

Role of the pretreatment neutrophil-to-lymphocyte ratio in the survival of primary parotid cancer patients

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Background: To analyze the value of the pretreatment neutrophil-to-lymphocyte ratio (NLR) in the survival of patients with parotid cancer.

Methods: In total, 249 patients were enrolled. Information including age, sex, pretreatment NLR, and pathologic variables such as, tumor stage, intraparotid node (IPN) metastasis, and follow-up findings was extracted and analyzed.

Results: IPN metastasis was noted in 45 (18.1%) patients, and the mean NLR was 2.48, with a range from 1.5 to 6.1. The NLR was significantly associated with tumor stage, disease stage, and disease grade. A total of 73 patients died of the disease, and the 10-year disease-specific survival (DSS) rate was 62%. In patients with an NLR < 2.48, the 10-year DSS rate was 68%; in patients with an NLR ≥ 2.48, the 10-year DSS rate was 58%, and the difference was significant ($P=0.006$). Cox model analysis showed that the NLR was an independent prognostic factor for DSS.

Conclusion: The long-term survival of primary parotid cancer patients is relatively favorable, and the pretreatment NLR is significantly associated with prognosis.

Keywords: parotid cancer, intraparotid node metastasis, neutrophil-to-lymphocyte ratio, prognosis

Introduction

Interactions between the tumor microenvironment and tumor cells have important roles in cancer progression, and the microenvironment includes, metabolic, inflammatory, and immune responses to stimuli from the surrounding tissue. Recent basic studies have showed that tumor metastasis, microvascular regeneration, and tumor cell proliferation abilities are promoted by the systemic inflammatory response.¹⁻³ The peripheral neutrophil-to-lymphocyte ratio (NLR) is a well-known inflammatory marker. Several authors have previously reported that a high NLR is significantly associated with poor survival in solid cancers,⁴⁻¹⁴ including head and neck squamous cell carcinoma and breast cancer. However, whether the NLR affects prognosis in patients with parotid cancer remains unknown; therefore, the current study aimed to clarify this question.

Patients and methods

The Zhengzhou University Institutional Research Committee approved our study. All participants signed an informed consent agreement for medical research before initial treatment, and all experiments were performed in accordance with relevant guidelines and regulations. This study was conducted in accordance with the Declaration of Helsinki.

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From January 2002 to December 2016, the surgical medical records of all patients (>18 years old) diagnosed with primary parotid cancer were retrospectively included. All related data, including age, sex, tumor stage, neck stage, pretreatment NLR, postoperative pathological report, operation record, adjuvant treatment, and follow-up information, of the enrolled patients were extracted and analyzed. All pathologic sections were re-reviewed. The tumor grade was defined according to the WHO 2017 classification, and the tumor stage was defined based on the AJCC eighth Edition staging system. In our cancer center, preoperative ultrasound and CT or MRI were routinely performed. In addition, frozen sectioning of the primary tumor was routinely performed; if the pathology was malignant, a total parotidectomy was performed.

The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count within 2 weeks before the initial treatment.^{4–14} The cutoff value calculated from the ROC curve, mean, tertile, or median in previous studies varied from 1.98–5;^{4–11} thus, the standard cutoff value remains unknown. In the current study, the cutoff value was defined as the mean value of the NLR.

The chi-squared test was used to assess the association between the NLR and the clinicopathologic variables. The Kaplan–Meier method was used to calculate the disease-specific survival (DSS) rate. The Cox proportional hazards method was used to determine the independent risk factors for DSS. All statistical analyses were conducted with the help of SPSS 20.0 (IBM Corporation, Armonk, NY, USA). A $P < 0.05$ was considered significant.

Results

In total, 249 patients (147 female and 102 male) were enrolled with a mean age of 47.7 (range: 19–73) years. Tumor stage was distributed as follows: T1 in 53 (21.2%) patients, T2 in 89 (35.7%) patients, T3 in 61 (24.5%) patients, and T4 in 46 (18.5%) patients. Perineural invasion and lymphovascular invasion were noted in 31 (12.4%) and 25 (10.0%) patients, respectively. Intraparotid node metastasis (IPN) was noted in 45 (18.1%) patients. The disease grade was distributed as follows: low grade in 123 (49.4%) patients, moderate grade in 89 (35.7%) patients, and high grade in 37 (14.9%) patients (Table 1). A negative margin was achieved in 237 (95.2%) patients. The mean NLR was 2.48, with a range from 1.5 to 6.1.

