Int J Clin Exp Med 2017;10(2):4023-4034
www.ijcem.com /ISSN:1940-5901/IJCEM0019031

Original Article

Can we identify the patients with clinically T1-2N0 oral tongue squamous cell carcinoma benefiting from neck dissection?

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Received November 1, 2015; Accepted January 27, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Objective: This retrospective study is to find reliably risk factor of lymph node metastasis and to discuss a reasonable neck management for T1-2N0 oral tongue squamous cell carcinoma. Methods: 136 cases were performed neck dissection (ND), 62 cases were under watch-and-wait (WW). The clinical, pathological, imaging and follow up data of two groups were analyzed. Results: There was no significance difference between group ND and group WW for recurrence and overall survive and the same result for the statue of neck lymph node between T1 and T2 patients. Among all patients the histopathological differentiation, vascular invasion and invasion thickness were significant for recurrence, overall survive and the statue of neck lymph node. The tumor thickness measured on MRI images had significant correlation with invasion thickness. Conclusion: For the patients with T1 OTSCC the WW protocol is recommended, for T2 cases, the WW protocol is also reasonable. The neck dissection should be considered in cases with poor differentiation, invasion thickness more than 4 mm measured on MRI images. For the patients with pathologically proved invasion thickness more than or equal to 4 mm or vascular invasion, neck dissection or more aggressive adjuvant treatment should be performed.

Keywords: Oral tongue squamous cell carcinoma, early stage, lymph node metastasis, neck dissection

Introduction

There has been a consensus that existence of the lymph nodes metastases is the strongest independent prognostic factor [1, 2]. Namely accurate nodal staging is crucial for therapy decision and determination of the patient's prognosis. Literature showing rates of occult nodal metastases ranging from 23% to 43% in patients with early-stage oral SCC supports elective treatment of the neck [3-7]. But the controversy on the neck treatment in patients with early stage clinically negative necks continues to seem to be a main topic in most head and neck cancer seminar.

The proposal of watch-and-wait and a strict observation schedule was supported by the report that outlined a sensitivity analysis on neck metastasis in cN0 patients [8]. A prospective, randomized clinical trial [9] comparing elective neck dissection and observation in cases of early stage oral tongue carcinoma, the five-year disease-specific survival was comparable, with no statistically significant difference between the two groups. Though the neck recurrence rate was higher in the observation group because of the strict follow-up schedule, salvage was possible in all cases.

Sentinel node biopsy (SNB) has also been proposed for staging of the cN0 neck in early-stage oral carcinomas. Numerous validation studies of SNB within the context of elective neck dissection have clearly proven the technical feasibility and accuracy of the SNB procedure [10-

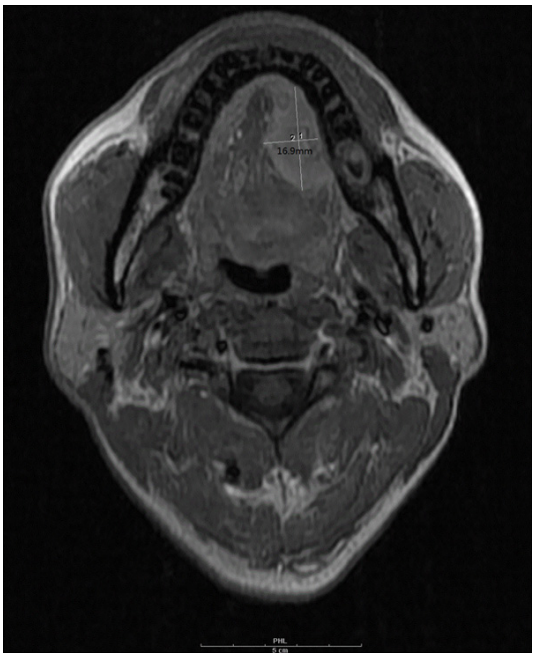

Figure 1. Invasion depth on MRI was defined on gadolinium-enhanced T1 weighted image.

15]. Two prospective observational studies with patients undergoing elective neck dissection only in case of a positive sentinel lymph node (SLN) have reported comparable results regard to tumor control in the neck to those achieved by elective neck dissection [10, 11].

Multiple retrospective studies [9, 16-19] and several prospective randomized controlled trials [9, 20-22] have compared elective neck dissection versus observation in T1-2N0 oral SCC, with the majority failing to demonstrate a survival advantage. In addition, the commonest postoperative complications were pain, numbness and later muscle weakness on the shoulder. It's reported the prevalence of shoulder dysfunction after elective neck dissection is 22% to 39%, despite the preservation of the spinal accessory nerve [23, 24].

In addition, patients presenting with regional failure after initial observation often present with more advanced disease and higher rates of extracapsular nodal spread, compromising both regional control and survival [25-28]. The prognostic impact of therapeutic decisions must also be considered. An elective neck dissection presents risks in the form of postoperative morbidity and mortality and impact on quality of life, but missing a neck metastasis may lead to late recurrences with a significant impact on prognosis. It's of great significant to find reliably risk factor of lymph node metastasis.

It has been reported that among all the factors influencing lymph node metastasis in oral tongue carcinoma, tumor depth is more important than tumor size [38-40]. B YERS [41] et al. reported that a muscular invasion depth exceeding 4 mm had more possibility to metastasize as a prognostic factor in oral tongue cancer, and S PIRO et al. 23 set 2 mm as a cutoff value. O'B RIEN et al. [42] reported that difference in the rate of survival and nodal metastasis was present with 4 mm. There is a strong correlation between MRI depth and the HP depth of oral tongue carcinoma and it is possible to predict nodal metastasis before surgery on the basis of tumor depth [43]. MR images provide satisfactory accuracy for the measurement of tumor thickness and staging of oral tongue cancer. Preoperative MRI is recommended to assist in treatment planning for patients with this disease [45].

