



Original Article

The influence of cervical lymph node number of neck dissection on the prognosis of the early oral cancer patients



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Abstract *Background/purpose:* The status of neck lymph nodes (LNs) plays an important role in survival of oral cavity cancer. Early stage oral cancer patients are still at a risk for locoregional metastasis. We aimed to determine the number of LNs that needs to be retrieved for adequate diagnosis and treatment of the neck tumor.

Materials and methods: We conducted a retrospective study of 126 oral cavity cancer patients who underwent wide excision and 3 types of neck dissection at MacKay Memorial Hospital, Taiwan. Data from the operative and pathology reports were collected and analyzed. The significant difference was defined as $p < 0.05$ by SPSS 21.0 and Prizm 5 software.

Results: There was a significant difference between the total retrieved LNs and tumor differentiation and nerve invasion on multivariate analysis. Receiveroperating characteristic (ROC) curve showed significant difference in the total number of neck LNs between the survival and expired groups. The cut-off point was 36.5 nodes. However, there was no difference in survival between supraomohyoid and modified radical neck dissection.

Conclusion: Retrieval of adequate LNs can improve oral cancer survival rates. If total number of neck nodes examined is <37 with poor differentiation and/or nerve invasion, early oral cancer patients with neck dissection have a lower survival rate and are candidates for adjuvant therapy.

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Introduction

Head and neck cancer is considered an important part of the global burden of cancer, mainly due to the widespread use of tobacco, alcohol, and cigarette. Oral cavity is the most predominant location of head and neck cancer. More than 90% of oral cavity cancers receive radical surgery as a primary treatment. The prognosis drops to nearly half when regional lymph nodes (LNs) are involved.¹ Therefore, adequate diagnosis and treatment of the neck tumor are important, besides optimal local tumor control. However, our clinical study revealed that early oral cancer patients with nodal negative still have 10%–15% chance of dying in survival proportion. This indicates that these patients still present regional micro-metastases risk. Approximately 7% of pathological nodal negative (pN0) cases have micro-metastasis unidentified in routine section.^{2–4} Unlike T3, T4 clinical nodal negative oral cancer patients, the treatment of clinically negative neck in patients with early-stage T1, T2 oral carcinoma is still controversial. Our previous study has shown that there was a significant difference on survival between the neck dissection and watch-and-see groups ($p = 0.005$) (Unpublished data). Prophylactic neck dissection can improve survival rate by 5% in early oral cancer patients. There are several clinic pathological factors that can influence the survival in early oral cancer, such as tumor size, positive lymph node ratio and the number of dissected lymph nodes. Surgical removed LN number can be a predictive prognosis factor in several cancers.^{5–9} Therefore, we investigated the relationship between survival, the number of retrieved neck LNs, and other associated risk factors.

Materials and methods

Clinical study

Our study is a retrospective review of a database including oral cavity cancer patients who underwent wide excision and 3 types of neck dissection (Supromohyoid neck dissection: level I to III; Selective neck dissection: level I to IV; Modified neck dissection: level I to V) from July 2000 to May 2014, with at least 12 months follow up at Mackay Memorial Hospital. One hundred thirty-nine patients with T1 or T2 node negative oral cancer were assessed for eligibility by the following inclusion criteria: (1) histological diagnosed as oral cavity squamous cell carcinoma staging I, II with neck dissection, and (2) received primary tumor wide excision and neck dissection as the initial treatment modality. The exclusion criteria were as follows: (1) recurrent or metastatic disease, (2) previously treated with radiation or chemotherapy, (3) history of synchronous or metachronous cancers, and (4) incomplete data or patients died with noncancer association. Based on these criteria, 126 patients were enrolled for subsequent analysis. Our research was approved by the Mackay Memorial Hospital institutional review board (15MMHIS160e) and was in compliance with the Helsinki Declaration. All patients were treated by 2 oral maxillofacial surgeons. Patients with positive cervical LNs, perineural invasion, perivascular or perilymphangenic invasion, and closed margin received post-operative

radiotherapy or adjuvant concurrent chemoradiation treatment according to the National Comprehensive Cancer Network (NCCN) guidelines.

Statistical analysis

We used independent t tests for continuous variables. A survival curve was illustrated with the Kaplan–Meier method. To compare the univariate survival distribution between neck dissections, a log-rank test was used. The independent predictors of mortality were identified by Cox proportional hazards models in a multivariate analysis for the significant risk factors observed in the univariate analysis.

