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The number and ratio of positive lymph nodes are independent prognostic factors for patients with major salivary gland cancer: Results from the surveillance, epidemiology, and End Results dataset

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ABSTRACT

Introduction: To investigate whether the positive lymph node number (PLNN) and positive lymph node ratio (PLNR) could predict the prognosis of patients with major salivary gland cancer (MSGC) and to identify the optimal cutoff points for these variables that stratify patients according to their risk of survival.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) database to identify all patients with MSGC between 1988 and 2014. A logistic regression analysis was carried out to evaluate the risk factors for lymph node metastasis (LNM) in MSGC. The X-tile program was used to identify the cutoff values for the PLNN and PLNR in MSGC patients with LNM. Cox proportional hazards regression models were performed to identify the predictors of cancer-specific survival (CSS).

Results: In the SEER database, 8668 eligible patients were identified and 3046 of them had LNM. The logistic regression analysis indicated that older age, male sex, larger tumor size, higher grade, tumor extension and high-risk pathology were associated with LNM. The X-tile program showed that a PLNN>4 and a PLNR>0.15 were prognostic indicators of CSS. A multivariable analysis indicated that, after the factors that might potentially affect the prognosis were adjusted for, the PLNN and PLNR were still associated with CSS.

Conclusions: Our Results demonstrated that the PLNN and PLNR were independent prognostic indicators for MSGC patients with lymph node metastasis.

Introduction

Salivary gland carcinomas (SGC) are uncommon, accounting for 3–6% of all head and neck cancers. The average rate for all salivary gland cancers is approximately 1.0–6.0 per 100,000 population [1–4]. Because of the rarity and large variety of pathological types, in-depth research on the diagnosis and treatment of this disease is lacking. The histological classification of SGC comprises 19 histological subtypes that have different prognoses, and the overall survival rates of SGC patients vary widely. Previous studies have shown that age, tumor grade and TNM stage are important prognostic factors for SGC [5–7]. It is also well known that lymph node metastasis (LNM) is closely related to the prognosis. We have previously demonstrated that the involvement level and number of positive lymph nodes are important factors in predicting the prognosis of patients with salivary duct carcinoma [8]. The eighth edition of TNM staging also incorporated more detailed descriptions of lymph node status, such as extranodal extension. However, TNM staging still has its limitations, and the effects of the lymph node metastasis status in salivary gland cancer still have not been studied with a large sample. Therefore, the concept of using the positive lymph node number (PLNN) and positive lymph node

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ratio (PLNR) as factors has caught our attention. Positive lymph node ratio is defined as the ratio of the number of metastatic lymph nodes to the number of removed lymph nodes. These have been reported as independent prognostic factors for patients with other head and neck cancers, such as thyroid cancer and head and neck squamous cell carcinoma [9–12].

In this study, we used the Surveillance, Epidemiology, and End Results (SEER) database to investigate whether the PLNN and PLNR could predict the prognosis of major SGC patients. Cutoff points for these factors were also identified in the study.

Materials and methods

Patients

The SEER database and SEER*Stat software (SEER*Stat 8.3.5) were used to analyze patients diagnosed with major salivary gland carcinoma (MSGC). Patients registered between 1988 and 2014 were included in this study, as the numbers of regional nodes examined and positive lymph nodes were not recorded before 1988. Major salivary gland cancers were defined by their primary sites and pathological types as follows: the primary site criteria included the parotid gland (C07.9), submandibular gland (C08.0), sublingual gland (C08.1), overlapping lesion of major salivary glands (C08.8) and major salivary gland, NOS (C08.9). Histological types were based on the WHO classification of salivary tumors and were limited to acinic cell carcinoma (8550), mucoepidermoid carcinoma (8430), adenoid cystic carcinoma (8200), polymorphous adenocarcinoma (8525), epithelial-myoepithelial carcinoma (8562), clear cell carcinoma (8310), basal cell adenocarcinoma (8147), sebaceous carcinoma (8410), adenocarcinoma (8140), salivary duct carcinoma (8500), myoepithelial carcinoma (8982), carcinoma ex pleomorphic adenoma (8941), carcinosarcoma (8980), small cell carcinoma (8041), large cell carcinoma (8012), lymphoepithelial carcinoma (8082), squamous cell carcinoma (8070), oncocytic carcinoma (8290) and sialoblastoma (8974) [13]. The extents of operations were designated according to RX Summ–Surg Prim Site (1998+) and regional nodes positive (1988+). Patients were excluded if the primary lesions were not surgically resected or if the regional lymph nodes were not evaluated. In addition, 22 cases with unknown or unrecorded positive lymph node statuses were also not included in the study.

