Intraparotid and cervical lymph nodes metastasis in primary parotid gland carcinoma—impact on clinical outcome

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Objective. The aim of this study was to investigate the prognostic value of evaluation of intraparotid and cervical lymph node metastases in primary parotid cancer.

Study Design. A retrospective medical chart review and histopathologic evaluation of all patients surgically treated for primary parotid cancer during the period 1993 to 2010 was performed. The presence and ratio of intraparotid and cervical lymph node metastases were assessed and determined as primary predictor variables. Overall survival (OS) and disease-free survival (DFS) were defined as primary outcome variables.

Results. In total, 50 patients were included. The presence of pathologic cervical lymph nodes ($P = .005$) and a high cervical lymph node ratio (LNR) ($P = .0001$) had a significant association with worse OS. Worse DFS was found in patients with a high cervical LNR ($P = .001$) and intraparotid lymph node metastases ($P = .029$). In high-grade carcinoma, a high LNR showed worse DFS ($P = .05$). A high cervical LNR ($P = .012$) and resection margin status ($P = .002$) were identified as independent prognostic markers for OS and the presence of intraparotid lymph nodes for DSS ($P = .05$).

Conclusions. Evaluation of patterns of lymph node metastases provides additional prognostic value in patients with primary parotid gland cancer. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:570−574)

Parotid gland malignancies are rare tumors, representing about 1% to 3% of head and neck cancers. Lymph node metastases are widely known to be negative prognostic factors in malignant diseases. Integrated in the tumor−node−metastasis (TNM) staging system, the extent, size, and laterality allow for accurate estimation of prognosis. However, the prognostic potential of patterns of lymph node metastasis in parotid malignancies has not been fully elucidated yet, and the TNM staging system only considers nodal metastases in the neck.

Interestingly, evaluation of intraparotid lymph node metastases has shown prognostic significance in nonmelanoma skin cancer, where these metastases have been identified as negative prognostic markers.[1] In primary parotid malignancies, periparotid lymph nodes positive for metastasis have been associated with a worse outcome.[2] Studies evaluating the impact of intraparotid lymph node metastases on prognosis are sparse, although there is some evidence that the clinical outcome is worse when positive nodes are present.[3,4]

Furthermore, the lymph node ratio (LNR) has additional prognostic potential. LNR is defined as the number of positive lymph nodes in relation to the total number of lymph nodes removed. Clinical prognostic significance has been shown in various types of cancer, including head and neck squamous cell carcinoma (SCC).[5-8] However, data regarding LNR, specifically in parotid cancer, are limited. In a recent study, the ratio of positive cervical lymph nodes was investigated, identifying LNR as an independent predictor for patients' overall survival (OS).[9] The relevance of intraparotid LNR has not yet been determined.

The aim of this study was to evaluate the patterns of intraparotid and cervical lymph node metastases of primary parotid gland malignancies and to determine the presence and density of positive lymph nodes, which subsequently impact patients' clinical outcomes.

MATERIALS AND METHODS

All patients surgically treated for primary parotid gland malignancies during the period 1993 to 2010 with complete clinical data were included in this study. All patients were treated at the Medical University of Vienna (Vienna, Austria). Staging was performed according to the Union for International Cancer Control's *TNM Classification of Malignant Tumors* (8th edition) recommendations, and treatment was planned by the institution's tumor board. In case of a positive clinical node (N+) in the neck, modified radical neck

Statement of Clinical Relevance

Evaluation of intraparotid and cervical lymph node metastases and patterns of lymph node ratio may increase prognostic accuracy in primary parotid gland cancer.

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dissection was performed, and levels I to V were included in the resection. Radical neck dissection was performed, when required, according to the extent of metastatic infiltration.

In case of a negative clinical node (N0) in the neck, generally selective neck dissection, including levels II and III, was performed, except for tumors of low stage and grade.

Histopathologic grading was stratified for low and high-grade tumors. Acinic cell carcinoma, basal cell carcinoma, and low-grade mucoepidermoid carcinoma were classified as low-grade carcinomas. High-grade mucoepidermoid carcinoma, adenocarcinoma, carcinoma ex pleomorphic adenoma, undifferentiated carcinoma, small cell carcinoma, sarcomatoid carcinoma, adenoid cystic carcinoma, and SCC were grouped as high-grade carcinomas.

