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The limited role of elective neck dissection in patients with cN0 salivary gland carcinoma

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ABSTRACT

Purpose: To evaluate whether elective neck dissection (END) was beneficial for cN0 patients with salivary gland carcinoma.
Materials and methods: The rates of regional failure-free survival and disease-free survival were calculated using Kaplan–Meier methods and Cox models. The risk factors for occult lymph node metastasis (OLNM) in cN0 patients undergoing END was analyzed using logistic regression. A nomogram was formulated to calculate the estimated probability of OLNM.
Results: Neck dissection was performed in 84 patients (43.3%). OLNM was detected in eight of the patients who underwent END. During the follow-up period, regional recurrences involving cervical lymph nodes were found in 10 patients. Cox model analysis revealed that neck dissection was not related to regional failure-free survival and disease-free survival. Logistic regression analysis revealed that older age, neural symptoms, and positive adjacent lymph nodes were associated with OLNM. A nomogram comprising age, neural symptoms, and adjacent lymph nodes was developed to predict the risk of OLNM.
Conclusion: The incidence of OLNM was low in cN0 patients after detailed preoperative evaluations. There was no strong evidence supporting END as a conventional therapy in cN0 patients with salivary cancers. Our nomogram is a simple and practical instrument for strengthening the prediction of OLNM.

1. Introduction

Elective or radical neck dissection is an important treatment for head and neck cancer (Ren et al., 2015; Green et al., 2016). Neck dissection is well recognized as a necessary treatment for patients with major salivary gland carcinomas exhibiting clinical evidence of nodal disease (Sood et al., 2016). However, a unified consensus on the management of neck cancer in patients with clinically negative nodes (cN0) has not been reached (Vander et al., 2012; Medina et al., 2016). The incidence of major salivary gland malignancies is relatively low worldwide (Emadzadeh et al., 2017; Levi et al., 2017), and many histological types exist (Seethala, 2009; Bobati et al., 2017), making clinical research of this disease difficult to perform. Considering certain unavoidable surgical complications, we believe that the decision on whether preventive neck dissection is performed for all patients with cN0 cancer should be based on the incidence of occult lymph node metastases and the influence on prognosis. Therefore, the purpose of this study is to evaluate whether elective neck dissection (END) is beneficial for all patients with clinically negative lymph nodes and to investigate the indications for END.

2. Materials and methods

Patients with major salivary gland carcinomas who underwent operations at Fudan University Shanghai Cancer Center from April 2006 to December 2016 were recruited to this study. All patients included in the study met the following the inclusion criteria: primary malignant tumor arising from a parotid and submandibular gland; no evidence of lymph node metastases before surgery;

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performance of detailed preoperative examinations; performance of initial treatment in our hospital; and no evidence of distant metastasis found during the initial treatment. Patients with non-salivary malignancies and metastases to the salivary gland, and those with tumors not treated surgically, were excluded from the study. The study was reviewed and approved by the Institutional Ethics Committee of Fudan University Shanghai Cancer Center.

All patients underwent physical examinations, ultrasound examinations, and imaging studies — computed tomography (CT) or magnetic resonance imaging (MRI) — to evaluate the primary lesions and cervical lymph nodes. Lymph node biopsy and positron emission tomography-CT were also performed for some patients to exclude node diseases. Clinical N0 disease was defined as the presence of lesions with no preoperative clinical evidence of cervical lymph node involvement.

In total, 194 patients with cN0 cancer were enrolled in this retrospective study. The patients had different pathological types of cancer, of which adenoid cystic carcinoma was the most common (22.7%), followed by mucoepidermoid carcinoma (20.1%), acinar cell carcinoma (17.0%), and salivary duct carcinoma (12.9%). All cases were divided into low-risk and high-risk categories according to the World Health Organization-recognized salivary gland malignancy risk stratification (Seethala, 2009). Eighty-four (43.3%) patients underwent END and the remaining 110 (56.7%) underwent primary tumor resection without END. END included modified radical neck dissection and selective I, II, and III END. Adjacent lymph node dissection (periparotid lymph node dissection or submandibular triangle dissection) was routinely performed. The adjacent nodes in patients with parotid gland cancer comprised parotid lymph nodes, intraparotid nodes, and subdigastric nodes. In patients with submandibular gland carcinoma, adjacent lymph node dissection meant submandibular triangle dissection. After the operations, 94 patients were treated with adjuvant radiotherapy and only 11 received chemotherapy. Among all 194 patients, 18 were followed up for <12 months after surgery — these patients were not included in the prognostic analysis. The median follow-up time for the other 176 patients was 52 months.