The demographic characteristics, including the age at diagnosis and gender, were directly obtained from the database. Grade information was grouped into grades I-II (well-differentiated and moderately differentiated) and grades III-IV (poorly differentiated and undifferentiated; anaplastic). All of the cases were divided into low-risk and high-risk categories according to the risk stratification of WHO-recognized salivary gland malignancies [14]. In addition, tumor sizes were identified according to the EOD 10 - size (1988–2003) and CS tumor size (2004+) classifications. Tumor extension from the primary lesion was defined according to the EOD 10 - extent (1988–2003) and CS extension (2004+) classifications. Extracapsular invasion and perineural invasion were both considered tumor extensions. Whether metastases happened at the time of diagnosis was determined using Derived AJCC M, 7th ed (2010+), Derived AJCC M, 6th ed (2004+), CS Mets at Dx (2004+), SEER Historic Stage A and Summary Stage 2000 (1998+) data. The TNM staging described in the AJCC Cancer Staging Manual (7th edition, 2010) was adopted to restage the tumors of the patients in the study. Because the SEER program did not record detailed information about staging prior to 2010, we re-evaluated the TNM staging according to other variables that were available in the database. External beam radiation and chemotherapy were represented by “yes” and “no evidence” due to the information missing from the SEER database.

Statistics

All of the demographic characteristics and clinicopathological

Table 1
Clinicopathological characteristics of 8668 patients with major salivary gland cancer in the SEER database and logistic regression for lymph node metastasis.

Variables	Incident nodal involvement (n. (%))	Univariable analysis		Multivariable analysis	
		OR (95% CI)	P value	OR (95% CI)	P value
Age					
≤54yr	701/3188 (22.0%)	1		1	
>54yr	2345/5480 (42.8%)	2.654 (2.403–2.931)	<0.001	1.656 (1.481–1.852)	<0.001
Gender					
Female	938/3732 (25.1%)	1		1	
Male	2108/4936 (42.7%)	2.220(2.023–2.437)	<0.001	1.414 (1.271–1.572)	<0.001
Tumor size					
≤21 mm	703/3209 (21.9%)	1		1	
>21 mm	2004/4671 (42.9%)	2.679 (2.419–2.965)	<0.001	1.604(1.428–1.801)	<0.001
Unknown	339/788 (43.0%)	2.691 (2.284–3.171)	<0.001	1.870 (1.553–2.252)	<0.001
Tumor site					
Parotid gland	2499/7235 (34.5%)	1		1	
Submandibular gland	450/1186 (37.9%)	1.159 (1.021–1.316)	0.023	0.925 (0.801–1.067)	0.284
Other	97/247 (39.3%)	1.226(0.945–1.589)	0.125	0.958 (0.717–1.280)	0.770
Grade					
Grade I-II	661/3254 (20.3%)	1		1	
Grade III-IV	1788/3009 (59.4%)	5.745 (5.135–6.427)	<0.001	3.444 (3.049–3.891)	<0.001
Unknown	597/2405 (24.8%)	1.295 (1.142–1.469)	<0.001	1.184 (1.020–1.374)	0.027
Tumor extension					
Negative	1257/5363 (23.4%)	1		1	
Positive	1737/3213 (54.1%)	3.844 (3.500–4.222)	<0.001	2.370 (2.133–2.633)	<0.001
Unknown	52/92 (56.5%)	4.246 (2.798–6.444)	<0.001	3.023 (1.916–4.769)	<0.001
Risk stratification					
Low-risk pathology	326/2297 (14.2%)	1		1	
High-risk pathology	2547/5896 (43.2%)	4.598 (4.046–5.226)	<0.001	2.009 (1.734–2.327)	<0.001
Unknown	173/475 (36.4%)	3.463 (2.778–4.318)	<0.001	2.814 (2.202–3.596)	<0.001