Statistical analysis

For data analysis, SPSS software version 25.0 (SPSS, Inc., Chicago, IL) was used. All P values were nominal 2-sided values, and the significance level was set at $P \leq .05$.

OS was defined as the period from initial treatment to death or last follow-up. Disease-free survival (DFS) was defined as the period from initial treatment to recurrence of disease or last follow-up. OS and DFS were estimated by using the Kaplan-Meier method. Differences were evaluated by using the log-rank test (Mantel-Cox). Cox regression was computed for univariate and multivariate analyses. Variables with a P value $< .2$ were further computed in a multivariate analysis. Spearmen correlation was used to calculate the association of ranked variables.

OS and DFS were defined as primary outcome variables. The presence of lymph nodes and LNR were determined as primary predictor variables. LNR was calculated by dividing the number of metastases by the number of all excised lymph nodes.

For statistical analyses, variables were dichotomized for the presence of cervical lymph nodes (N0 vs N+), presence of intraparotid lymph nodes (N0 vs N+), cervical LNR (low [< mean] versus high [> mean]), intraparotid LNR (low [< mean] versus high [> mean]), and resection margins (R0 vs R1 and R2).

Ethical considerations

Approval for this study was obtained from the institutional ethics committee (EK1925/2015).

RESULTS

Patients' characteristics

In this study, 50 patients with primary parotid cancer were evaluated. Mean age at diagnosis was 58.6 years (range 30−84 years) and the mean follow-up period was 98.2 months (range 4−275 months). The 5-year OS rate was 62%. All patients underwent surgical treatment, followed by postoperative radiotherapy in some cases (32 cases). Primary curative surgery was performed in 50 patients. Partial parotidectomy was performed in 14 cases, partial resection followed by total parotidectomy in 9 cases, and primary total parotidectomy in 27 cases. Selective neck dissection was performed in 31 cases, modified radical neck dissection in 10 cases, and radical neck dissection in 3 cases. In 6 cases, there was no indication for neck dissection.

Radiotherapy was administered in 64% of cases. Interestingly, patients in need for radiotherapy showed significantly worse OS (P = .001), but not DFS (P = .143), in Kaplan-Meier analyses. Furthermore, a significant correlation of high-grade histopathology was found with performance of adjuvant radiotherapy (Spearmen correlation 0.467; P = .001).

Univariate analysis revealed that the pathologic tumor stage (P = .041), presence of cervical lymph node metastases (P = .005), cervical LNR (P = 0.001), and margin status (P = .013) were significant predictors for the OS rate. Multivariate analysis demonstrated the cervical LNR (P = .012) and margin status (P = .002) as independent predictors for OS. For DFS, the presence of intraparotid lymph nodes (P = .041) and the cervical LNR (P = .004) were determined as significant predictors. In multivariate analysis, the presence of intraparotid lymph nodes remained a significant predictor for DFS (P = .05). Patients' characteristics are shown in Table I.

Cervical lymph node metastasis

Neck dissection was performed in 44 patients: selective neck dissection in 32, modified radical neck dissection in 9, and radical neck dissection in 3 cases.

Positive nodes in the neck were observed in 25 cases; among these, occult metastases were found in 9 (18%) clinical N0 cases. When the Kaplan-Meier analysis was performed, the presence of cervical lymph node metastasis was significantly correlated with worse OS (P = .005), whereas no significant correlation was observed with DFS (P = .086) (Figure 1).

Cervical lymph node metastases ratio

The cervical LNR was calculated in 44 specimens, and mean ratio was 0.1325 (13%) positive nodes. A ratio above the mean was observed in 13 cases and below the mean in 31 cases. The Kaplan-Meier analysis revealed that the cervical LNR was significantly correlated with OS (P = .0001) and DFS (P = .001) (see Figure 1).

Intraparotid lymph node metastasis

results of the histopathologic examination of intraparotid lymph nodes were available for 36 cases, and among these, positive nodes were present in 14 and no metastases in 22 specimens. In the Kaplan-Meier analysis, no significant correlation with OS (P = .347) was observed, but a significant correlation with DFS was observed (P = .029) (Figure 2).