A receiver-operating characteristic (ROC) curve was generated and Youden index (sensitivity + specificity - 1) was estimated to find the optimum cut-off point of LNs number. A value of $p < 0.05$ was considered statistically significant. Statistical Package for the Social Sciences (SPSS) for Windows (Version 21.0; SPSS, Chicago, IL, USA) software and Prism 5.0 were used for the statistical analysis.

Table 1 Demographics and clinical pathological characteristics of T1, T2 N0 oral cancer patients (total 126 cases) with neck dissection.

	N (%)
Age	52.9 (30–87)
Sex	
Male	112 (88.9)
Female	14 (11.1)
Location	
Tongue	52 (41.3)
Buccal	51 (40.5)
Gum	10 (7.9)
Palate	8 (6.3)
Other	5 (4.0)
T & Stage classification	
I	43 (34.1)
II	83 (65.9)
Depth of invasion	Mean = 5.24 mm (0.5–23 mm)
Differentiation	
Well	55 (43.7)
Moderate	65 (51.6)
Poor	6 (4.7)
Nerve invasion	
N-	115 (91.3)
N+	11 (8.7)
Vascular invasion	
V-	124 (98.4)
V+	2 (1.6)
Radiotherapy	
Negative	110 (87.3)
Positive	16 (12.7)
Recurrent	
Negative	112 (88.9)
Positive	14 (11.1)
Prognosis	
Survival	115 (91.3)
Expired	11 (8.7)

Results

A total number of 126 patients with pathologically T1 or T2 nodal negative oral cavity cancer who underwent neck dissection were included in our study. Demographics and clinical pathological characteristics of early stage oral cancer patients with neck dissection are shown in Table 1. The mean age of patients was 52.9 years (30–87 years) and almost 89% of the patients were males. Tongue and buccal were the most predominant locations of early oral cancer. The mean depth of tumor invasion was 5.24 mm. Moderate differentiation was observed in more than half of patients (51.6%) and poor differentiation in only 6 (4.7%) cases. There were 11 (8.7%) cases with nerve invasion and 2 (1.6%) cases with lymph-vascular invasion. Sixteen (12.7%) patients were consulted to receive radiotherapy because of poor differentiation, nerve invasion, or lymph-vascular invasion. Local regional tumor recurrence was found in 14 (11.1%) cases. The prognosis was good with a mean survival rate of 91.3%.

There was a significant difference between the total retrieved LNs number and radiotherapy, tumor differentiation, and nerve invasion by univariable cox regression analysis. However, only tumor differentiation, nerve invasion, and total retrieved LNs number had a significant difference by multivariable analysis (Table 2). We also tried to

investigate the relationship of total retrieved LNs number between negative and positive LNs to rule out LNs cell immune reaction (Fig. 1); statistical analysis showed no significant difference. Nevertheless, a significant difference in the total number of retrieved LNs was observed between the survival and expired groups (Fig. 2). The ROC curve showed there was a significant relationship in the total number of neck LNs between survival and expired groups. The cut-off point was 36.5 LNs by Youden index analysis. We finally divided the early oral cancer patients into 2 groups, the ≥ 37 and < 37 LNs groups. There was a significant difference in the survival rate between these 2 groups ($p = 0.019$) (Fig. 3). Table 3 shows the demographics and clinical pathological characteristics of the early stage oral cancers in different locations.

No correlation was observed in the retrieved LNs number between each location of the oral cavity cancers ($p = 0.333$ one-way ANOVA). We also found that there was no significant difference between the LNs number and local recurrent patients ($p = 0.522$). The mean time to recurrence was 26.8 months after surgery. The recurrent patients were distributed as follows: 6 cases in the tongue, 6 cases in the buccal, 1 case in the gum, and 1 case in the palate. Nine (62.3%) recurrent patients were found within 24 months after surgery, and 6 recurrent cases (42.9%) were presented at one and a half year after surgical treatment.

Table 2 Univariable and multivariable analysis for T1, T2 N0 oral cancer patients.