The purpose of this study was to determine if neck dissection reduces regional recurrence and improves survival when compared to watch-and-wait in patients with T1-2N0 oral tongue squamous cell carcinoma (OTSCC) and to find if there are any prognostic factor supporting neck dissection or not.

Patients and methods

A retrospective chart review was performed of 198 patients with T1-2N0 OTSCC who underwent a tongue wide local resection of the primary lesion with or without neck dissection at department of head and neck between 2006 and 2009. None of them had received preoperative chemotherapy or radiotherapy. Demographic data and information on clinical presentation, imaging, operative details, histopathology and follow-up were documented for analysis using a preapproved proforma.

The patients were clinically diagnosed before surgery based on CT or MRI, and ultrasonographic findings. Of all, 161 patients were examined with a MRI system before glossectomy. The tongue and neck MRI protocol included unenhanced axial and coronal T1-weighted sequences, axial T2-weighted sequences, and contrast-enhanced axial and coronal T1-weighted sequences. This examination was per-

Table 1. Basic data of enrolled patients (n=198)

Factors	Neck dissection group (n=136)	WW group (n=62)	*P*
Gender			0.074
Male	74	33	
Female	62	29	
Age (years)			0.535
>60	38	22	
<60	98	40	
Pathological grade			0.857
1 (Well)	85	34	
2 (Moderately)	40	22	
3 (Poorly)	11	6	
T classification			0.169
T1	67	34	
T2	69	28	
Recurrence			0.031
No	109	41	
Yes	27	21	
Vital state (at follow-up)			0.888
Dead	23	11	
Alive	113	51	

Table 2. Relationship between neck lymph node metastasis and characteristic of patients in ND group

Factors	Neck dissection group (n=136)		
	Positive	Negative	P
T classification			0.276
T1	10	57	
T2	14	55	
Pathologic grade			0.142
Well	18	67	
Moderately	3	37	
Poorly	3	8	
Thickness			0.045
<4 mm	1	26	
>4 mm	23	86	
Vascular invision			0.002
No	13	95	
Yes	11	18	

formed using the 1.5-Tsystem. Gd-DTPA- contrast T1 weighted images were achieved with settings of TR (repetition time) 450 ms, TE (echo time) 15 ms at the axial and coronal plane, section thickness 3 mm, field of view (FOV) 23 cm and acquisition matrix 256×256. Invasion depth on MRI was defined as tumor thickness, assessed by the same radiologist on gadolinium-enhanced T1 weighted image and T2 weighted image, measured as follows: The reference line was determined as a horizontal line connecting the mucosal junction of the tumor and the length perpendicular to this line towards the deepest point of tumor infiltration was measured (**Figure 1**).

136 patients underwent wide local resection of the primary lesion with neck dissection, and 62 patients without neck dissection. Based on the operation project we divide the patients into neck dissection group and watch-and-wait group. The surgical specimen was fixed in formalin, embedded in paraffin, stained with hematoxylin-eosin, a 3-mm slice was then made into a slide. Using a X12.5 microscope, maximal tumor depth was measured in the same way as for MRI.

Most patients were reviewed 6 weekly in the first year, 3 monthly in the second year, then 6 monthly until 5 years. After this time, patients were reviewed every 6 to 12 months. Follow-up consisted of clinical history and examination with radiological assessment reserved for patients with clinical suspicion of recurrence. 48 patients with biopsy-proven squamous cell carcinoma were identified during follow-up and received neck dissection and postoperation radiotherapy.

Statistics

Statistical analysis was performed using PASW Statistics 17.0 (SPSS, Chicago, IL). All statistics were 2-sided and a value of $P<0.05$ was considered statistically significant. Overall survival was calculated from the date of surgery to the date of death or last follow-up. For disease-special survival, patients that died from causes other than oral tongue SCC were censored at the time of death. Regional recurrence was defined as pathologically proven tumor relapse in the neck. Survival curves were generated by the Kaplan-Meier method when appropriate. We carry out chi-square test to analysis the status of neck dissection with T classification, Pathological grade, Thickness and Vascular invasion. The clinical significance of tumor invasion depth on the MRI was investigated by evaluating the correlation and the accuracy between MRI and HP depth of TSCC.