The cutoff values of tumor size and age were determined by ROC curve.
Extracapsular invasion and perineural invasion were both considered as tumor extension.

Table 2
Univariable and multivariable analysis for CSS in 8668 patients with major salivary gland cancer.

Variables	No.	Cause-specific survival			
		Univariable analysis		Multivariable analysis	
		Log-rank (χ2)	P value	HR (95% CI)	P value
Age					
≤54yr	3188			1	
>54yr	5480	265.594	<0.001	1.609 (1.424–1.19)	<0.001
Gender					
Female	3732			1	
Male	4936	122.937	<0.001	1.105 (0.988–1.236)	0.079
Tumor size					
≤33 mm	5501			1	
>33 mm	2379	493.132	<0.001	1.749 (1.564–1.956)	<0.001
Unknown	788	27.499	<0.001	1.172 (0.978–1.405)	0.086
Tumor site					
Parotid gland	7235			1	
Submandibular gland	1186	54.617	<0.001	1.427 (1.254–1.624)	<0.001
Other	247	2.764	0.096	1.031 (0.769–1.382)	0.837
Grade					
Grade I-II	3254			1	
Grade III-IV	3009	585.328	<0.001	1.921 (1.662–2.220)	<0.001
Unknown	2405	31.124	<0.001	1.313 (1.104–1.563)	0.002
Tumor extension					
Negative	5363			1	
Positive	3213	791.926	<0.001	1.810 (1.607–2.039)	<0.001
Unknown	92	12.942	<0.001	1.283 (0.758–2.170)	0.354
Risk stratification					
Low-risk pathology	2297			1	
High-risk pathology	5896	286.755	<0.001	1.454 (1.213–1.742)	<0.001
Unknown	475	89.429	<0.001	1.791 (1.362–2.355)	<0.001
Lymph node status					
Negative	5622			1	
Positive	3046	1165.137	<0.001	2.666 (2.364–3.007)	<0.001
M stage					
M0	8175			1	
M1	493	539.203	<0.001	1.988 (1.722–2.295)	<0.001
External beam radiation					
Yes	5075			1	
No evidence	3593	201.157	<0.001	0.922 (0.816–1.042)	0.192
Chemotherapy					
Yes	896			1	
No evidence	7772	406.131	<0.001	0.760 (0.667–0.867)	<0.001

The cutoff values of tumor size and age were determined by X-tile program.
Extracapsular invasion and perineural invasion were both considered as tumor extension.

Table 3
Univariable analysis of the influence of different PLNN and PLNR count on CSS in 3046 patients with lymph node involvement.