Expired 11 Survival 115	Univariable (Cox regression analysis)		Multivariable Method: Forward stepwise	
	Hazard Ratios (95% CI)	<i>p</i> -value	Hazard Ratios (95% CI)	<i>p</i> -value
Tumor size				
T1	1.0	0.822		
T2	1.165 (0.308–4.407)			
Radiotherapy				
Yes	4.844			
No	1.0	0.012*		
Age	0.981 (0.929–1.034)	0.471		
Differentiation				
Well	1.0			
Moderate	3.086 (0.641–14.860)	0.160		
Poor	12.728 (1.788–90.593)	0.011*	12.845 (1.655–99.677)	0.015*
Tumor thickness	1.093	0.253		
Nerve invasion				
(+)	19.957	<0.001***	14.496 (3.486–60.272)	<0.001***
(–)	1			
Vascular invasion				
(+)	7.459	0.057		
(–)	1.0			
Lymph nodes number/each level				
I	0.974	0.749		
II	0.875	0.087		
III	0.924	0.306		
IV	1.002	0.979		
V	0.859	0.320		
Lymph nodes (Total number)	0.953 (0.885–0.988)	0.017*	0.935 (0.876–0.998)	0.044*
Recurrent				
Yes	1.139	0.869		
No	1.0			

* Statistically significant ($P < 0.05$). *** statistically significant ($P < 0.001$).

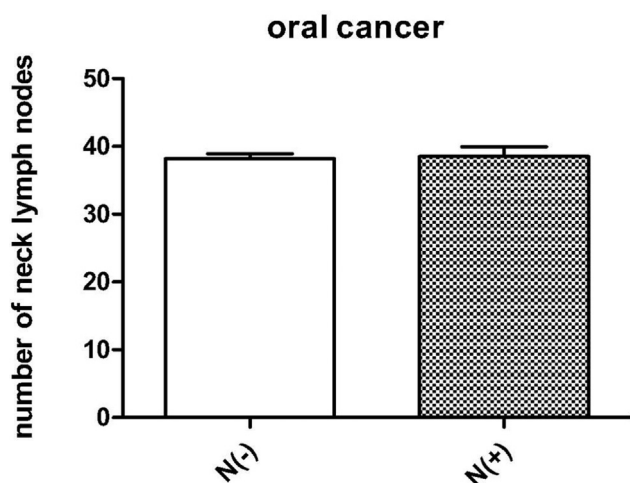


Figure 1 Unpaired t test showing no difference in the number of examined neck lymph nodes between the nodal positive and nodal negative oral cancer groups; $p = 0.89$.

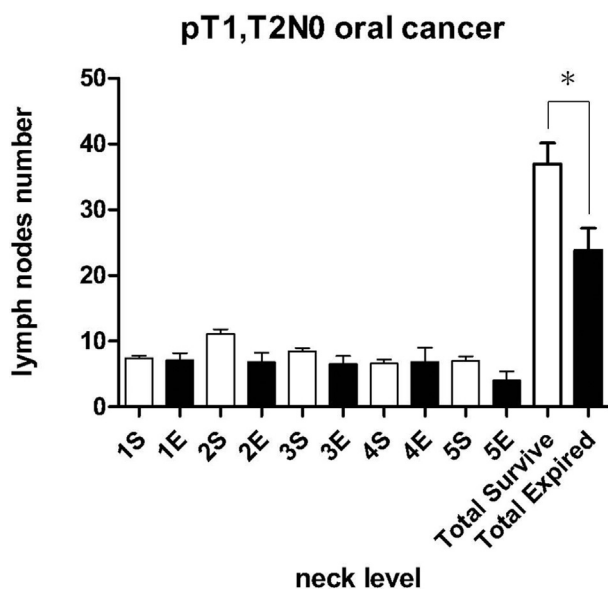


Figure 2 Mann Whitney test showing significant difference in the total examined lymph nodes number between the total survival and total expired groups of pT1, T2N0 oral cancer patients; $p = 0.038$; 1S: neck level 1 survival group; 1E: neck level 1 expired group; 2S: neck level 2 survival group; 2E: neck level 2 expired group; 3S: neck level 3 survival group; 3E: neck level 3 expired group; 4S: neck level 4 survival group; 4E: neck level 4 expired group; 5S: neck level 5 survival group; 5E: neck level 5 expired group; Total survival: total neck level of the survival group; Total expired: total neck level of the expired group.