All clinical and pathological statistics obtained in the study were analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R 3.4.3 (http://www.r-project.org/). The chi-square test or Fisher exact probability test was used to compare the clinicopathological characteristics of patients between the END(−) group and END(+) group. An independent *t*-test was employed for quantitative variables. The regional failure-free survival and disease-free survival rates were calculated using Kaplan–Meier methods and compared using the log-rank test. Cox proportional hazards regression models were used to assess the predictors of prognosis in multivariate analyses. Logistic regression analysis was used to evaluate the risk factors for lymph node metastasis in patients with cN0 cancer undergoing neck dissection. Based on the results of the multivariable analysis, a nomogram was formulated with R, using the 'rms' package to calculate the estimated probability of lymph node metastases in patients with cN0 cancer. A *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The clinical and demographic characteristics of all 194 patients are shown in Table 1. The patients comprised 98 male and 96 female patients aged 14–85 years (average, 50 years). Most of the primary lesions were located in the parotid gland (78.4%). Compared with the END(−) group, the END(+) group had a larger proportion of male patients ($p = 0.013$) and a significantly higher incidence of aggressive characteristics, such as a higher T stage ($p = 0.000$), perineural invasion ($p = 0.000$), and extracapsular invasion ($p = 0.002$). There were also differences in the pathological types between the two groups ($p = 0.000$). Adjuvant neck irradiation was performed in 48 patients (57.1%) in the END(+) group compared with 51 patients (46.4%) in the END(−) group ($p = 0.137$).

Table 1
Characteristics of cN0 patients with major salivary gland carcinoma treated with/without neck dissection.

Variables	Groups		*p*-value
	END(−) (110)	END(+) (84)	
Age (y)	48.20 ± 15.08	52.67 ± 17.17	0.167
Sex n (%)			**0.013**
Male	47 (42.7)	51 (60.7)	
Female	63 (57.3)	33 (39.3)	
Tumor size (mm)	2.34 ± 1.11	2.59 ± 1.22	0.686
Tumor site n (%)			0.523
Parotid gland	88 (80.0)	64 (76.2)	
Submandibular gland	22 (20.0)	20 (23.8)	
Perineural invasion n (%)			**0.000**
Positive	24 (21.8)	43 (51.2)	
Negative	86 (78.2)	41 (48.8)	
Extracapsular invasion n (%)			**0.002**
Positive	12 (10.9)	24 (28.6)	
Negative	98 (89.1)	60 (71.4)	
T Stage n (%)			**0.000**
T1	39 (35.5)	18 (21.4)	
T2	40 (36.4)	11 (13.1)	
T3	8 (7.3)	12 (14.3)	
T4a/T4b	23 (20.9)	43 (51.2)	
Risk stratification n (%)			**0.000**
Low-risk category	69 (62.7)	26 (31.0)	
High-risk category	41 (37.3)	58 (69.0)	
Pathological type n (%)			**0.000**
Adenoid cystic carcinoma	19 (17.3)	25 (29.8)	
Mucoepidermoid carcinoma	21 (19.1)	18 (21.4)	
Acinar cell carcinoma	27 (24.5)	6 (7.1)	
Salivary duct carcinoma	8 (7.3)	17 (20.2)	
Malignant pleomorphic adenoma	15 (13.6)	2 (2.4)	
Others	20 (18.2)	16 (19.1)	

cN0, clinically negative nodes; END, elective neck dissection.