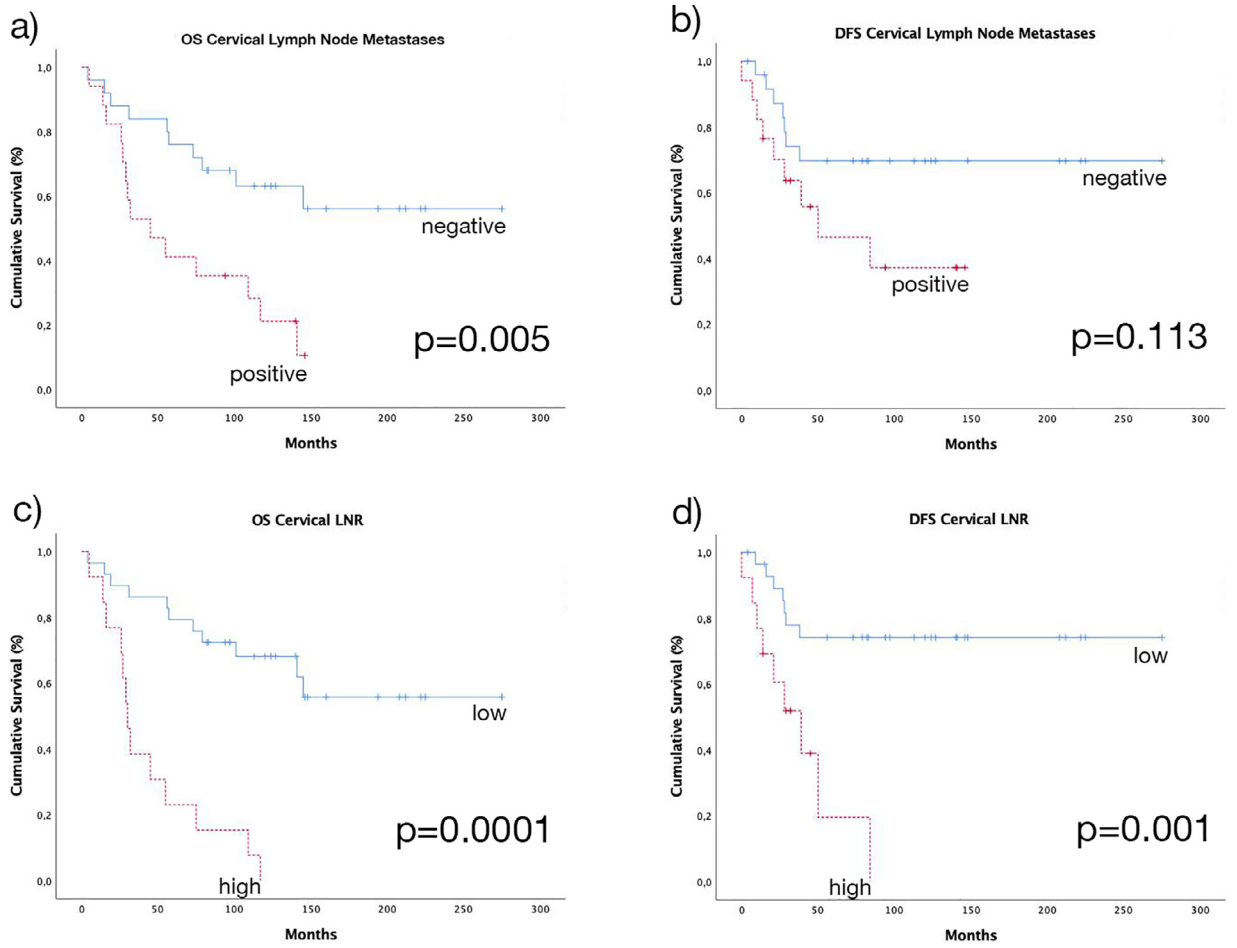

Fig. 1. Kaplan-Meier curves for overall survival (OS) and disease-free survival (DFS) relating to the presence of cervical lymph node metastases **(a, b)** and cervical lymph node ratio (LNR) **(c, d)**.

Intraparotid lymph node metastasis ratio

The intraparotid LNR was calculated in 36 specimens, with a mean ratio of 0.21 (21%) positive nodes. A ratio above the mean was observed in 13 cases and below the mean in 23 cases. The Kaplan-Meier analysis revealed that the intraparotid LNR was not significantly correlated with OS (P = .660) or DFS (P = .056) (see Figure 2).