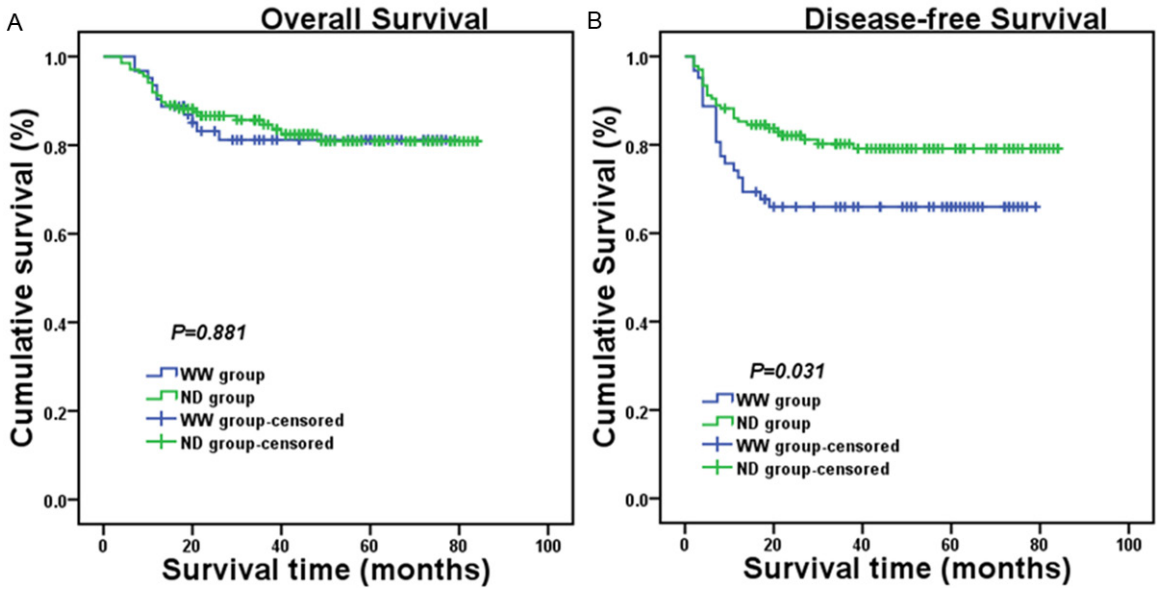

Figure 2. Neck dissection or watch-and-wait affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients (n=198) receiving neck dissection (n=136) versus under watch-and-wait (n=62) for overall survival (P=0.881) (A) and disease-free survival (P=0.031) (B).

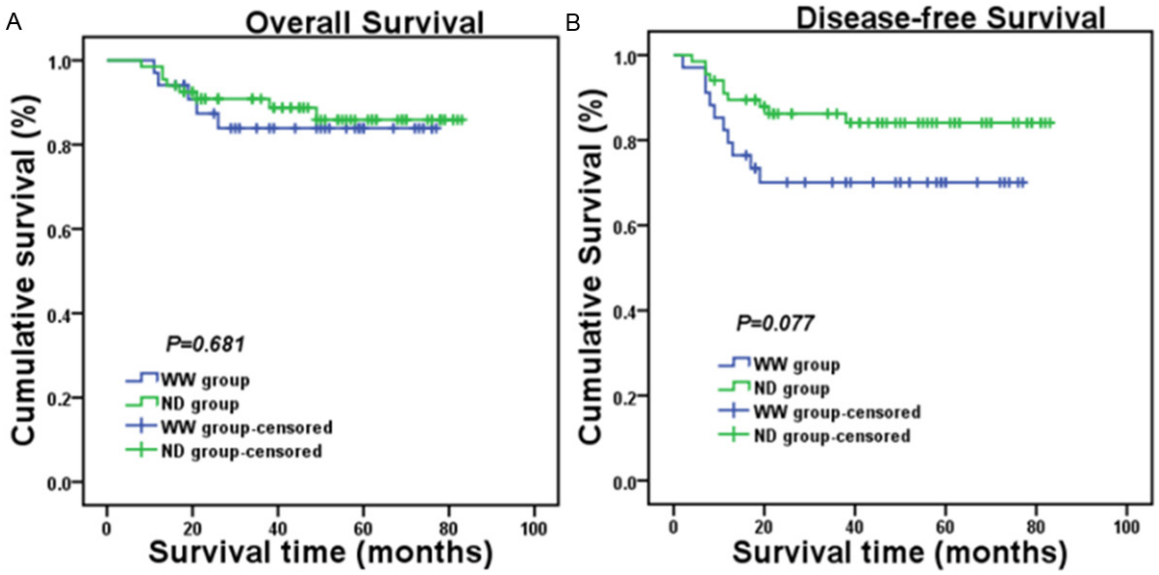

Figure 3. Neck dissection or watch-and-wait affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1N0 OTSCC patients (n=101) receiving neck dissection (n=67) versus under watch-and-wait (n=34) for overall survival (P=0.681) (A) and disease-free survival (P=0.077) (B).

Results

The basic data of all enrolled patients

All data of enrolled patients are showed in **Table 1**. A total of 198 patients (107 men, 91 women) were enrolled. The mean age in neck dissection group was 54 years (range, 24-84 years), watch and wait group is 51years (20-86 years). The median follow up of neck dissection group is 45 months (4-84 months), and watch and wait group is 43 months (6-83 months). Six patients of neck dissection group and two patients of watch and wait group were lost and deemed as censored data. Statistical analysis find the difference in gender, age, Pathological grade, T classification is not significant (P=