3.2. Risk factors for regional failure-free survival and disease-free survival

Among the 176 patients who were followed up for >1 year, treatment failure occurred in 31 (17.6%) during the follow-up period, including 19 cases of locoregional recurrence and 19 cases of distant metastasis. Ten patients (5.7%) experienced regional failure involving cervical lymph nodes; seven of these were patients who had undergone neck dissection. Most of the failures occurred in levels II and III, but one case was found to have lymph node metastases in level IV, and two failures happened in level I.

The Kaplan–Meier method revealed that age ($p = 0.000$), sex ($p = 0.008$), tumor size ($p = 0.008$), tumor site ($p = 0.002$), perineural invasion ($p = 0.009$), extracapsular invasion ($p = 0.006$), T stage ($p = 0.002$), risk stratification ($p = 0.000$), and neck dissection ($p = 0.034$) were independent risk factors for regional failure. In the multivariate analysis, only extracapsular invasion ($p = 0.014$) was correlated with cervical lymph node recurrence. The multivariate analysis showed that whether neck dissection ($p = 0.701$) was performed did not affect the probability of cervical lymph node recurrence (Table 2).

The risk factors for disease-free survival in patients with cN0 cancer are shown in Table 3. The univariate analysis showed that age ($p = 0.012$), tumor size ($p = 0.001$), tumor site ($p = 0.000$),

Table 2
Univariate and multivariate analysis for regional failure-free survival in cN0 patients (176 cases).

Variables	Number of patients	Regional failure-free survival		
		Univariate analysis	Multivariate analysis	
		p-value	HR (95% CI)	*p*-value
Age, yr				
≤60	124	–	1	
>60	52	0.000	3.716 (0.732–18.862)	0.113
Sex				
Female	86	–	1	
Male	90	0.008	–	0.891
Tumor size, mm				
≤25	116	–	1	
>25	60	0.008	1.840 (0.287–11.781)	0.520
Tumor site				
Parotid gland	137	–	1	
Submandibular gland	39	0.002	1.018 (0.194–5.355)	0.983
Perineural invasion				
No	116	–	1	
Yes	60	0.009	0.872 (0.124–6.116)	0.891
Extracapsular invasion				
No	134	–	1	
Yes	42	0.006	20.277 (1.836–223.925)	**0.014**
T stage				
T1, 2	100	–	1	
T3, 4	76	0.002	8.926 (0.269–296.610)	0.221
Risk stratification				
Low risk	86	–	1	
High Risk	90	0.000	–	0.888
Neck dissection				
No	95	–	1	
Yes	81	0.034	1.492 (0.193–11.510)	0.701
Adjuvant radiotherapy				
No	82	–	1	
Yes	94	0.264	0.919 (0.163–5.174)	0.924

cN0, clinically negative nodes.

perineural invasion ($p = 0.000$), extracapsular invasion ($p = 0.011$), T stage ($p = 0.000$), risk stratification ($p = 0.000$), and neck dissection ($p = 0.034$) were prognostic indicators for disease-free survival. Multivariate analysis revealed that risk stratification of tumors ($p = 0.002$) was related to disease-free survival, but that neck dissection was not an independent risk factor.

3.3. Factors related to pN+ and development of the nomogram for pN+

In total, 84 patients with cN0 cancer who underwent END were examined using univariate and multivariate logistic regression analyses to investigate the factors related to occult lymph node metastasis (Table 4). The numbers of lymph nodes removed in these patients are shown in Fig. 1. Occult metastases in the neck dissection specimens were detected in eight (9.5%) of the patients who underwent END. In univariate analysis, older age ($p = 0.043$) and positive adjacent lymph nodes ($p = 0.013$) were significantly associated with a high prevalence of pathologically positive lymph nodes. The multivariate analysis revealed that older age ($p = 0.030$), neural symptoms ($p = 0.034$), and positive adjacent lymph nodes ($p = 0.018$) were the independent predictors of occult lymph node metastasis.

To predict the risk of occult lymph node metastasis, a prognostic nomogram model consisting of the independent factors was established (Fig. 2).