Subgroup analyses according to grading

In this cohort, 14 cases were low-grade carcinomas, and 36 cases were high-grade carcinomas. Kaplan-Meier analyses revealed significantly worse OS (P = .018) and DFS (P = 0.031) in patients with high-
grade carcinoma. In the low-grade subgroup, no further analysis of lymphatic metastases patterns was performed because of the small sample size. In high-grade carcinomas, results similar to the whole cohort could be observed. The presence of cervical metastases was significantly correlated with OS (P = .042) but not DFS (P = .112). Furthermore, a high cervical LNR was significantly associated with worse OS (P = .0001) and DFS (P = .003). The presence of intraparotid lymph node metastases was significantly correlated with worse DFS (P = .05) but not OS (P = .279). Interestingly, in contrast to the rates found in the whole cohort, DFS was significantly worse (P = .05) in patients with a high LNR, although no correlation with OS (P = .279) could be observed.

Comparison of matched intraparotid and cervical lymph node metastases

For 29 patients, matched pairs of cervical and intraparotid lymph node specimens were available. Concordant positive or negative intraparotid and cervical nodes were found in 20 patients (69%). In 16 patients (55%), neither intraparotid nor cervical metastases were present. Positive intraparotid and cervical nodes were present in 4 patients (14%). Discordance of positive nodes was observed in 9 patients (31%). Intraparotid, but not cervical, metastases were found in 5 cases (17%),

