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Do Lymph Node Ratio and Histopathologic Parameters Have Any Prognostic Value in Primary Parotid Gland Carcinomas?

Original Investigation

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Abstract

Objective: To analyze the demographic characteristics and the pathological results of neck dissection in primary parotid gland (PG) cancer patients, and to investigate the effects of histopathological parameters (perineural invasion, lymphovascular invasion, and extracapsular spread), neck metastasis, stage and lymph node ratio (LNR) on survival.

Methods: Patients who underwent parotidectomy for malignant PG tumors between 2000 and 2019 years were retrospectively reviewed from the medical records. Thirty patients who were treated with parotidectomy and neck dissection were included in the study. Lymph node ratio was calculated as the ratio of the number of metastatic lymph nodes (LN) to the total number of excised LNs. Tumor stage, regional LN metastasis, LNR, perineural invasion, lymphovascular invasion, and extracapsular spread were reviewed for the effects on survival with the Kaplan–Meier analysis.

Results: The study included 17 (57%) male and 13 (43%) female patients. Their mean age was 67.93±16.90 years (range, 50–85 years). The average number of the excised LN was 26.03±11.79 (range, 3–50). Mean LNR was 0.16±0.26. The Kaplan–Meier analysis showed that neck metastasis ($p=0.001$) and LNR ($p<0.001$) were associated with shorter survival times compared to perineural invasion ($p=0.818$), lymphovascular invasion ($p=0.154$), extracapsular spread ($p=0.410$) and stage ($p=0.294$). In multivariate COX regression analysis, only LNR had a statistically significant difference ($p=0.027$) compared to the other parameters.

Conclusion: The present study suggests that LNR and neck metastasis are associated with shorter survival times in PG cancers. Lymph node ratio can be used as a prognostic marker in these patients.

Keywords: Parotid cancer, lymph node metastasis, neck, survival, lymph node ratio

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Introduction

Salivary gland tumors are rare and represent 0.3% of all malignant neoplasia. Malignant salivary gland tumors constitute approximately 3–6% of all head and neck cancers (1). Seventy percent of the salivary gland tumors are seen in the parotid gland (PG) and 17–34% of the PG tumors are malignant (1-4).

While it is well known that the prognosis of head and neck squamous cell carcinomas is largely dependent on lymph node (LN) metastasis, the treatment of neck metastasis in PG carcinomas has received little attention. There are still controversies on the treatment planning of node-negative neck in PG cancers. Some authors recommend elective neck dissection (END) for malignant PG tumors, whereas others recommend neck dissection for only LN-positive patients or some specific tumor types (5, 6). The rarity, diversity, and heterogeneity of these tumors lead to more complex and complicated treatments.

Lymph node ratio (LNR) is defined as the ratio of the number of positive LNs to the number of total LNs removed with neck dissection. It has been reported that it predicts the survival of patients with head and neck cancers such as oral cavity, larynx, and hypopharynx cancers (7, 8). Metastasis to the LNs of the neck in head and neck cancers generally has significant prognostic importance. The number, laterality, and size of metastatic LNs in the neck are used for staging in salivary gland cancers according to the tumor-node-metastasis (TNM) staging system (9). Extranodal spread of metastasis is also the other factor affecting survival. Lymph node ratio has been indicated to be a newly proposed parameter over staging and survival in salivary gland cancers (10). An increase in the number and ratio of positive LNs is closely associated with increased overall and cancer-specific mortality (11).

In this article, we aimed to analyze patients' demographic characteristics and the clinical and pathological results of neck dissection in primary PG cancer patients. The effects of histopathological parameters (perineural invasion, lymphovascular invasion, and extracapsular spread), neck metastasis, stage, and LNR on the survival of patients were also evaluated and discussed.