Number of PLNs	No.	5-year CSS	Log-rank (χ2)	P value	Ratio of PLNs	No.	5-year CSS	Log-rank (χ2)	P value
= 1	1197	74.4%			>0 & <0.1	717	68.1%		
>1	1849	49.2%	132.388	<0.001	≥0.1	2329	56.9%	24.282	<0.001
≤2	1702	71.4%			<0.2	1232	65.5%		
>2	1344	43.5%	183.469	<0.001	≥0.2	1814	55.5%	27.254	<0.001
≤3	2000	68.8%			<0.3	1616	63.5%		
>3	1046	40.8%	176.283	<0.001	≥0.3	1430	55.1%	20.807	<0.001
≤4	2155	68.0%			<0.4	1874	62.9%		
>4	891	37.0%	201.055	<0.001	≥0.4	1172	54.1%	22.772	<0.001
≤5	2294	66.8%			<0.5	1996	62.2%		
>5	752	35.1%	192.671	<0.001	≥0.5	1050	54.5%	15.060	<0.001
≤6	2388	66.2%			<0.6	2232	62.1%		
>6	658	33.2%	190.932	<0.001	≥0.6	814	52.5%	21.147	<0.001
≤7	2462	65.5%			<0.7	2350	61.6%		
>7	584	31.1%	185.382	<0.001	≥0.7	696	52.6%	17.856	<0.001
≤8	2518	65.1%			<0.8	2423	60.7%		
>8	528	30.0%	193.114	<0.001	≥0.8	623	54.9%	7.583	0.006
≤9	2575	64.5%			<0.9	2512	59.9%		
>9	471	29.5%	181.547	<0.001	≥0.9	534	57.7%	1.361	0.243
≤10	2615	64.0%			<1.0	2579	58.7%		
>10	431	29.3%	170.258	<0.001	≥1.0	467	63.4%	2.082	0.149

features were obtained from the SEER database. A logistic regression analysis was carried out to evaluate the risk factors for LNM in patients with MSGC. The survival curves were estimated using the Kaplan-Meier method, and the differences between the curves were analyzed using log-rank tests. Cox proportional hazards regression models were performed to identify the predictors of CSS in multivariable analyses. The cutoff points for the PLNN and PLNR were determined using the X-tile 3.5.0 software (Yale University, New Haven, CT, USA) for patients with lymph node metastasis based on the minimum P values and the maximum $\chi 2$ test statistic values of log-rank tests. The cutoff points for age and tumor size were determined by receiver operating characteristics (ROC) curve or X-tile program in different analysis models. P-values of less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

In the SEER database, 8668 eligible patients, including 3732 females and 4936 males, were identified for the period from 1988 to 2014. Their clinical and demographic characteristics are summarized in Table 1. Cases of missing data for variables were recorded as "unknown". The ages of the patients ranged from 3 to 101 years old, and most of the tumors occurred in patients who were relatively older. A substantial proportion of the primary lesions were located in the parotid gland (83.5%). There were 493 patients diagnosed with distant metastases at the initial treatment when primary lesions and lymph nodes were resected. More than half of the patients (5075, 58.5%) received external beam radiation, and only 896 (10.3%) underwent chemotherapy. The incidences of nodal metastasis for different variables are also presented in Table 1. The median follow-up time was 49 months. During the follow-up period, 1521 (17.5%) patients died due to MSGC.

Risk factors for nodal metastasis

The potential risk factors associated with lymph node metastasis for all 8668 patients are shown in Table 1. A univariable analysis indicated that older age (>54 years old, $P < 0.001$), male sex ($P < 0.001$), larger tumor size (>21 mm, $P < 0.001$), submandibular gland tumor location ($P = 0.029$), higher grade ($P < 0.001$), tumor extension ($P < 0.001$) and high-risk pathology ($P < 0.001$) were all significantly associated with higher odds of nodal metastasis. In a multivariable analysis, all of the above factors except for tumor site were negative prognostic indicators for LNM.

Identification of cutoff values for PLNN and PLNR

Table 2 shows that both the univariable and multivariable analyses confirmed lymph node metastasis as an independent predictor of poor CSS.

To further assess the effects of different PLNN and PLNR values on CSS, we used their continuous values to analyze the corresponding Kaplan-Meier Results in patients with at least one positive cervical lymph node (Table 3). The PLNN values ranged from 1 to 10, and the PLNR values ranged from 0.1 to 1.0. The 5-year CSS and $\chi 2$ values are listed in Table 3. As boundary values for the PLNN and PLNR were increased, the $\chi 2$ values reached maximums at 4 for the PLNN and 0.2 for the PLNR.