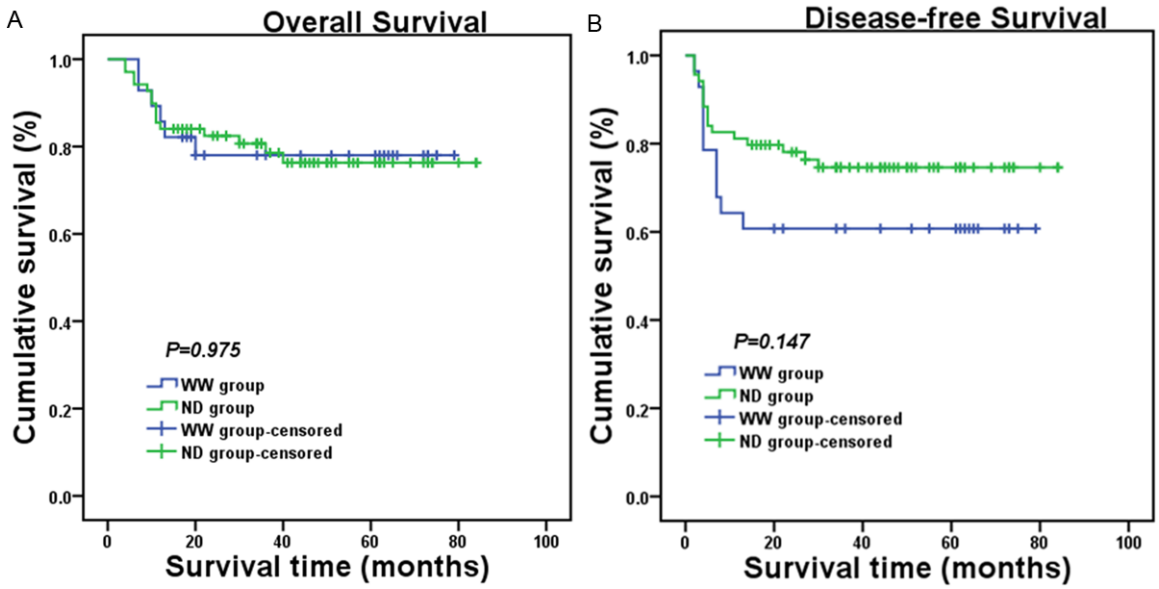

Figure 4. Neck dissection or watch-and-wait affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT2N0 OTSCC patients (n=97) receiving neck dissection (n=69) versus under watch-and-wait (n=28) for overall survival (P=0.957) (A) and disease-free survival (P=0.147) (B).

0.074, 0.535, 0.857, 0.169). All 136 patients in neck dissection group received lateral elective neck dissection, including 15 functional whole neck dissections (level I, II, III, IV, V), 121 supraomohyoid neck dissection (level I, II, III). 24 patients were confirmed lymph node metastasis by postoperative pathological examination, of which six were N1 and 18 were N2 in accordance with the lymph node classification guidline from American Joint Committee on Cancer (AJCC). During the follow-up, there was no evidence supporting recurrence in these 24 patients. Of the other 112 patients, 27 were confirmed lymph node recurrence the median recurrence time is 68.9 months, 23 patients died from the tongue cancer. Of 62 cases in watch-and-wait group, 21 patients received the neck dissection, and 16 patients were confirmed lymph node recurrence, the rate of lymph node recurrence is 25.8% (16/62). The median recurrence time is 7 months (range, 2-19 months), 11 patients died from the tongue cancer. The relationship between neck lymph node metastasis and characteristic of patients are showed in **Table 2**.

Survival analysis

The cumulative 3-year OS rate for the ND group was 83.1% when compared with 82.3% for the WW group (*P*=0.881). The cumulative 3-year DFS rate for the ND group was 80.1% when compared with 66.1% for the WW group (*P*=0.031), respectively (**Figure 2**).

Of 101 T1 patients, the cumulative 3-year OS rate and 3-year DFS for the ND group was 88.1%, 85.1% when compared with 85.3%, 70.6% for the WW group (*P*=0.681, 0.077), respectively (**Figure 3**). And for 97 T2 patients, the cumulative 3-year OS rate and 3-year DFS for the ND group was 78.3%, 75.4% when compared with 78.6%, 60.7% for the WW group (*P*=0.957, 0.147), respectively (**Figure 4**). Furthermore, in a subset analysis, we compared the statue of neck dissection between patients with different T classification (T1 and T2). There was no statistically significant differences (*P*=0.276). This supports our subjective experience that the different T classification of early OTSCC patients is not associated with lymph node metastasis.

Of all patients, there are 119 patients with well differentiation, 62 patients with moderately differentiation and 17 patients with poor differentiation. The cumulative 3-year OS rate for the different pathologic grade was 84.3%, 84.0% and 70.6% (*P*=0.446). The cumulative 3-year DFS rate for the different pathologic grade (well, moderately and poorly) was 77.3%, 79.0% and 52.9% (P=0.077), respectively (**Figure 5**).