Methods

The study was approved by the Clinical Research Ethics Committee of Mersin University (decision no: 2023/193, date: 29.03.2023). Patients who underwent parotidectomy for malignant PG tumors between 2000 and 2019 were retrospectively reviewed from the medical charts. Fifty-nine patients were found to have been operated on for malignant tumors of the PG. Two patients had lymphoma, four patients had metastasis to the PG, and 14 patients had an invasion of the PG by a facial skin and scalp melanoma (two patients) or a squamous cell carcinoma (12 patients); thus, these 20 patients were excluded from the study. Six patients who were treated with parotidectomy alone were also excluded. The remaining 33 patients had undergone parotidectomy and neck dissection. Among these 33 patients, three who had died from causes (one heart attack, one cerebrovascular event, and one liver failure) other than PG cancer were also excluded. Eventually, 30 patients who were treated with parotidectomy and neck dissection were included in our study. Demographic features, clinical examination findings, surgical and histopathologic results, and overall survival times were retrieved from patients' medical charts. Tumor sizes were measured based on the larger diameter of the tumor on histopathological examination. Tumor staging was assessed according to the recent World Health Organization TNM classification of malignant tumors (9). Histopathological results of parotidectomy and neck dissection specimens were analyzed in terms of histopathologic tumor type, tumor grade, metastasis to LNs, extracapsular spread, and lymphovascular and perineural invasion. Lymph node ratio was calculated as the ratio of the number of metastatic LN to the total number of excised LNs. LNRs were categorized into four groups: 0, 0.001–0.1, 0.11–0.5, and >0.5 (12). The number of metastatic LNs was also grouped as 0, 1, 2–4, 5–10, and >10.

Nodal involvement in histopathological results was assessed in terms of age, gender, histopathological grade, T stage, and perineural and lymphovascular invasion. High-grade mucoepidermoid carcinoma, solid-type adenoid cystic carcinoma, adenocarcinoma not otherwise specified, squamous cell carcinoma, salivary duct carcinoma, carcinoma ex pleomorphic adenoma, and undifferentiated carcinoma were accepted as high-grade tumors on final histopathological examination.

Patients were treated with complete superficial, total, or radical parotidectomy and additional neck dissection. Small-sized superficial tumors were removed from the PG with complete superficial parotidectomy, while larger or deep lobe tumors were removed with total parotidectomy. The facial nerve was sacrificed in the presence of preoperative facial paralysis or when the facial nerve was considerably infiltrated by a tumor. After sacrificing the facial nerve, the facial nerve was not reconstructed. Branches of the facial nerve directed toward the eye were preserved as much as possible when the tumor was located in the lower segment of the PG. If there was a high index of suspicion for a malignant parotid tumor in the result of the preoperative examination or the fine needle aspiration biopsy (FNAB), a frozen section was applied. Visible level II LNs during parotidectomy were selected for a frozen section in patients who did not have any clinically preoperative nodal involvement. Neck dissection was considered in patients with suspected malignant tumors when physical examination, imaging methods, FNAB, frozen section and final histopathologic examination (high-grade tumors) were evaluated. An END including levels I, II and III was therefore used in patients without clinically involved LNs in the neck, whereas patients with clinical nodal involvement were treated with modified radical neck dissection or radical neck dissection. According to the final histopathological report of the parotidectomy material, patients who did not accept neck dissection with a second operation were referred to radiation oncology and/or medical oncology if deemed necessary. The need for radiotherapy (RT) ± chemotherapy (CT) after histopathological examination of the specimens of parotidectomy and neck dissection was also evaluated by the Head and Neck Cancer Board.

Tumor stage, regional LN metastasis, LNR, perineural invasion, lymphovascular invasion, and extracapsular spread were reviewed with Kaplan–Meier analysis for their effects on survival.

Statistical Analysis

Statistical analysis was done with SPSS version 23 (SPSS., Inc, IBM, Armonk, NY). Data were shown as mean ± standard deviation for continuous variables and the number of cases was used for categorical ones. Data were reviewed for normal distribution using the Shapiro–Wilk test. Disease-specific survival times were calculated for each patient. The Kaplan–Meier survival analysis was used to evaluate LN metastasis, LNR, perineural invasion, perivascular invasion, extracapsular spread, and stage on survival of the patients. A COX regression analysis was also done to assess the effects of multiple independent variables on survival status. A p-value of <0.05 was considered statistically significant.

Results

In our study, there were 17 (57%) male and 13 (43%) female patients. Their mean age was 67.93±16.90 years (range, 50–85). Fourteen patients had the tumor on the right-side PG and sixteen had the tumor on the left-side PG. Mean tumor size was 39.16±18.31 mm. Patients had undergone superficial parotidectomy (eight patients), total parotidectomy (five patients), or radical parotidectomy (17 patients).

Histopathological results demonstrated that the most common tumors in the PG were mucoepidermoid carcinoma, adenoid cystic carcinoma, and squamous cell carcinoma, respectively. The distribution of the remaining tumor types is given in Table 1.