Next, X-tile plots were constructed, and a maximum $\chi 2$ log-rank value of 200.1160 was produced after applying 4 as the optimal cutoff point for the PLNN to divide the cohort into high- and low-risk subgroups in terms of CSS. In a similar manner, the maximum $\chi 2$ was 40.7267 when the cutoff value for the PLNR was 0.15 (Fig. 1).

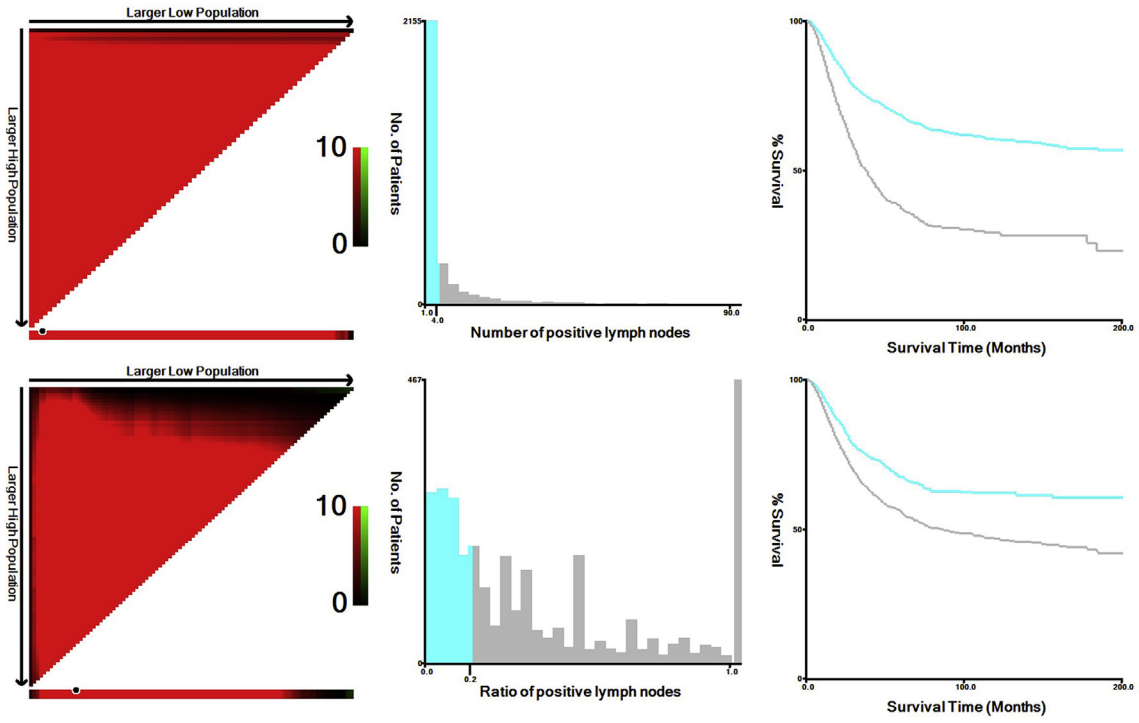

Fig. 1. X-tile analysis of survival data from the SEER registry. X-tile analysis was performed based on patient data obtained from the SEER registry, equally divided into training and validation sets. X-tile plots of training sets were shown in the left panel. The optimal cut-points highlighted by the black circle in the left panels were shown on histograms of the entire cohort (middle panels) and Kaplan-Meier plots (right panels). P values were determined by using the cut-points defined in the training set and applying them to the validation set. The optimal cut-off point for PLNN was 4, $\chi 2 = 200.1160$, $P < 0.001$. The optimal cut-off point for PLNR was 0.15, $\chi 2 = 40.7267$, $P < 0.001$.

Table 4
Univariable and multivariable analysis for CSS in 3046 patients with lymph node involvement (PLNN).