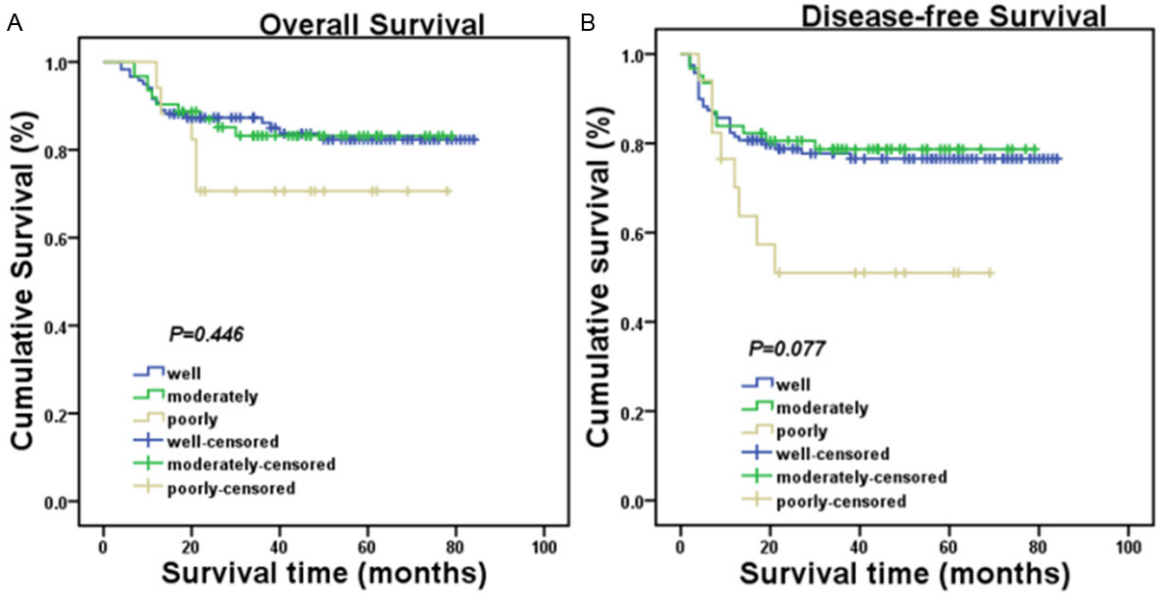

Figure 5. The different pathologic grade affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients with different pathologic grade (119 well, 62 moderately and 17 poorly) for overall survival (P=0.002) (A) and disease-free survival (P=0.021) (B).

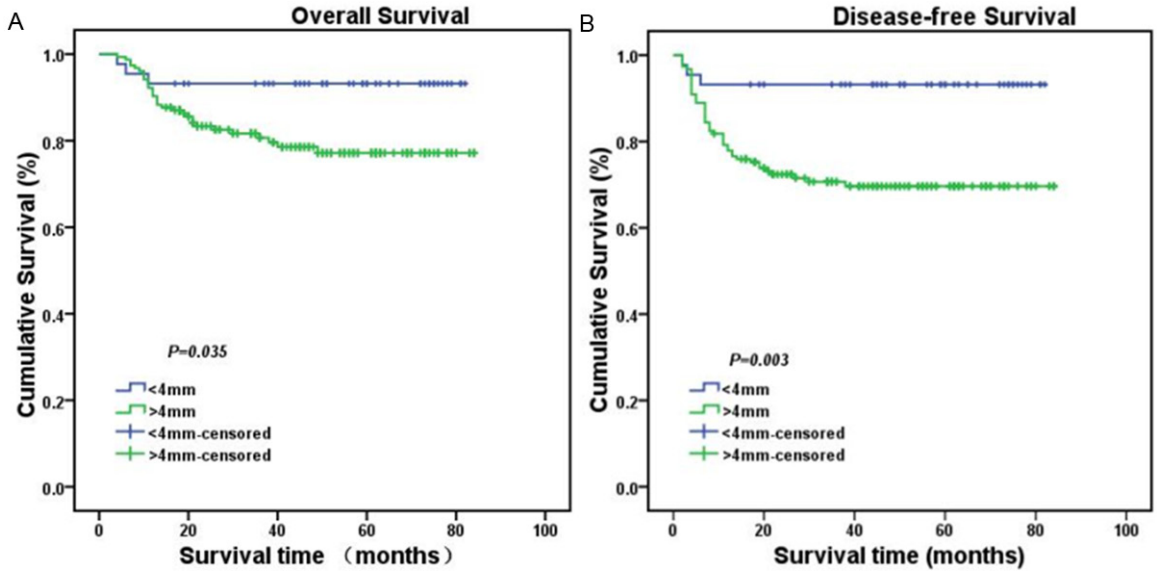

Figure 6. Invasion thickness affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients with different invasion thickness (154 patients with invasion thickness less than 4 mm, 44 patients with invasion thickness more than or equal to 4 mm) for overall survival (P=0.035) (A) and disease-free survival (P=0.003) (B).

Furthermore, in a subset analysis, we found the correction between the statue of neck dissection and different pathologic grade (well, moderately and poorly) was no statistically significant differences (*P*=0.142). This does not get along with our subjective experience that the early TSCC patients with the poor differentiation are more challenging and association with more probability of lymph node metastasis.

There are 44 patients with invasion thickness less than 4 mm, 154 patients with invasion thickness more than or equal to 4 mm. The cumulative 3-year OS rate for the different inva-

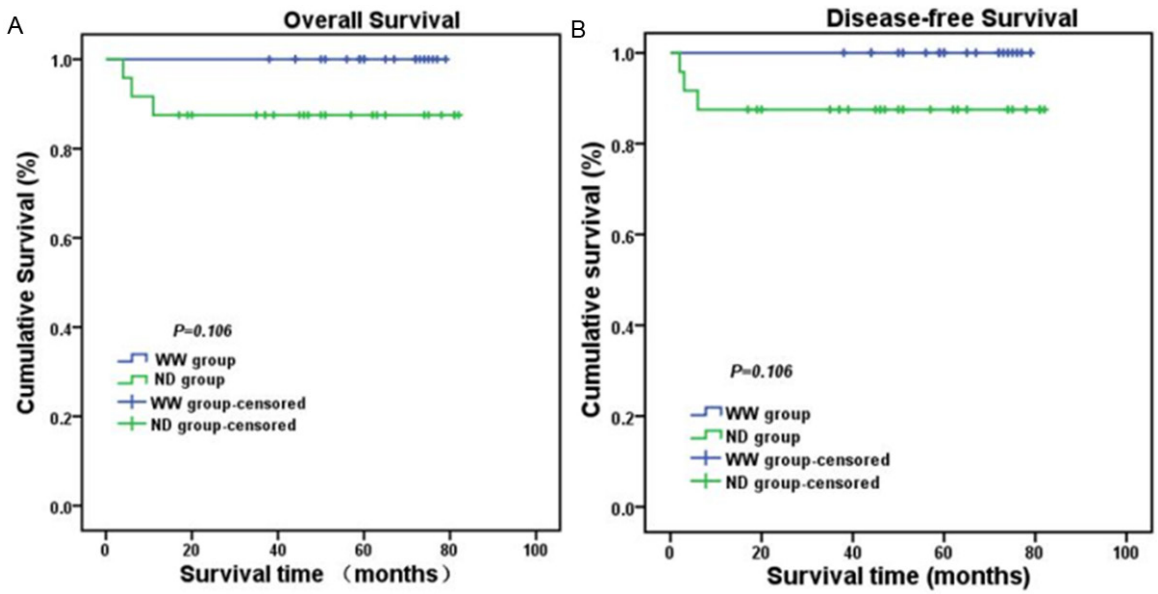

Figure 7. Neck dissection or watch-and-wait affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients with invasion thickness less than 4 mm receiving neck dissection (n=24) versus under watch-and-wait (n=20) for overall survival (P=0.106) (A) and disease-free survival (P=0.106) (B).