In total, 189 (75.9%) patients were classified as cN0, and 57 patients underwent neck dissection; positive neck disease was reported in 18 patients. In total, 60 patients were

Table 1 Distribution of parotid gland cancers

Cancer subtype	n (%)
High grade (n=37)	
Parotid duct carcinoma	14 37.8%
Mucoepidermoid carcinoma	19 51.4%
Spindle cell carcinoma	1 2.7%
Adenocarcinoma not otherwise specified	2 5.4%
Small cell carcinoma	1 2.7%
Intermediate grade (n=89)	
Mucoepidermoid carcinoma	64 71.9%
Adenoid cystic carcinoma	22 24.7%
Myoepithelial cancer	3 3.4%
Lower grade (n=123)	
Mucoepidermoid carcinoma	84 68.3%
Acinic cell cancer	20 16.3%
Pleomorphic low grade adenocarcinoma	6 4.9%
Epithelial-myoepithelial carcinoma	8 6.5%
Basal cell adenocarcinoma	5 4.1%

classified as cN+ and underwent neck dissection; positive neck disease was reported in 50 patients.

When analyzing the association between the NLR and clinicopathologic variables, it was noted that the NLR was significantly associated with tumor stage, disease stage, and disease grade (Table 2).

During our follow up with a mean time of 89.4 (range: 8–190) months, 132 patients had received radiotherapy, 27 patients received adjuvant chemotherapy, and 10 patients received herceptin treatment; in these 10 patients, staining for Her2 was 2+ in 6 cases and 3+ in four cases. A total of 73 patients died of the disease, and the 10-year DSS rate was 62%. When analyzing the predictors for DSS, it was noted that a high NLR was associated with a poorer prognosis in patients with an NLR <2.48 the 10-year DSS rate was 68% and in patients with an NLR ≥ 2.48 , the 10-year DSS rate was 58%; the difference was significant ($P=0.006$, Figure 1). Further, the Cox model proved that the NLR was an independent predictor of DSS (Table 3).

Discussion

The importance of the NLR in patients with parotid cancer has rarely been analyzed, and to the best of the authors' knowledge, to date, only two papers have focused on this question.^{15,16} Damar et al¹⁵ found that the NLR was significantly lower in patients with benign salivary tumors than that in patients with malignant salivary gland tumors, and the NLR also significantly differed with disease grade. Similar findings were also noted in the current study. Moreover, we also noted that a higher NLR was related to more advanced stage disease. Kawakita et al¹⁶ described an NLR >2.5 in patients with salivary duct carcinoma,

Table 2 Association between neutrophil-to-lymphocyte ratio and clinical pathologic variables

Variables	Neutrophil-to-lymphocyte ratio		P-value
	<2.48 (n=111)	≥2.48 (n=138)	
Age, years			
<50	47	63	0.601
≥50	64	75	
Sex			
Female	71	76	0.156
Male	40	62	
Tumor stage			
T1+ T2	73	69	0.012
T3+ T4	38	69	
Node stage			
N0	85	104	0.824
N+	26	34	
Disease stage			
I+II	61	56	0.024
III + IV	50	82	
Perineural invasion			
Positive	11	20	0.276
Negative	100	118	
Lymphovascular invasion			
Positive	9	16	0.363
Negative	102	122	
Intraparotid node metastasis			
Positive	21	24	0.756
Negative	90	114	
Tumor Grade			
Low	63	60	0.006
Intermediate	40	49	
High	8	29	

indicating that there was a nearly 2-fold risk for death in overall survival compared to baseline levels. The current study also found that a high pretreatment NLR was associated with an increased mortality risk. A similar finding was also reported for other solid malignancies. Yu et al⁶ described that head and neck cancer patients with elevated pretreatment NLRs in peripheral blood were prone to local invasion and distant recurrence and had poor prognosis. Kano et al⁴ analyzed the data for 285 patients with head and neck cancer treated with concurrent chemotherapy and found that there were significant relationships between a high NLR and hypopharyngeal or oropharyngeal cancer; N2b to N3; T3 to T4; and clinical stage III to IV. In further survival outcomes, a high NLR was significantly associated with decreases in disease-free survival and overall survival. Recently, Dell'Aquila et al⁷ also proved the prognostic value of the pretreatment NLR in metastatic colorectal cancer.

The exact mechanism underlying the associations between clinical pathologic variables as well as prognosis and the NLR remains unknown, and some possible explanations can be mentioned based on previous evidence. The pretreatment NLR reflects the status of the immune system and systemic inflammation. The elevation of neutrophils is a sign of local and systemic inflammatory responses. Several cytokines and angiogenic factors are produced by neutrophils, and these agents play important roles in promoting tumor development.¹⁷ Additionally, hematological markers might be surrogate markers of cancer cachexia, which is related to poor survival.^{15,18} On the other hand, lymphocytes are associated with immune