4. Discussion

Cervical lymph node metastasis plays an important role in the prognosis of major salivary gland carcinoma, with regional metastasis reportedly occurring in approximately 10–40% of these patients (Armstrong et al., 1992; Wang et al., 2012; Nobis et al., 2014; Honda et al., 2018) Therefore, standardized neck management is particularly important for this disease. There is a consensus that neck dissection should be performed in patients with clinically confirmed neck metastasis (Vander et al., 2012; Bradley, 2015; Sood et al., 2016). Nevertheless, no agreement has been reached regarding the indication for END in patients with cN0 salivary cancer, which is in contrast to the clear indications for END in cases of head and neck squamous cell carcinoma (Bar and Chalian, 2008; Shen et al., 2017) and thyroid cancer (McAlister et al., 2014; Schoppy and Holsinger, 2014).

In our retrospective study, 43.2% of patients with cN0 cancer underwent END, and these patients actually had a higher proportion of aggressive features. Occult neck metastases were found in only 9.5% of the patients who underwent END. Our analysis of the characteristics of the disease showed that some factors, such as extracapsular invasion and risk stratification of pathological types, might influence the rate of neck recurrence and distant metastasis. This is also consistent with the results of previous studies (Hong et al., 2015; Jegadeesh et al., 2015; Yoo et al., 2015). However, our study did not reveal the effects of END on improving the prognosis. Our logistic regression analysis of patients undergoing END allowed us to identify some variables that can predict metastasis of occult lymph nodes, and we established a prognostic nomogram model accordingly.

Studies over the past few decades have shown that END has an important influence and great clinical value in the treatment of salivary gland cancer. Some researchers have insisted that END should be carried out in all cases of primary salivary carcinoma (Zbaren et al., 2005; Kawata et al., 2010; Nobis et al., 2014). This

Table 3
Univariate and multivariate analysis for disease-free survival in cN0 patients (176 cases).

Variables	Number of patients	Disease-free survival		
		Univariate analysis	Multivariate analysis	
		p-value	HR (95% CI)	*p*-value
Age, yr				
≤60	124	–	1	
>60	52	0.012	1.322 (0.605–2.886)	0.484
Sex				
Female	86	–	1	
Male	90	0.078	1.557 (0.689–3.521)	0.287
Tumor size, mm				
≤25	116	–	1	
>25	60	0.001	1.546 (0.682–3.505)	0.297
Tumor site				
Parotid gland	137	–	1	
Submandibular gland	39	0.000	1.309 (0.590–2.903)	0.508
Perineural invasion				
No	116	–	1	
Yes	60	0.000	1.252 (0.409–3.833)	0.693
Extracapsular invasion				
No	134	–	1	
Yes	42	0.011	1.875 (0.796–4.415)	0.150
T stage				
T1, 2	100	–	1	
T3, 4	76	0.000	2.596 (0.589–11.436)	0.207
Risk stratification				
Low risk	86	–	1	
High risk	90	0.000	10.844 (2.365–49.727)	**0.002**
Neck dissection				
No	95	–	1	
Yes	81	0.000	1.949 (0.768–4.945)	0.160
Adjuvant radiotherapy				
No	82	–	1	
Yes	94	0.168	0.827 (0.372–1.836)	0.640

cN0, clinically negative nodes.

recommendation is mainly based on the following aspects. First, these researchers considered that no reliable preoperative predictors for lymph node metastasis were currently identifiable. Second, occult metastases can also be observed in patients with low-grade carcinomas. Finally, the rate of lymph node metastasis is high, and positive lymph nodes are difficult to discover preoperatively in these patients. Nevertheless, a substantial proportion of doctors have stated that END should only be performed in patients with high-grade pathological types and aggressive lesions (Sheahan et al., 2004; Ali et al., 2014; Lau et al., 2014; Lee et al.,

Table 4
Univariate and multivariate logistic regression for pN+ in cN0 patients undergoing neck dissection (84 cases).