When T stages were reviewed, 14 patients had an early-stage tumor (T2) and 16 had an advanced-stage tumor (T3 and T4). Fourteen patients (46.7%) had no positive LN (N0) and 16 patients (53.3%) had metastasis to the regional LNs, with N1 in five and N2 in 11 patients (Table 2). Patients with metastatic LNs had high-grade malignancies except for one patient with adenoid cystic carcinoma (cribriform pattern). When the relation between T stage and regional metastasis was reviewed, metastasis rates were 42.8% in T2, 100% in T3, and 50% in T4. The 5-year disease-free survival rates were 28.6% in T2 tumors, 25% in T3 tumors, 16.6% in T4 tumors, and 23.3% overall.

Table 1. Distribution of the histopathological diagnosis of the patients

Histopathology	n=30
Mucoepidermoid carcinoma	
Low-grade	1
High-grade	9
Adenoid cystic carcinoma	5
Squamous cell carcinoma	5
Adenocarcinoma, NOS	2
Salivary duct carcinoma	3
Acinic cell carcinoma	1
Sebaceous adenocarcinoma	1
Carcinoma ex pleomorphic adenoma	1
Polymorphous low-grade adenocarcinoma	1
Undifferentiated carcinoma	1

n: Number of patients, NOS: Not otherwise specified

The average number of the excised LN was 26.03±11.79, range 3–50. The mean number of excised metastatic nodes was 3.46±5.65, range 1–19. Mean LNR was 0.16±0.26. Patients' LNR and the number of positive LN are shown in Table 3. Occult metastasis rate was 20% and these patients had mucoepidermoid carcinoma (three patients), adenoid cystic carcinoma (one patient), salivary duct carcinoma (one patient), and undifferentiated carcinoma (one patient).

The Kaplan–Meier analysis revealed that positive neck metastasis (p=0.001) (Figure 1) and LNR (p<0.001) (Figure 2) were associated with shorter survival times compared to perineural invasion (p=0.818), lymphovascular invasion (p=0.154), extracapsular spread (p=0.410) and stage (p=0.294).

In multivariate COX regression analysis, only LNR showed a statistically significant difference (p=0.027) compared to the other parameters, with neck metastasis (p=0.625), perineural invasion (p=0.185), lymphovascular invasion (p=0.505), extracapsular spread (p=0.971), and stage (p=0.787) (Table 4).

Discussion

The most common PG tumors were mucoepidermoid carcinoma, adenoid cystic carcinoma, and squamous cell carcinoma in our study. The 5-year disease-free survival rates were 28.6% in T2 tumors, 25% in T3 tumors, 16.6% in T4 tumors, and 23.3% overall. We found the mean LNR as 0.16±0.26. The occult metastasis rate was 20%. Sixteen patients (53.3%) had metastasis to the cervical LNs. The COX regression analysis suggested that LNR could be associated with survival in PG cancers. Based on Kaplan–Meier analysis, we found that LNR and neck metastasis had a negative effect on survival rates.

The PG is the largest salivary gland and houses a vast majority of neoplastic masses in the salivary glands. The nature of neoplastic masses in the PG is predominantly benign rather than malignant. Malignant salivary gland tumors are also mostly seen in the PG and the most common malignant PG tumor is mucoepidermoid carcinoma (2). Like other head and neck cancers, they tend to be seen more commonly in older and male patients.

Table 2. Histopathologic tumor type, T, N, and M stages, RT/CT treatment and survival times of the patients who underwent parotidectomy and neck dissection