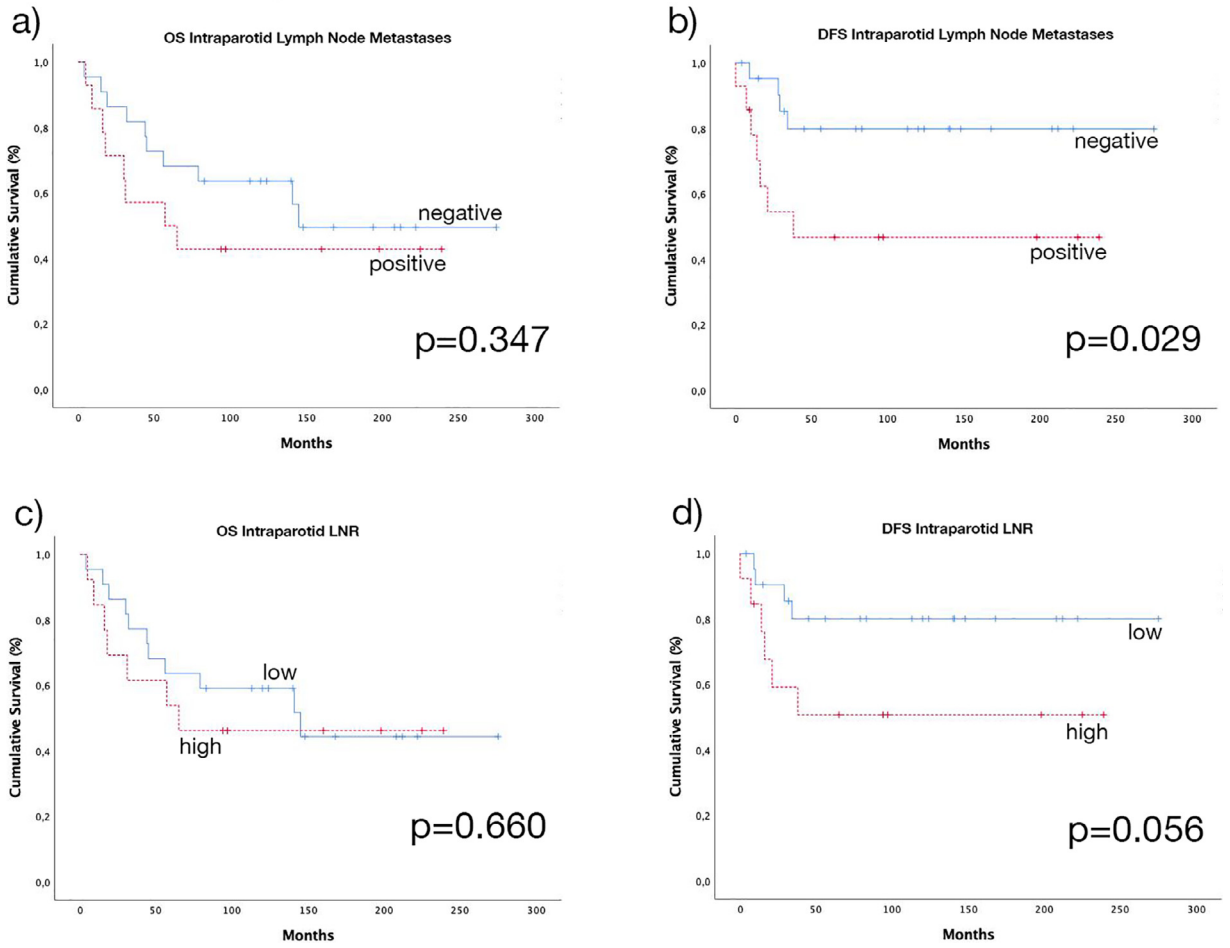

Fig. 2. Kaplan-Meier curves for overall survival (OS) and disease-free survival (DFS) relating to the presence of intraparotid lymph node metastases **(a, b)** and intraparotid lymph node ratio (LNR) **(c, d)**.

whereas cervical, but not intraparotid, metastases were observed in 4 patients (14%).

DISCUSSION

Surgery is the paramount treatment option in parotid gland cancer. Ablation of the primary tumor is frequently complemented by neck dissection. However, exact evaluation of lymph node specimens offers interesting prognostic potential. N (nodal) staging is a routinely used marker to estimate the prognosis, although in parotid gland cancer, further stratification of the localization of lymph node metastases may also be useful. LNR is a known prognostic factor for various types of cancer, including bladder, esophageal, and skin carcinomas and head and neck SCCs.[10] However, studies evaluating the prognostic potential of lymph node metastasis patterns and LNR in parotid gland cancer are scarce.

The results of this study revealed interesting insights regarding prediction of clinical outcome. Nodal staging, which is based on the presence of lymph node metastasis, is a relevant prognostic factor in parotid gland cancer; however, localization of positive lymph nodes with regard to intraparotid, periparotid, or cervical origin has not been further differentiated. Previous studies have shown that evaluation of the presence of intraparotid and/or periparotid lymph node metastases offers additional prognostic potential.[2] In our study, the presence of pathologic cervical lymph nodes correlated significantly with OS in Kaplan-Meier analyses, and the presence of metastatic intraparotid nodes significantly correlated with DFS. However, pathologic nodal staging is based on the presence of any lymph node metastasis, not on intraparotid or extraparotid localization. Therefore, in routine clinical practice, precise determination of localization may be of significant prognostic value.

In various cancer entities, including esophageal and head and neck SCCs, LNR has been determined to be a superior prognostic marker.[8-10] LNR is calculated by dividing the number of lymph node metastases by the number of all excised lymph nodes. The results of our study indicate that accurate evaluation of LNR provides additional prognostic potential in parotid cancer. LNR value is influenced by tumor factors in relation to the true number of metastases as well as the accuracy of surgical

and pathologic procedures. In the investigated cohort, the presence of positive cervical nodes significantly correlated with worse OS, but correlation with DFS did not achieve statistical significance. Indeed, LNR of cervical metastasis revealed significant prognostic impact with regard to OS and DFS and, therefore, might serve as a superior prognostic marker. As a further demonstration of the prognostic relevance of LNR, in subgroup analyses of patients with high-grade carcinomas, DFS was found to be significantly worse when intraparotid LNR was high.

Cervical LNR could be determined as an independent prognostic factor for OS in the multivariate analysis. Interestingly, similar observations regarding the prognostic value of cervical LNR were made in another study of salivary gland cancer.[9]

Another relevant aspect of metastatic spread in parotid gland cancer is the discordance of intraparotid and cervical metastasis patterns. In our cohort, we observed concordant intraparotid and cervical lymph node metastases in 69% of patients. Interestingly, in 14% of specimens, cervical metastases were found, although intraparotid pathologic lymph nodes were absent. This could be attributed to real skip metastasis. Therefore, the absence of intraparotid lymph node metastases must not be considered a prognosticator for the absence of cervical lymph node metastases.

CONCLUSIONS

In this study, we found that precise evaluation of patterns of lymph node metastases and LNR are relevant prognostic factors in patients with parotid gland cancer and are potentially useful in clinical practice. Future prospective studies should be performed to accumulate relevant data to support these findings.

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