Variables	Incident nodal involvement	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex					
Female	4/33	1		1	
Male	4/51	0.617 (0.143–2.660)	0.517	0.263 (0.031–2.243)	0.222
Age, yr					
≤55	1/44	1		1	
>55	7/40	9.121 (1.069–77.822)	**0.043**	16.391 (1.316–204.237)	**0.030**
Neural symptoms					
No	6/77	1		1	
Yes	2/7	4.733 (0.752–29.786)	0.098	16.227 (1.231–213.953)	**0.034**
Tumor size, mm					
<30	4/57	1		1	
≥30	4/27	2.304 (0.530–10.020)	0.266	2.311 (0.241–22.109)	0.467
Gross extracapsular invasion					
No	5/60	1		1	
Yes	3/24	1.571 (0.345–7.164)	0.559	0.646 (0.066–6.300)	0.707
Macroscopic perineural invasion					
No	6/62	1		1	
Yes	2/22	0.949 (0.221–4.073)	0.944	0.310 (0.038–2.546)	0.276
Adjacent lymph nodes					
Negative	5/76	1		1	
Positive	3/8	8.520 (1.565–46.380)	**0.013**	14.021 (1.558–124.141)	**0.018**

pN+, positive pathological lymph node; cN0, clinically negative nodes; neural symptoms: facial paralysis, severe pain and facial numbness for parotid gland carcinoma and numbness of tongue, tongue dyskinesia, severe pain and deviation of mouth angle for submandibular gland carcinoma.

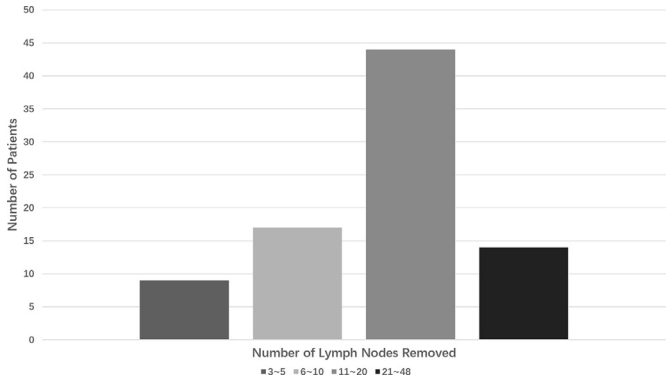

Fig. 1. Distribution of number of lymph nodes removed in cN0 patients undergoing neck dissection.

2014) to avoid unnecessary operations and complications. This is because previous studies have suggested relatively low proportions of positive lymph nodes and good prognoses in patients with low-grade carcinomas. However, a definitive pathological diagnosis and the degree of differentiation are difficult to confirm before surgery in patients with salivary gland carcinomas (Schmidt et al., 2011).