Variables	No.	Cause-specific survival			
		Univariable analysis		Multivariable analysis	
		Log-rank ($\chi 2$)	P value	HR (95% CI)	P value
Age					
≤44yr	321			1	
>44yr	2725	38.406	<0.001	1.667 (1.319–2.106)	<0.001
Gender					
Female	938			1	
Male	2108	9.169	0.002	1.054 (0.919–1.210)	0.451
Tumor size					
≤30 mm	1462			1	
>30 mm	1245	107.054	<0.001	1.639 (1.434–1.875)	<0.001
Unknown	339	2.128	0.145	1.112 (0.892–1.385)	0.346
Tumor site					
Parotid gland	2499			1	
Submandibular gland	450	27.113	<0.001	1.425 (1.219–1.667)	<0.001
Other	97	0.242	0.623	1.135 (0.800–1.611)	0.477
Grade					
Grade I-II	661			1	
Grade III-IV	1788	67.392	<0.001	1.529 (1.274–1.836)	<0.001
Unknown	597	6.865	<0.001	1.185 (0.931–1.509)	0.167
Tumor extension					
Negative	1257			1	
Positive	1737	114.557	<0.001	1.410 (1.222–1.628)	<0.001
Unknown	52	0.538	0.463	0.809 (0.426–1.538)	0.519
Risk stratification					
Low-risk pathology	326			1	
High-risk pathology	2547	24.166	<0.001	1.167 (0.922–1.478)	0.199
Unknown	173	10.205	0.001	1.425 (1.003–2.025)	0.048
Number of PLNs					
≤4	2155			1	
>4	891	201.055	<0.001	1.775 (1.552–2.028)	<0.001
M stage at diagnosis					
M0	2714			1	
M1	332	140.032	<0.001	1.867 (1.585–2.200)	<0.001
External beam radiation					
Yes	2252			1	
No evidence	794	0.000	0.999	1.170 (1.010–1.355)	0.036
Chemotherapy					
Yes	658			1	
No evidence	2388	36.011	<0.001	0.915 (0.789–1.062)	0.242

The cutoff values of tumor size and age were determined by X-tile program.
Extracapsular invasion and perineural invasion were both considered as tumor extension.

Therefore, 4 and 0.15 were chosen as the most appropriate cutoff points for the positive lymph node number and ratio, respectively.

Impact of the PLNN and PLNR on CSS in patients with nodal metastasis

The univariable analysis showed that the PLNN (>4) and PLNR (>0.15) were both associated with poor prognosis in patients with nodal metastasis. In the Cox proportional hazards model, a multivariable analysis indicated that, after the factors that might potentially affect the prognosis were adjusted for, the PLNN (>4, HR = 1.775, 95% CI: 1.552–2.028, P < 0.001) and PLNR (>0.15, HR = 1.503, 95% CI: 1.308–1.727, P < 0.001) were still independent prognostic factors of CSS respectively (Tables 4 and 5).

Discussion

Along with the deepening of research into salivary gland carcinoma, prognostic factors for this disease have been widely recognized by surgeons and oncologists in formulating a therapeutic schedule and prognosis criterion. Many models have been established for predicting prognoses [5,15], and almost all of the research has demonstrated the prognostic value of cervical lymph node metastasis. We have known that LNM of salivary cancer had its certain regularity [16]. Nevertheless, how the status of lymph node metastasis, including the size, location and number involved, influenced the prognosis was seldom studied. Moreover, the lymph node staging used in the eighth AJCC TNM classification is mainly based on the sizes and extranodal extensions of the involved lymph nodes. In this staging system, the exact number and ratio of LNs are not discussed in detail. In our opinion, the PLNN and PLNR could cooperatively reflect two important factors: regional spread and surgical treatment, which were both essential in predicting the prognosis. In addition, the number and ratio of LNs were easy to obtain, and classifications based on them were very convenient. Therefore, we thought that they were both worthy of clinical research and application.