				Lymph node				
P.no	**Histopathological type**	**T stage**	**N stage**	**Metastasis**	**Metastatic**	**Reactive**	**Postoperative RT/CT**	**Survival (months)**
1	Adenoid cystic carcinoma	T2	N0	-	-	42	RT + CT	106 (alive)
2	Squamous cell carcinoma	T3	N2b	-	7	29	RT + CT	2
3	Adenoid cystic carcinoma (solid)	T4b	N1	-	2	18	RT + CT	33
4	Adenocarcinoma, NOS	T2	N0	-	-	6	CT	22
5	Squamous cell carcinoma	T4a	N0	-	-	18	RT + CT	68 (alive)
6	Mucoepidermoid carcinoma (high grade)	T4a	N2b	-	3	20	-	15
7	Squamous cell carcinoma	T3	N2b	-	5	12	RT	3
8	Mucoepidermoid carcinoma (high grade)	T2	N2b	-	19	-	RT	10
9	Adenoid cystic carcinoma	T2	N0	-	-	37	-	3
10	Salivary duct carcinoma	T4a	N2b	-	18	8	-	66
11	Mucoepidermoid carcinoma (high grade)	T4a	N2b	-	7	18	-	1
12	Mucoepidermoid carcinoma (high grade)	T4a	N0	-	-	31	-	55
13	Acinic cell carcinoma	T2	N0	-	-	28	-	76
14	Mucoepidermoid carcinoma (high grade)	T3	N1	-	1	31	-	84
15	Sebaceous adenocarcinomas	T4a	N0	-	-	28	-	6
16	Mucoepidermoid carcinoma (high grade)	T4a	N0	-	-	41	RT + CT	14
17	Mucoepidermoid carcinoma (low grade)	T2	N0	-	-	47	RT	125 (alive)
18	Mucoepidermoid carcinoma (high grade)	T2	N2b	-	6	11	CT	15
19	Salivary duct carcinoma	T4a	N2b	-	19	4	RT + CT	24
20	Squamous cell carcinoma	T4a	N0	-	-	33	-	17 (alive)
21	Mucoepidermoid carcinoma (high grade)	T2	N1	-	1	49	RT + CT	3
22	Salivary duct carcinoma	T2	N1	-	1	2	-	25
23	Squamous cell carcinoma	T2	N0	-	-	21	-	46
24	Adenoid cystic carcinoma (cribriform)	T2	N0	-	-	26	RT + CT	49 (alive)
25	Adenocarcinoma, NOS	T3	N2b	-	5	17	RT + CT	8 (alive)
26	Adenoid cystic carcinoma (cribriform)	T4a	N2b	-	5	11	RT	7 (alive)
27	Mucoepidermoid carcinoma (high grade)	T4a	N0	-	-	11	RT	4 (alive)
28	Carcinoma ex pleomorphic adenoma	T2	N2b	-	4	42	CT	29
29	Polymorphous low-grade adenocarcinoma	T2	N0	-	-	24	RT	107 (alive)
30	Undifferentiated carcinoma	T2	N1	-	1	12	-	23 (alive)

CT: Chemotherapy, P. no: Patient number, RT: Radiotherapy

Table 3. Classification of LNRs of patients with a node-positive neck

LNR (mean: 0.13)	**Number of patients (%) n=30**
0	14 (47%)
0.001–0.1	5 (17%)
0.11–0.5	8 (26%)
>0.5	3 (10%)
Positive lymph node	
0	14 (47%)
1	5 (17%)
2–4	2 (6%)
5–10	6 (20%)
>10	3 (10%)

LNR: Lymph node ratio, n: Number of patients

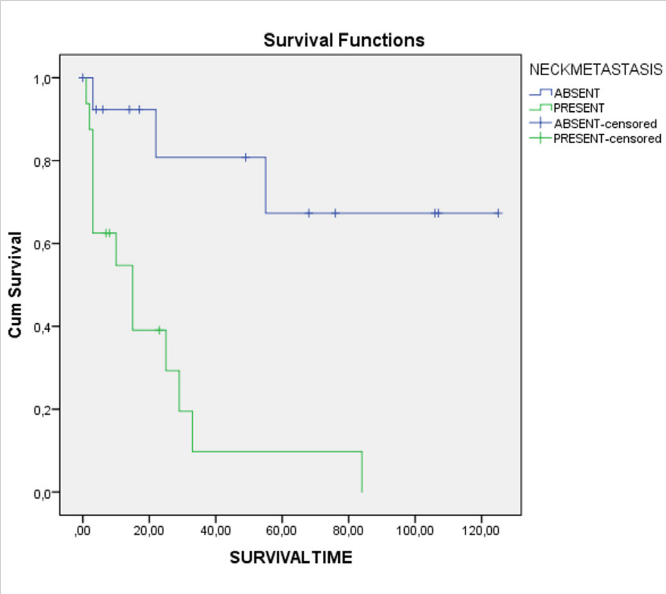

Figure 1. Kaplan–Meier survival analysis as to whether neck metastasis is present or absent