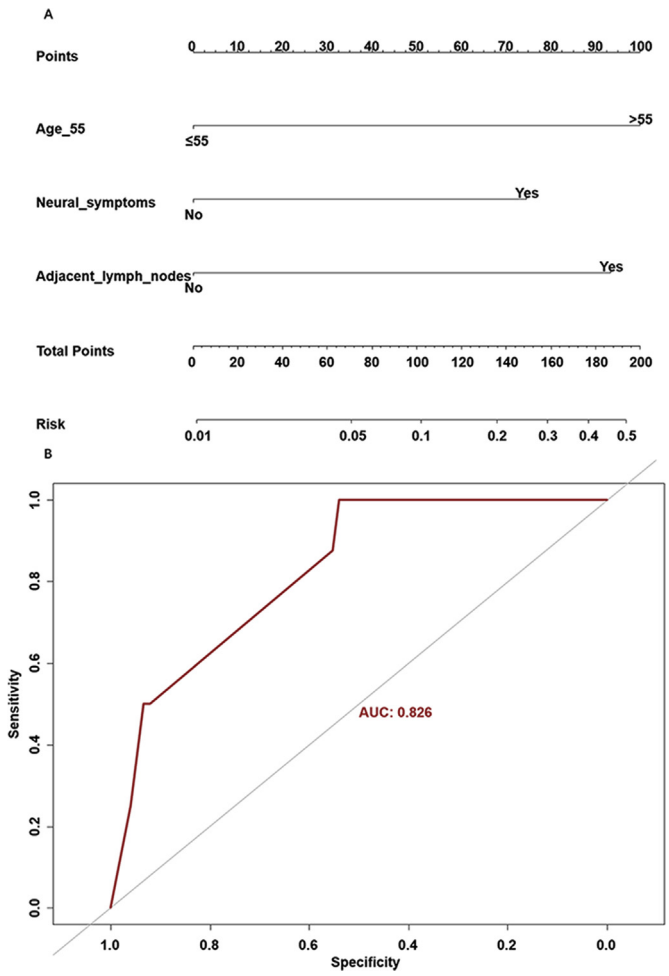

Fig. 2. (A) Nomogram for predicting occult cervical lymph node metastasis. (B) ROC curve for occult cervical lymph node metastasis, AUC = 0.826.

Our study did not indicate the effect of END in terms of improving clinical outcomes, and the incidence of occult lymph node metastases in patients with cN0 cancer who underwent END was relatively low. This reminds us that neck dissection is not fully applicable to all patients with salivary gland cancer. A better understanding of the patterns of cervical lymph node metastasis would promote the application of END in selected patients. We believe that the most important determinant is the accuracy and sensitivity of the preoperative examination, including ultrasound and other imaging. In our study, all patients underwent ultrasound scans and one or more further imaging examinations (CT or MRI) to evaluate the cervical lymph node metastatic status; however, a substantial proportion of previous studies did not use such detailed examinations to evaluate the lymph node metastasis potential. We consider that this might be one of the reasons for the relatively lower proportion of occult neck metastasis in our study. Leng et al. (2016) reported that the sensitivity of ultrasound detection of cervical lymph node metastasis was 84% in patients with esophageal cancer. Studies of thyroid cancer also showed the essential role of ultrasound in the preoperative examination of lateral neck lymph nodes (Hwang and Orloff, 2011; Al-Hilli et al., 2016). Park et al. (2017) and Jin et al. (2016) reported that CT or MRI could improve the diagnostic accuracy for cervical lymph node metastasis in patients with head and neck cancers, and that the sensitivities exceeded 80%. We believe that a combination of ultrasound imaging and other diagnostic technologies (Razfar et al., 2010) can further improve the diagnostic accuracy and avoid unnecessary neck dissection. Another important determinant in the decision-making process for neck dissection is the efficacy of elective neck irradiation in neck cancer management. In a study by Herman et al. (2013), no recurrence was observed among patients who received ENI. The authors considered that patients with cN0 high-grade salivary gland carcinomas who underwent postoperative radiotherapy did not benefit from neck dissection. Meanwhile, radiation therapy seemed to be adequate for treating subclinical lymph node disease if was given in adequate doses. Overall, we believe that END should be performed in suitable patients with cN0 salivary gland carcinomas.

Based on our logistic analysis, a simple and practical nomogram was built to help assess the possibility of occult cervical lymph node metastasis. All variables required for the model were easily obtained before or during surgery in the hope that the surgeons could make a decision during the operation. The histological diagnosis was not included because immediate evaluation by intraoperative frozen section was difficult (Kawata et al., 2010).

This study had several limitations. First, this was a retrospective study in a single center, and we were unable to standardize the indications for END and the extent of neck dissection in our cohort. Selection bias was unavoidable. Second, the research population was relatively small because of the rarity of this disease. Finally, dozens of pathological types of salivary gland cancer were present among the patients, limiting the results obtained.

5. Conclusions

Complete imaging examinations should be performed to evaluate the potential for cervical lymph node metastasis in patients with salivary gland cancer. The incidence of occult neck metastases is low in patients with cN0 cancer after detailed preoperative evaluations. In our experience, there is no strong evidence supporting END as a conventional therapy in patients with cN0 salivary gland cancer. Choosing suitable patients to undergo END can be reliable and avoid unnecessary complications. Our nomogram is a simple and practical instrument with which to strengthen the prediction of occult lymph node metastasis.

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Conflicts of interest

No conflicts of interest to be declared.

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