The number or density of lymph nodes found in a pathological examination has been considered a predictor of outcomes for many tumors [17–19]. In salivary gland carcinoma, the value of the lymph node density (LND) in predicting the prognosis was first suggested by Suzuki et al. [20]. They found that an LND ≥0.38 in patients exhibiting pathological lymph node involvement was significantly related to a shorter overall survival time. A similar conclusion was later drawn in salivary adenoid cystic carcinoma as well [21]. Recently, our study of salivary duct carcinoma [8] first proposed that the number of positive lymph nodes could be a prognostic indicator. However, all of the results of the studies above were

Table 5
Univariable and multivariable analysis for CSS in 3046 patients with lymph node involvement (PLNR).

Variables	No.	Cause-specific survival			
		Univariable analysis		Multivariable analysis	
		Log-rank ($\chi 2$)	P value	HR (95% CI)	P value
Age					
≤44yr	321			1	
>44yr	2725	38.406	<0.001	1.681 (1.330–2.124)	<0.001
Gender					
Female	938			1	
Male	2108	9.169	0.002	1.090 (0.949–1.251)	0.221
Tumor size					
≤30 mm	1462			1	
>30 mm	1245	107.054	<0.001	1.659 (1.451–1.897)	<0.001
Unknown	339	2.128	0.145	1.131 (0.907–1.409)	0.274
Tumor site					
Parotid gland	2499			1	
Submandibular gland	450	27.113	<0.001	1.481 (1.267–1.732)	<0.001
Other	97	0.242	0.623	1.113 (0.785–1.579)	0.547
Grade					
Grade I-II	661			1	
Grade III-IV	1788	67.392	<0.001	1.664 (1.388–1.995)	<0.001
Unknown	597	6.865	<0.001	1.184 (0.930–1.507)	0.170
Tumor extension					
Negative	1257			1	
Positive	1737	114.557	<0.001	1.497 (1.298–1.726)	<0.001
Unknown	52	0.538	0.463	0.820 (0.431–1.560)	0.546
Risk stratification					
Low-risk pathology	326			1	
High-risk pathology	2547	24.166	<0.001	1.187 (0.936–1.506)	0.157
Unknown	173	10.205	0.001	1.550 (1.091–2.202)	0.014
Ratio of PLNs					
≤0.15	1057			1	
>0.15	1989	41.085	<0.001	1.503 (1.308–1.727)	<0.001
M stage at diagnosis					
M0	2714			1	
M1	332	140.032	<0.001	1.955 (1.661–2.302)	<0.001
External beam radiation					
Yes	2252			1	
No evidence	794	0.000	0.999	1.164 (1.005–1.348)	0.043
Chemotherapy					
Yes	658			1	
No evidence	2388	36.011	<0.001	0.832 (0.719–0.962)	0.013

The cutoff values of tumor size and age were determined by X-tile program.
Extracapsular invasion and perineural invasion were both considered as tumor extension.

based on small sample populations or specific pathological types, which were not sufficiently convincing. Thus, we searched the SEER database, which covers approximately 28% of the population of the United States, to explore whether the PLNN and PLNR could be prognostic parameters for patients with MSGC. We also wanted to determine the most suitable cutoff values using the X-tile program.

The incidences of lymph node involvement reported in previous articles were approximately 20–40% [22–25], and 35% of the patients in our study had LNM at diagnosis. Based on our logistic regression analysis of LNM, age, sex, tumor size, grade and tumor extension were predictive factors for lymph node metastasis, which was also consistent with the results of previous studies [16,24,26–28]. Beyond clinicopathological features, Ettl et al. [24] also investigated the effects of aberrations and amplifications of EGFR, HER2, MET and PTEN on lymph node metastasis. Their findings demonstrated that the molecular markers PTEN and MET were significant predictors of LNM, whereas HER2 and EGFR did not reach significant levels as predictors in a multivariable analysis. An earlier study also showed that VEGF expression was involved in the progression of SGC and was associated with neck node metastasis [29]. From our point of view, prognostic molecular markers are especially meaningful and can help identify individualized treatments. These results could establish a scientific basis for choosing the option of neck dissection for MSGC patients.

