3,7,19} and for occult disease from 0%\textsuperscript{16} to 4%.\textsuperscript{6} We found histologically proven lymph node metastasis in 47% of these cases and a 44% rate of occult disease. For mucoepidermoid carcinomas, reported data range from 18%\textsuperscript{7} to 57%,\textsuperscript{17} and for occult lymph node metastasis, from 10%\textsuperscript{16} to 14%.\textsuperscript{6} We identified a 33% overall incidence and a 30% occult metastasis rate. However, these results are somewhat limited as we did not differentiate low- and high-grade mucoepidermoid carcinomas. The reported incidence of lymph node metastasis for adenosquamous carcinomas varies from 0%\textsuperscript{16} to 17%,\textsuperscript{7} whereas in our series metastases were found in 39% of all patients. There are only few data for myoepithelial carcinoma. Regis et al\textsuperscript{17} recently reported a rate of 33.3% for nodal metastasis, which is comparable to our data (22%). Oncocytic carcinoma is a very rare tumor entity and lymph node metastasis has been reported.\textsuperscript{20} We found no lymph node metastasis in this group. For carcinomas, ex pleomorphic adenoma lymph node involvement has been reported to be as high as 52%,\textsuperscript{21} which is higher than our rate (20%).

There is clear evidence that the extension of the primary tumor predicts the rate of lymph node metastasis in major salivary gland cancers. The reported rates range from 7%\textsuperscript{6} to 16%\textsuperscript{17} for T1-T2 tumors and from 20%\textsuperscript{6} to 52%\textsuperscript{17} for T3-T4 tumors. We found higher rates than expected in small primary tumors, ie, 29% for T1 and 54% for T2 tumors.

In general, for all other cancers of the head and neck, elective ND is indicated in patients with no evidence of clinical metastasis, with a 15% to 20% risk for harboring occult metastatic disease, and for whom surgery is the treatment of the primary lesion.\textsuperscript{22} Based on these considerations, for cancers of the salivary glands, elective ND has not been recommended in the past for T1 and T2 tumors and low-risk tumors.\textsuperscript{5,8,23} In this study we report incidences of lymph node metastasis in high-risk tumors similar to those in the literature. However, in some low-risk types the rate is higher than previously reported. Although our study has the same limitations as other previous retrospective reports, we believe that in view of the number of patients and the uniformity of the surgical approach to the cervical nodes, our estimates may reflect the true prevalence of lymph node metastasis in the majority of salivary gland cancers.

Our data and several previous studies have shown that the N stage is an independent predictor for survival in cancer of the salivary glands. Therefore, we believe that treatment of the neck is an essential issue for these patients. Medina\textsuperscript{9} assumed that elective radiation therapy instead of ND should be performed in patients for whom postoperative radiation therapy is indicated by the characteristics of the primary tumor. However, he also points out that experience with elective radiation treatment of squamous cell carcinomas of the upper aerodigestive tract may not be generalizable to salivary gland cancers. On the basis of our estimates and that we treat salivary gland cancers primarily surgically, our preferred approach is to treat the neck surgically. We assume that there is no significant additional morbidity due to the elective ND, especially compared with elective radiation therapy. However, with this study we cannot prove the impact of elective ND on regional control or survival. The disease-free survival rate for 5 years is 62% for our series treated preferentially with ND, which is comparable to data reported in the literature.\textsuperscript{24}

Since it is generally accepted that salivary gland carcinomas are associated with poor radiosensitivity, it should equally be understood that lymph node metastasis from such tumors will behave likewise. If surgery is generally believed to be more promising for the control of the primary tumor, then surgery might also be suited for the oncologic control of the neck.

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REFERENCES