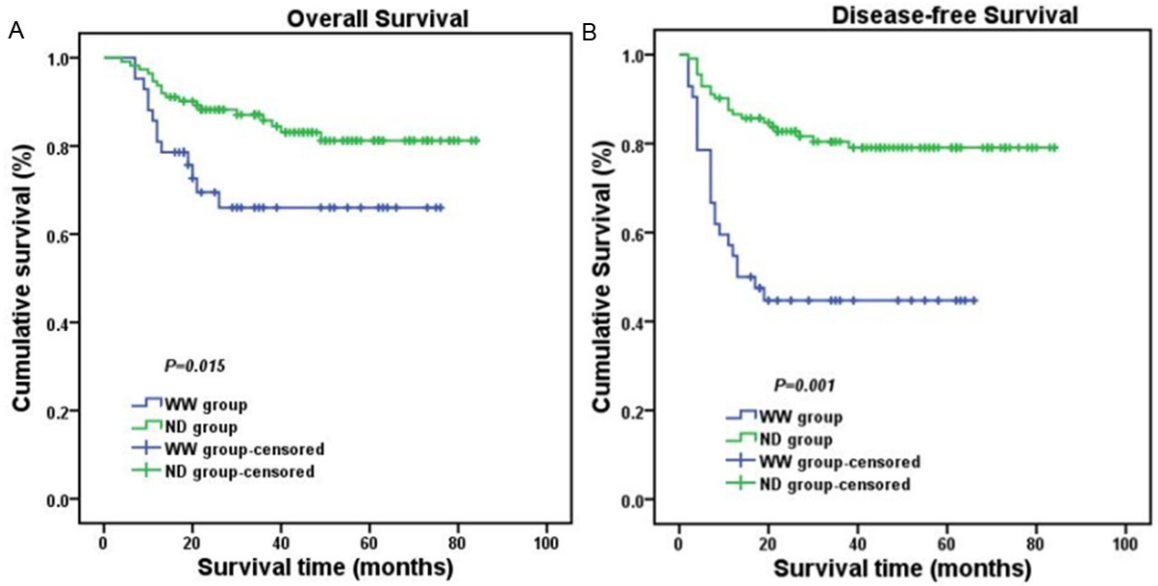

Figure 8. Neck dissection or watch-and-wait affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients with invasion thickness more than or equal to 4 mm receiving neck dissection (n=112) versus under watch-and-wait (n=42) for overall survival (P=0.015) (A) and disease-free survival (P=0.001) (B).

sion thickness was 93.2% and 79.9% (*P*= 0.035). The cumulative 3-year DFS rate for the different invasion thickness was 93.2% and 70.8% (*P*=0.003), respectively (**Figure 6**). Of 44 patients with invasion thickness less than 4 mm, both the cumulative 3-year OS rate and 3-year DFS for ND group were 87.5% when compared with 100% for WW group (*P*=0.106), respectively (**Figure 7**). And for 154 patients with invasion thickness more than or equal to 4

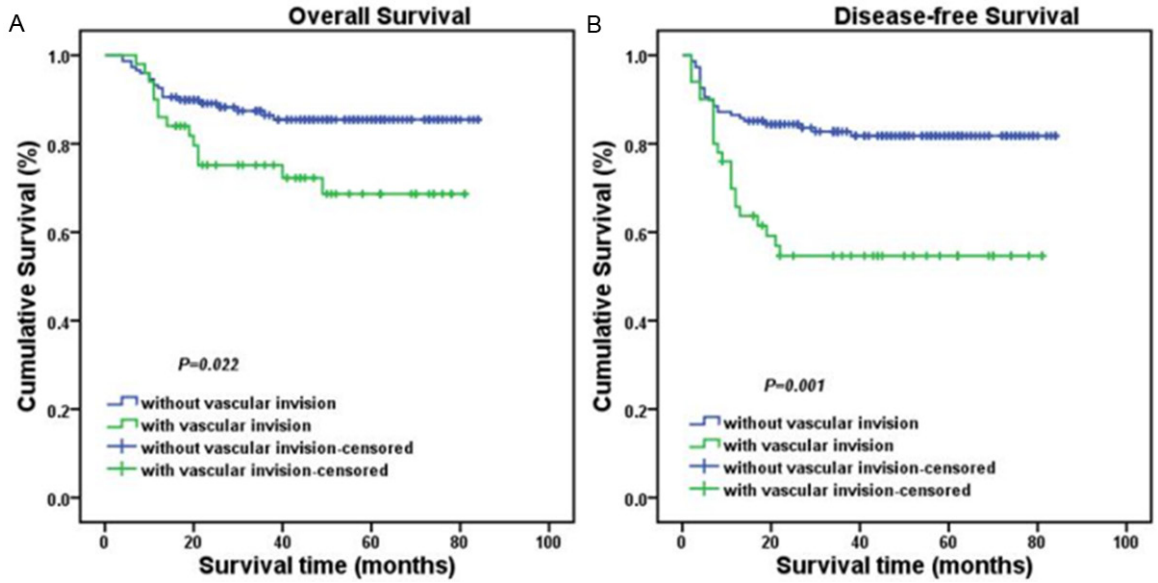

Figure 9. Vascular invasion affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients with or without vascular invasion (50 with vascular invasion, 148 without vascular invasion) for overall survival (P=0.022) (A) and disease-free survival (P=0.001) (B).