Using the X-tile program and the Cox multivariable analysis model, we obtained the result that a PLNN>4 and a PLNR>0.15, as independent indicators, were related to survival for MSGC patients with lymph node metastasis. PLNN and PLNR values were obtained based on the number of positive lymph nodes and the total number of resected lymph nodes. This information was easy to obtain from postoperative materials. Identification of the cutoff values requires a deep and complete understanding of the pathological data. Of course, it is noteworthy that the accuracies of the PLNN and PLNR are often affected by several factors. The most important is the extent of the surgery [30]. If the range of lymph node resection is not sufficient, the counts will be inaccurate. However, an excessive resection range will increase the operative risk and also influence the statistical number of lymph nodes. Thus, a standardized and appropriate operative procedure is essential. On the other hand, the harvesting protocol for specimens and the number of lymph nodes examined by pathologists were also important factors [12,30], thus the same standards must be applied when evaluating LNs. Therefore, the exactly use of PLNN and PLNR in evaluating prognosis is based on the above conditions, or the prognostic significance will be limited. That is also why both measures should be included when predicting prognosis. The number of positive nodes can directly reflect the lymph node status, but the number of examined lymph nodes would limit the maximal number of positive lymph

nodes and influence the effect of PLNN. Therefore, PLNR can help reflect better the lymph node status to guarantee the reliability. Accordingly, both PLNN and PLNR were explored and confirmed to have prognostic value in the study.

In addition, the PLNN and PLNR might have predictive effects for postoperative radiation. Postoperative radiotherapy was proven to be practical and effective for increasing survival rates in major salivary gland carcinoma patients [31–34]. However, because of its adverse effects [35] and results from previous studies indicating that not all patients benefit from adjuvant radiation [8,36], the indications for postoperative radiotherapy remain controversial. Feinstein et al. [36] proposed that advanced nodal disease could be considered a stratification factor in future trials for locally advanced salivary gland cancers. Thus, we hypothesized that the PLNN and PLNR were perhaps good predictors for planning the range and dose of postoperative radiation.

There were several limitations to this study. First, all of the patients included in the study were from the SEER database, so it was difficult to control for their baseline characteristics. Second, the SEER database lacked information regarding some tumor characteristics, such as perineural invasion, and some of the cases had incomplete information. This could potentially be a cause of bias. Third, regional dissemination tends to be orderly in MSGC, progressing from adjacent nodes to upper cervical lymph nodes then to the lower jugular region and posterior cervical triangle. The involvement levels may also be important in predicting the prognosis, but the positions of positive lymph nodes were not available in the SEER database. In the future, this issue should be addressed by in-depth research into which numbers, sizes and involvement levels of lymph nodes are relevant. Fourth, the quality of the surgical resections and the number of lymph nodes harvested and examined would directly influence the calculations of LNs [12,30]; this was hard to control for when using the SEER database. Lastly, this research was a retrospective study, and further clinical research is necessary to confirm the Results.

Conclusions

Our study showed that age, gender, the degree of differentiation and the local conditions of the primary lesions were risk factors for lymph node metastasis in MSGC patients. We have demonstrated the importance of the positive lymph node number and positive lymph node ratio in identifying patients with lymph node metastasis at high risk of treatment failure. Importantly, both measures are recommended to be included when predicting prognosis and the usefulness of them should depend on deciding correctly on the appropriate extent of surgery and on using standardized protocols for evaluation of lymph nodes by pathologists. The optimal cutoff values for the PLNN and PLNR were 4 and 0.15, respectively.

Conflict of interest statement

None declared.

Declarations of interest

None.

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