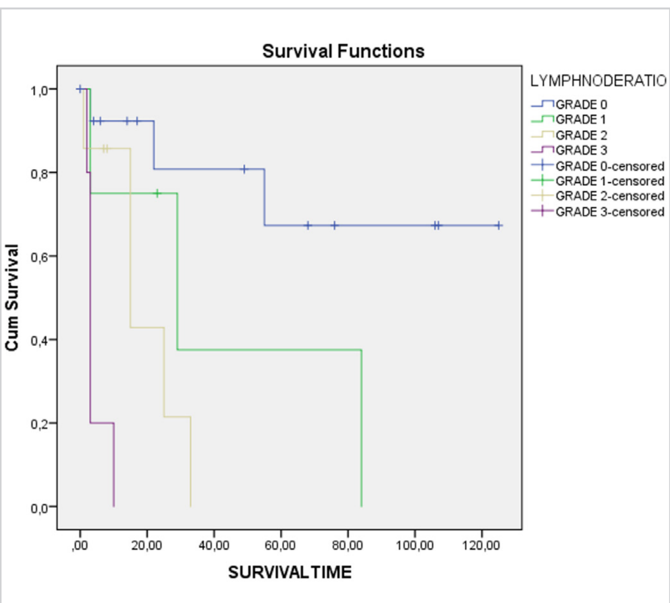

Figure 2. The effect of lymph node ratio in Kaplan–Meier survival analysis

Neck dissection plays an important role in the management of malignant head and neck tumors and it is well-known that neck metastasis significantly reduces the survival rates of patients. LN-positive neck with PG cancers requires therapeutic neck dissection as a part of treatment, but the approach to LN-negative neck with primary parotid cancers remains unclear regarding END. Elective neck dissection is not recommended routinely for all LN-negative necks in primary PG cancers except for the high risk of neck metastasis. Primary PG cancers are relatively uncommon and they have numerous histopathologic subtypes. Therefore, deciding on and planning for neck dissection for each histopathological subtype of primary PG cancer can be difficult. High-grade tumors and high T (T3/T4) stages have been shown to have a higher risk for metastasis to the neck and may need an END if the neck is clinically N0 (cN0) (13, 14). On the other hand, observation without END after parotidectomy may be sufficient in patients under the age of 60, T1 and T2 tumors, and low-grade tumor histology in cN0 necks (6). Occult neck metastasis rates have been suggested to be 12–48% (15-18). Additionally, the histological grade and final pathological diagnosis of the tumor can usually not be detected before the surgery. Therefore, deciding about END can remain a controversial issue. Fine needle aspiration biopsy and peroperative frozen section may give information about malignant versus benign tumor histology. The occult metastasis to level II LNs is more common than other neck levels and the detection of metastasis to level II or periparotid LNs on frozen section biopsy or FNAB may indicate the need for neck dissection (19). So, these two entities may prevent unnecessary neck dissections by distinguishing malignant tumors from benign ones. High-grade tumor histology after parotidectomy without neck dissection in cN0 neck may require a second operation for neck dissection. The occult metastasis rates of PG cancers are 4.3% in T1 or T2 tumors, 35% in T3 or T4 tumors, 6.1% in low or intermediate-grade tumors, and 24.2% in high-grade tumors in cN0 patients (20). Also, occult nodal disease occurs in 13.6% of cN0 patients (20). In our study, we performed an END in high-grade tumors, T3 and T4 tumors, and positive level II or periparotid LNs on FNAB or frozen section biopsy. The most common malignant primary PG tumor was mucoepidermoid carcinoma, followed by

Table 4. Multivariate COX regression analysis of various parameters over disease-specific survival

Parameter	β	Standard error	p-value	95.0% confidence interval for β	
				Lower bound	Upper bound
Neck metastasis	0.595	1.217	0.625	0.167	19.700
Lymph node ratio	1.067	0.484	0.027	1.126	7.499
Extracapsular spread	-0.033	0.893	0.971	0.168	5.567
Stage	-0.167	0.616	0.787	0.253	2.831
Perineural invasion	-0.922	0.695	0.185	0.102	1.555
Lymphovascular invasion	0.405	0.608	0.505	0.456	4.934

adenoid cystic carcinoma and squamous cell carcinoma in our study. We found that occult metastasis rates were 20% in our patients.