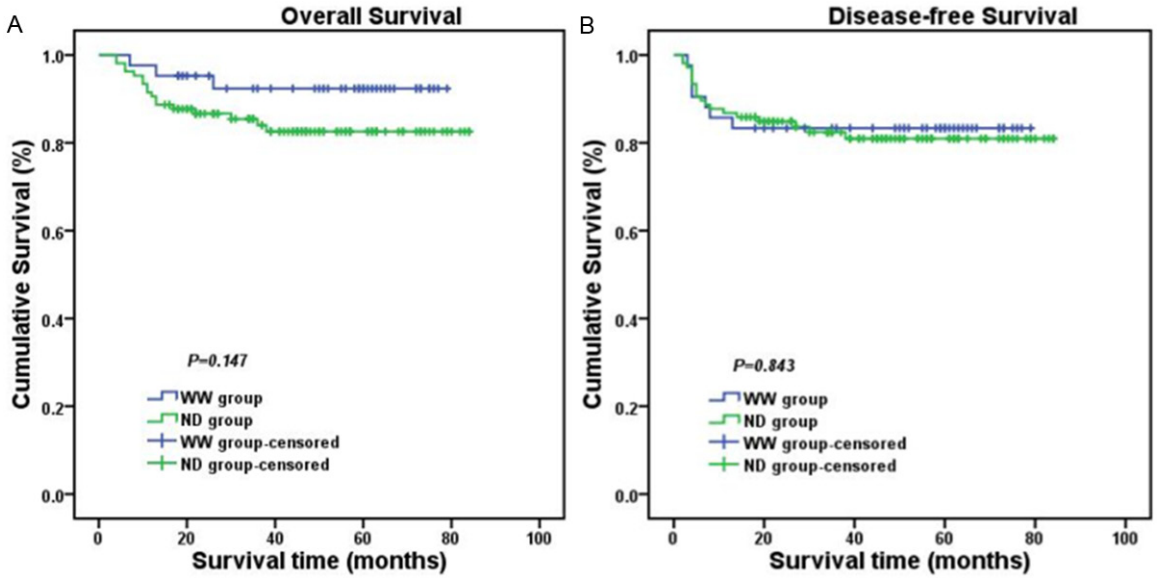

Figure 10. Neck dissection or watch-and-wait affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients with vascular invasion receiving neck dissection (n=29) versus under watch-and-wait (n=21) for overall survival (P=0.050) (A) and disease-free survival (P=0.001) (B).

mm, the cumulative 3-year OS rate and 3-year DFS for ND group was 83.9%, 80.4% when compared with 69.0%, 45.2% for WW group (*P*=0.015, 0.001), respectively (**Figure 8**). Furthermore, in a subset analysis we found the statue of neck dissection was association with different invasion thickness (*P*=0.045). The tumor thickness measured on MRI images had significant correlation with invasion thickness (*P*=0.012). This supports our subjective experience that the early OTSCC patients with invasion thickness more than or equal to 4 mm are more challenging and association with more probability of lymph node metastasis.

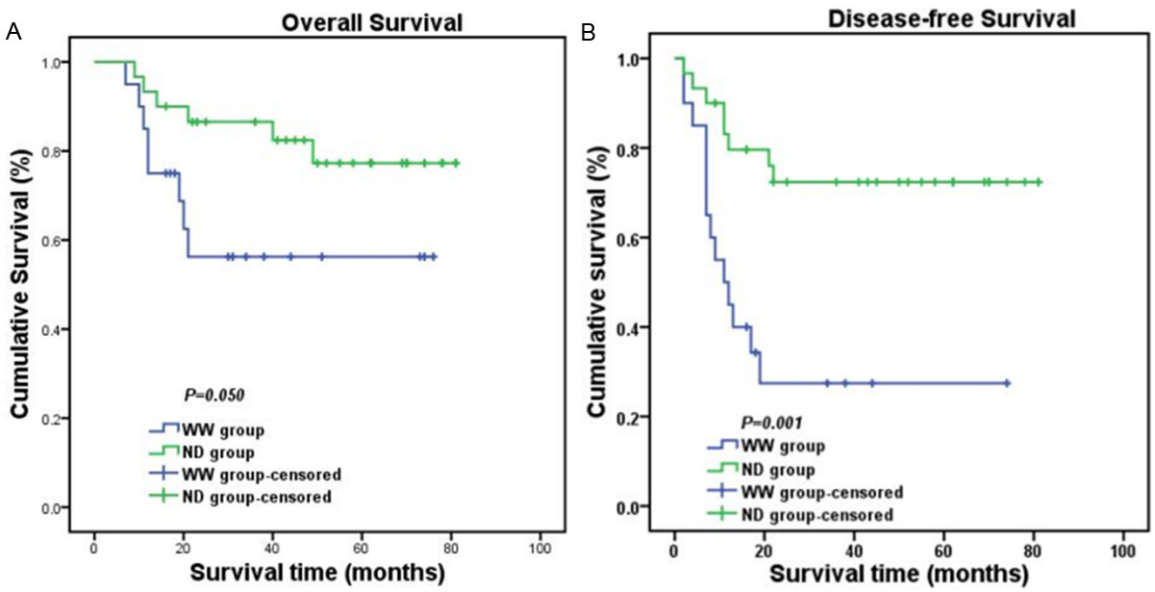

Figure 11. Neck dissection or watch-and-wait affects overall survival and disease-free survival. Kaplan-Meier curves with univariate analysis (log-rank) for cT1-2N0 OTSCC patients without vascular invasion receiving neck dissection (n=107) versus under watch-and-wait (n=41) for overall survival (P=0.843) (A) and disease-free survival (P=0.147) (B).