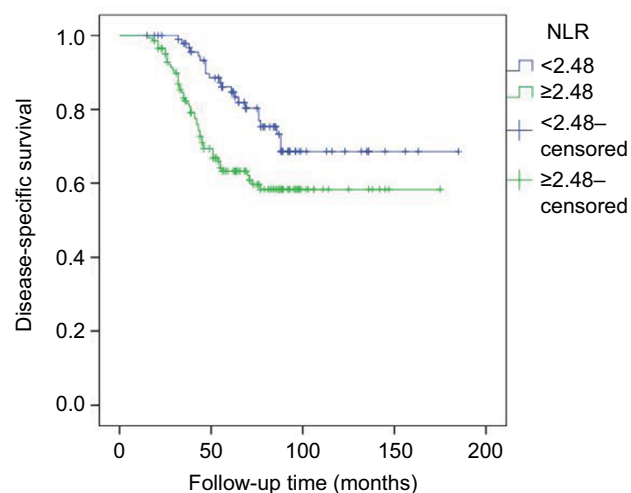
**Figure 1** Disease-specific survival in patients with different NLRs.**Note:** $P=0.006$.**Abbreviation:** NLR, neutrophil-to-lymphocyte ratio.

Table 3 Univariate and multivariate analysis of the predictors for disease-specific survival in patients with parotid cancer

Variables	Univariate	Cox model	
	P-value	P-value	OR (95% CI)
Age, years (<50 vs ≥50)	0.246		
Sex (Female vs male)	0.167		
Tumor stage (T1+ T2 vs T3+ T4)	0.004	0.087	2.647 (0.913–5.688)
Node stage (N0 vs N+)	0.002	0.123	1.997 (0.798–4.754)
Disease stage (I+II vs III+IV)	<0.001	0.002	2.114 (1.467–6.337)
Perineural invasion	<0.001	0.222	3.135 (0.687–7.541)
Lymphovascular invasion	<0.001	<0.001	2.874 (1.226–7.684)
Intraparotid node metastasis	0.013	0.003	1.845 (1.054–4.531)
NLR (<2.48 vs ≥2.48)	0.006	0.016	1.223 (1.013–2.442)
Disease grade	<0.001		
Low			
Intermediate		0.187	2.113 (0.906–7.221)
High		0.017	3.269 (1.678–10.336)
Radiotherapy	0.458		
Chemotherapy	0.367		
Herceptin	0.088		

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

surveillance and act by eliminating cancer cells.¹⁹ Therefore, a high NLR is considered to predict worse prognosis.

Another interesting finding was that IPN metastasis was associated with poor survival. Little data is available on this topic. The reported IPN metastasis rate varied from 15% to 38%, and it was significantly associated with tumor stage, disease grade, and neck node stage.^{20–27} With regard to survival analysis, only four papers have aimed to clarify this question. Lim et al²² might be the first to find that, compared to patients without IPN metastasis, patients with a cN0 neck tumor and IPN metastasis were more likely to develop locoregional recurrence. In a study published by Klusmann et al,²⁰ univariate analysis reported that the involvement of IPN was an additional, significant, risk factor for tumor recurrence in 55 patients with pN+ tumors. Recently, Nisa et al²³ described that decreased disease-free survival could be expected in patients with IPN involvement. Our previous research showed that patients with metastasis in more than 2 IPNs had the worst prognosis.²⁸ Our current finding is consistent with that of previous reports. The N parameter in the TNM classification refers to regional, cervical lymph nodes, and IPN metastasis was not included in any of the groups of neck lymph nodes. Therefore, IPN seems to be a local factor, not a regional factor.²⁷ Therefore, the presence of more metastatic nodes may decrease survival, mimicking advanced tumor stage. A similar finding was also reported by O'Brien et al²⁹ after analyzing 87 patients with cutaneous squamous cell carcinoma of the parotid gland.

Herceptin has been described in the treatment of Her2+ parotid cancer, and most previous studies have reported that the application of herceptin could increase loco-regional

control and prolong survival.^{30–32} Unfortunately, a significant association between good prognosis and herceptin was not achieved in the current study. We did not expect this result, and possible explanations may include the following: first, there were only 10 patients receiving herceptin treatment; and second, unlike previous case reports, most of the 10 patients did not have strong positivity for Her2, which might be the most likely cause of this variation.

Limitations

Limitations of the current study must be acknowledged. Firstly, this was a retrospective study, and there is inherent bias that might decrease the statistical power; and second, it should be recognized that neutrophil and lymphocyte counts are nonspecific parameters because they can be influenced by concomitant conditions, such as infections or inflammation.^{4–10}

Conclusion

The long-term survival of primary parotid cancer patients is relatively favorable, and the pretreatment NLR is significantly associated with prognosis.

Data sharing statement

All data generated or analyzed during this study are included in this published article. The primary data can be obtained from the corresponding author.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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