Histopathological results of surgical specimens may show the survival of patients with PG cancer. Histopathological factors associated with poor prognosis have been clearly known for decades. These factors are high-grade tumors, and perineural and lymphovascular invasion, as well as metastasis to regional LNs, especially with extracapsular invasion, and closely associated with low survival rates. For these reasons, high N stages, two or more metastatic LNs, and extracapsular spread may require postoperative adjuvant RT. Many studies have shown the effects on survival of the number of metastatic LNs. When the number of metastatic LNs increases in patients with major salivary gland cancers, cancer-specific survival decreases (21). LNRs have also been suggested to be closely related to the life expectancy of major salivary gland tumor patients (22). Higher LNR in minor salivary gland cancers has been reported to be associated with shorter survival times (23). Debates over the impact on the survival of LNR are ongoing and LNR values >0.15–0.38 have been shown to be associated with poor prognosis (11, 21, 23, 24). However, Hong et al. (25) found a cutoff value of 4.0 for LNR in high-grade salivary gland cancers. LNR could be affected by the numbers of both metastatic and non-metastatic LNs in neck dissection materials. When the number of metastatic LNs is high or the number of non-metastatic LNs is low in neck dissection materials, LNR may be expected to be a higher number. The extension of END can change LN numbers in occult neck metastases. Clinically and radiologically evident metastatic LNs may show that the LNR will be higher. A metastatic LN number greater than four is also associated with poor prognosis (21). Furthermore, the LNR and the number of metastatic LNs can be predictive of the need for postoperative RT after parotidectomy along with neck dissection. Similar to other studies, we suggest that LNR has a negative impact on survival in primary PG cancers.

Aro et al. (10) proposed a new classification system for nodal staging based on the number of metastatic LNs in salivary gland cancers. They divided the numbers of metastatic LNs into three groups as N1: one to two LNs, N2: three to 21 LNs, and N3: 22 or more LNs. Lee et al. (11) proposed another N staging system based on the numbers of positive LNs, where node negative is N0, one positive LN is N1, and ≥ two positive LNs or extracapsular extension is N2.

Some histologic factors can provide information about tumor aggressiveness, such as perineural invasion, extracapsular extension, and lymphovascular invasion that can cause locoregional recurrences and poor prognosis (26, 27). At the same time, these histologic factors require postoperative adjuvant therapies (RT ± CT) (27). Histopathological grade and preoperative facial paralysis can be significant predictors for occult metastasis in cN0 patients (28). Histopathologically positive nodes (pN+) can occur in 77–87% of clinically node-positive LNs (cN+) (6, 28).

Most of the studies about LNR have used data from Surveillance, Epidemiology, and End Results due to the rarity of primary PG cancers (21, 29). Hong et al. (25) suggested that the median number of total excised LN and metastatic LN were 27 (range, 1–135) and two (range, 0–68), respectively, in salivary gland cancers. Their series included I–III or I–IV elective and therapeutic neck dissections. They found a significant association between LNR and overall survival. High LNR may be related to shorter disease-specific, disease-free, and overall survival (23). The number of excised LNs >18, the number of positive LNs >4, and the LNR >33.33% are associated with poor prognosis (24). Lei et al. (29) proposed four risk groups (R0, R1, R2, and R3) based on LNR cutoff points, which were ≤0.17 in R1, 0.17–0.56 in R2, >0.56 in R3 and 5-year cause-specific survival was 88.6% in R0, 57.2% in R1, 53.1% in R2 and 39.7% in R3.

The present study has some limitations. These limitations are being a single-center study, having a small patient population, and its retrospective nature.

Conclusion

The present study suggests that LNR and neck metastasis are associated with shorter overall survival times in PG cancers. Lymph node ratio may be used as a prognostic marker in patients with PG cancer. Our results should be supported with larger prospective studies for more detailed prognostic information about primary PG cancers.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Mersin University (decision no: 2023/193, date: 29.03.2023).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: C.Ö., H.G., O.İ., K.K.B., R.B.A., K.G., Concept: C.Ö., O.İ., Y.V., R.B.A., K.G., Design: C.Ö., H.G., Y.V., K.K.B., K.G., Data Collection and/or Processing: C.Ö., O.İ., K.K.B., R.B.A., K.G., Analysis and/or Interpretation: C.Ö., H.G., O.İ., Y.V., K.G., Literature Search: C.Ö., H.G., O.İ., K.K.B., R.B.A., K.G., Writing: C.Ö., H.G., Y.V.

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Main Points

- The higher number of metastatic lymph nodes in primary parotid gland cancers may be associated with poor prognosis.
- Higher lymph node ratios may be associated with lower 5-year survival rates.
- Neck metastasis in primary parotid gland cancers may be associated with a shorter life expectancy.
- Neck dissection along with parotidectomy provides information about histopathological parameters (e.g., neck metastasis, lymph node ratio).
- Given the rarity of primary parotid gland cancers, the lymph node ratio needs to be supported by further studies in larger patient populations.

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