There are 50 patients with vascular invasion, 148 patients without vascular invasion. The cumulative 3-year OS rate for the patients with or without vascular invasion was 72.0% and 86.5% (*P*=0.022). The cumulative 3-year DFS rate for the patients with or without vascular invasion was 56.0% and 82.4% (P=0.001), respectively (**Figure 9**). Of 50 patients with vascular invasion, the cumulative 3-year OS rate and 3-year DFS for ND group was 80.0%, 73.3% when compared with 60.0%, 30% for WW group (P=0.050, 0.001), respectively (**Figure 10**). And for 148 patients without vascular invasion, the cumulative 3-year OS rate and 3-year DFS for ND group was 82.1%, 84.0% when compared with 83.3%, 92.9% for WW group (P=0.843, 0.147), respectively (**Figure 11**). Furthermore, in a subset analysis, we found the statue of neck dissection was association with the statue of vascular invasion (P=0.002). This supports our subjective experience that the early TSCC patients with vascular invasion are more challenging and association with more probability of lymph node metastasis.

Discussion

It is well known that the surgical removal of cancer is one of the most important treatments for OTSCC and locoregional control is closely connected with survival [2, 29]. As it is extremely difficult to salvage from recurrence after initial surgery [2], the first surgical management of the neck should include proper extent if indicated. In OTSCC, it has been reported that lymph node metastases usually occur in level I, II or III in several post-surgical pathologic studies [25, 30]. I-III is widely accepted as an elective treatment for clinically node-negative OSCC patients. But it also had been pointed that the postoperation complications all occurred in patients after neck dissection. Other studies have already evaluated the morbidity after different types of neck dissection procedures [23, 31, 32]. In addition, several authors have reported equivalent regional control and survival rates with protocols of adjuvant therapy, such as radiotherapy or chemo-radiotherapy, compared to ND [33-35]. However, most patients who had pathologically proven lymph nodes metastasis received high dose post-operative adjuvant therapy; therefore, it is difficult to assess whether the control of neck disease was accomplished by proper surgery or by adjuvant therapy.

The purpose of our study was to retrospective analysis the prognosis of patients undergoing wide local resection with or without neck dissection, in order to discover reliable factor

reflecting the poor prognosis or high rates of metastasis, which may help to identify the early OTSCC patient who need neck dissection or other adjuvant therapy. All patients included in our study had early stage OTSCC and were treated surgically approach, almost all the operation protocols were made via the department consultation. But this is only a retrospective analysis the patients, without the uniform post operation protocol, such as radiotherapy or chemo-radiotherapy.

First of all, we found the estimated 3-year OS and DFS between the neck dissection group and watch and wait group, though there is a tendency that the prognosis of ND group is better than WW group. This result is in accordance with other reports [9, 16-22]. But the conclusion that proved lymph node metastasis indicate the poor prognosis have been approved universally [1, 2]. Moreover, we found the T1 and T2 classification has no notable impact on the statue of lymph node metastasis or the prognosis. This viewpoint is different from the result reported by CP Zhang et al. [36]. The difference may be on account of the effect of post operation adjuvant therapy. Because of the limited enrolled patients and the uniformity of number of patients with the different differentiated degree, there is no significant difference of the cumulative 3-year OS and DFS between the different differentiated degree. Based on previous study we choose the 4 mm as the cutpoint for the invasion thickness [17, 18, 37]. B YERS et al. [41] reported that a muscular invasion depth exceeding 4 mm had more possibility to metastasize as a prognostic factor in oral tongue cancer, O'B RIEN et al. [42] reported that difference in the rate of survival and nodal metastasis was present with 4 mm. However the cutoff value of 9 mm was also recommend, in which only tongue cancer of lateral tongue origin was included [46].

We found the poor differentiation, invasion thickness more than or equal to 4 mm and vascular invasion signify high rates of metastasis. Especially, the statue of differentiated degree can be informed through preoperative biopsy. Namely, neck dissection is recommended for the patients with the poor differentiation, which goes along with previous report [17, 37]. The later two factors also reflect the poor prognosis. Though both result are from the postoperative pathological diagnosis to some extent. They can also suggest more aggressive adjuvant treatment.

In conclusion, first of all, we should recommend all patients suspected oral tongue cancer to receive MRI, and pay more attention to the invision depth. We suggest that the patients with T1 OTSCC the WW protocol is recommended, For T2 cases, the ND protocol is also reasonable. The neck dissection should be considered in cases with poor differentiation. For the patients with proved invasion thickness more than or equal to 4 mm or vascular invasion, neck dissection or more aggressive adjuvant treatment should be performed.

Acknowledgements

This study was supported by grants from the Fundamental Research Funds for the Central Universities (No. 11ykpy43), Guangdong Natural Science Foundation (S2012040006622).

Disclosure of conflict of interest

None.

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