Discussion

In oral cavity cancer, cervical nodal metastasis plays an important role in overall and disease-free survival. Importantly, wide excision with elective neck dissection provides good tumor control and survival benefits.^{9,10} However, it is

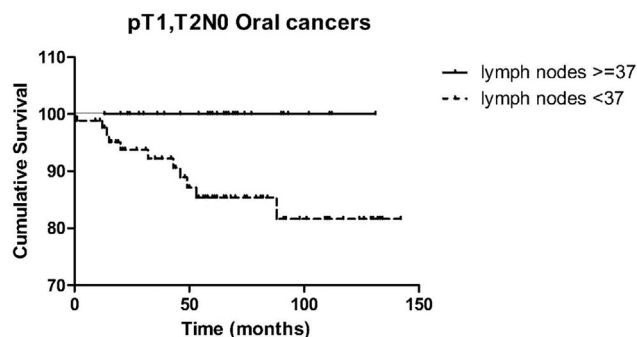


Figure 3 Kaplan–Meier curves showing a significant difference in survival between the total retrieved lymph nodes number ≥ 37 and < 37 ; $p = 0.019$.

still controversial whether elective neck dissection in early stage oral cancer should be performed to improve survival.^{3,11} Multiple surgical morbidities are also taken into account for neck dissection, including wound, nerve, and vascular complications. In this study, there was a significant difference in survival between the neck dissection and watch-and-see groups ($p = 0.0053$) (Fig. 4). It was shown that prophylactic neck dissection can improve survival rate in early oral cancer patients. The results are similar to those reported by D’Cruz et al. (2015).¹⁰

When the number of examined LNs is insufficient for diagnosis, the nodal stage may be under-estimated, which is called as stage migration. There is evidence that stage migration toward higher pathological TNM stages, as the total number of resected nodes, increased in esophageal cancer.¹² It has been suggested that at least 10 nodes should be retrieved to designate an esophageal pN0 cancer.¹³ In gastric cancer, stage migration is approximately 10%.⁶ Metastases LNs ratio has been observed to be completely unrelated to the number of retrieved nodes, but the incidence of stage migration was even higher when less than 10 nodes were retrieved.¹⁴ In the letter to the British Journal of Cancer, Dr Sobin¹⁵ stated that a number of at least 15 examined regional LNs is used as a guideline to diagnose a case as pN0 gastric. However, the editor suggested that this guideline was too strict and fewer nodes were also sufficient. American Joint Committee on Cancer recommends that a minimum of 12 LNs should be examined to ensure adequate staging in colorectal cancer. Xingmao et al. suggested 13 LNs was recommended as the minimum number of LNs in patients with stage II colorectal cancer.¹⁶ This result was consistent with observed in other studies of breast, pancreatic and lung cancer.^{7,8,17–19} However, several studies have shown that the number of LNs does not influence neck recurrences or clinical outcomes;^{20–22} all these studies were seldom mentioned in oral cavity cancers. About 150 LNs have been observed on every side of neck.²³ According to Amar et al., the mean number of resected LNs was 27, with 24 cases of selective dissection and 31 cases of radical dissection.²⁴ In our study, the mean number of neck dissection LNs was 33. There was no relationship between the number of neck dissected LNs and each tumor location, even though tongue and buccal cancers were the predominant ($p = 0.333$). Furthermore, there was a significant difference in the retrieved LNs

Table 3 Demographics and clinical pathological characteristics of early stage oral cancers on different locations.

	Total	Tongue	Buccal	Gum	Palate	Other	<i>p</i> -value
Cases (N)	126	52	51	10	8	5	
Mean age, years	52.9 (30–87)	50.6 (30–83)	52.5 (31–87)	54.7 (31–71)	65.6 (52–80)	58.4 (47–67)	<i>p</i> = 0.001*
LN (N)	33	34.0	30.6	34.4	40.5	28.8	<i>p</i> = 0.333
Recurrent (N)	14	6	6	1	1	0	
Mean, months	26.8 (8–58)	27.6 (12–53)	26.2 (8–58)	31 (31)	17 (17)	0	
Mean survival	115/126 (91.3%)	46/52 (88.5%)	48/51 (94.1)	8/10 (80%)	8/8 (100%)	5/5 (100%)	<i>p</i> = 0.317

LN: lymph nodes; Other: including mouth floor and lips.

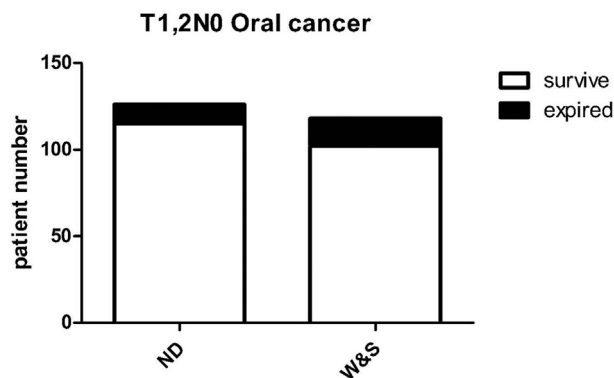


Figure 4 Unpaired t test showing significant difference in survival and expired between the ND and W&S groups of the T1, T2 N0 oral cancer patients; *p* = 0.005; ND: neck dissection; W&S: watch-and-see.

number between each neck dissection type (*p* < 0.001). However, Ampil et al. stated that the number of cervical LNs should be removed and examined to achieve sufficient reliability is unclear in oral cavity cancer.²⁵ Patients with less than 18 LNs had lower survival rate, which was confirmed in the multivariate analysis.²⁶ In addition, LN ratio could serve as an independent prognostic factor in oral squamous cell carcinoma.^{27–30} Amar et al. proposed that patients with 30 or more LNs had a better loco-regional control and higher 2-year survival rates in tongue and mouth floor epidermoid carcinoma.²⁴ Tsai et al. thought that clinical N0 OSCC patients undergoing primary surgery with more than 24 nodes had longer overall survival compared with those who had 24 or fewer nodes in multivariable analyses.³¹ Liao et al. demonstrated that extracapsular spread, the level and the number of LNs metastasis were associated with poor clinical outcomes.³² In contrast, Kagawa et al. found that LNs size is significantly correlated with oral cancer outcome.³³ Overall, the management of clinical N0 neck in T1, T2 oral cancer patients remains controversial.¹¹ Routine selective neck dissection is not warranted in T1N0 patients, but T2 cases should be considered for prophylactic selective neck dissection.⁵ Our study showed that at least 37 LNs should be retrieved to have high survival rate. It seems that there was no difference between the types of neck dissection and survival (*p* = 0.431). In contrast, there was a significant difference

between the type of neck dissection and examined LNs number (*p* < 0.001). A correlation between the LNs number and survival rate (*p* = 0.038). Tumor differentiation and perineural invasion are not correlated with the retrieved LNs number (*p* = 0.519, *p* = 0.339). We also divided early oral cancer patients into 2 groups, the ≥ 37 and < 37 LNs. Although there was a significant difference in the survival rate between these 2 groups (*p* = 0.019), no correlation with the type of neck dissection was observed (*p* = 0.208). It could be reasonable deducted that there are several factors that determine the retrieved LNs number, and inadequate LNs examined will determine underestimated stage or stage migration that cause poor survival. Therefore, we can perform supraomohyoid neck dissection instead of modified radical neck dissection in early oral cancer patients to have the similar survival. In presence of a total LNs number of less than 37 with perineural invasion or poor differentiation in the final pathology examination, radiation oncology consultation should be suggested and regular follow up should be performed.

The rates of oral squamous cell carcinoma recurrence vary from 18% to 76% for patients who underwent standard treatment, and it is considered the major cause of poor survival rates.³⁴ Some studies have corroborated that the median time to recurrence is 7.5 months after treatment, and 86% of the recurrence occurs within 24 months.^{35,36} Our study population was focused on early cancer and it is reasonable to show lower recurrent rate (11.1%). Interestingly, there were only 64% of recurrent carcinomas occurred within 2 years, compared with other studies.^{36,37} This indicates that still almost 36% of recurrent cancers can occur over 24 months after surgery in early stage oral cancer. Patients with recurrent cancer have a clinical challenge with regard to the determination of the most appropriate therapeutic option. Only a small group of patients are candidates for salvage surgery and about 30%–45% of these have poor survival rates.³⁸ This study showed when recurrent carcinoma was presented, the survival rate decreased from 94% to 71%. Salvage surgery, re-irradiation, or their combination with chemotherapy, are usually the best choices of treatment when the prognosis is poor.

Prophylactic neck dissection can improve T1 or T2 N0 oral cancer survival rate and retrieval of adequate LNs can improve oral cancer survival rate. If the total number of neck nodes retrieved is less than 37, we should consider the possibility of stage migration. Patients' close follow up or

radiotherapy consultation should be considered. Tumor poor differentiation and nerve invasion are also risk factors for survival.

Declaration of Competing Interest

The authors declare no conflict of interest.

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