

Lymph node yield as a prognostic factor in clinically node negative oral cavity squamous cell carcinoma

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ABSTRACT

Objectives: To determine the prognostic significance of nodal yield in patients with clinically node-negative (cN0) oral cavity squamous cell carcinoma (OCSCC).

Methods: This retrospective observational study included 40 patients with cN0 OCSCC who underwent treatment with at least 6 months of follow-up data from November 2012 to April 2020. We recorded the variables, including patient demographics, cancer site, tumor-node-metastasis (TNM) staging, type of treatment, lymph node yield (LNY), histopathologic diagnosis, and recurrence. The recorded data were analyzed with descriptive and inferential statistics using specific tests.

Results: Our study cohort comprised of 27 males and 13 females with a mean age of 60.08 ± 13.153 years. Tongue (55%) was the commonly affected site. Seventeen (42.5%) patients belonged to TNM stage II. The mean LNY in our study was 38.65 ± 25.41 (range 7-98). Following surgery, 19 (47.5%) patients further received adjuvant therapies. Recurrence was reported only in 4 (10%) patients. There was no significant difference between LNY and recurrence rate ($p=0.892$). Factors including, age ($p=0.121$), gender ($p=0.209$), site ($p=0.519$), size of tumor ($p=0.416$) did not influence the LNY.

Conclusion: There is no correlation between LNY and recurrence in cN0 OCSCC patients in our study. Meticulous neck dissection and thorough pathologic reporting prevents TNM under staging and improves the overall survival and prognosis.

Keywords: lymph node yield, oral cavity squamous cell carcinoma, recurrence, selective neck dissection, cN0

*Saudi Med J 2021; Vol. 42 (12): 1357-1361
doi: 10.15537/smj.2021.42.12.20210572*

Oral cavity squamous cell carcinoma (OCSCC) accounts for 2% of all cancers, with an annual incidence of over 300,000 cases worldwide.¹ Factors including, age, gender, the primary site of the tumor, depth of invasion, lymph node (LN) involvement are considered independent prognostic indicators of OCSCC.² Among these, cervical lymphadenopathy is the most important prognostic indicator of OCSCC; however, the cervical metastasis differs among different oral cavity sites and the clinical stage of the tumor, due to differences in the lymphatic drainage. Currently, surgical resection of the tumor along with selective neck dissection (SND) is the standard treatment of choice for clinically node-negative (cN0) tumors if the risk of occult nodal disease of the neck is $\geq 20\%$.³

The total number of LNs retrieved during the neck dissection constitutes the lymph node yield (LNY). Previous studies have reported an improved prognosis and survival with higher LNY as it increases the probability of resecting the potential tissue with the occult disease.^{4,5} However, there is a lack of definitive results suggesting an association between higher LNY in different head and neck cancer variants and improved oncologic outcome. Lack of specific guidelines on the extent of neck dissection from SND, minimum LNY values required to eliminate the risk of occult disease attribute to the variable clinical outcome. Moreover, differences in the techniques and protocol followed by the surgeons and pathologists in different institutions also play a role.⁶ This study aimed to determine the prognostic significance of nodal yield in patients with cN0 OCSCC.

Methods. We conducted an analytical retrospective observational study in Otolaryngology, Head and Neck Department at King Fahad Medical City, Riyadh, Saudi Arabia. After obtaining clearance from the institutional ethics committee (ref no.: 21-167 dated 26.04.2021), we screened the Institution's electronic medical records of all patients treated for OCSCC from 2012 to 2020. We excluded all patients with clinically positive nodes during tumor-node-metastasis (TNM) staging (8th edition) and other head and neck malignancies. We included a total of 40 patients with TNM staging (clinical and radiological) without nodal involvement

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

(cN0) who underwent neck dissection with at least 6 months follow-up data for the final analysis.

We recorded the following details: the patient demographics (age, gender), site of cancer, TNM staging based on clinical and radiographic findings,⁷ types of treatment, number of LNs dissected, histopathologic diagnosis, and recurrence. Considering the cN0 staging, all patients underwent supramylohyoid neck dissection (level I to level III). The number of LNs extracted and counted by the pathologist was termed as LNY. The reappearance of cancer within 6 months following treatment was considered persistent disease or treatment failure, while reappearance beyond 6 months was considered a recurrence.

Statistical analysis. The recorded data entered in Microsoft excel was imported to SPSS version 21 (IBM Corp, Armonk, NY, USA) for statistical analysis. Continuous variables were expressed as mean and standard deviations, and categorical variables were expressed as frequency and percentages. The relationship between the LNY and recurrence was assessed using the Man-Whitney U test. Furthermore, the study cohort was categorized into 2 groups based on the median LNY for further analysis. Baseline variables related to the LNY and recurrence rate were analyzed using Man-Whitney or Fischer exact test. A p -value of <0.05 was considered statistically significant.

Results. Our study cohort comprised of 40 (male=27; females=13) cN0 patients who underwent treatment for histologically diagnosed OCSCC. Patients belonged to the age range of 34 years to 86 years with a mean age of 60.08 \pm 13.153 years. Tongue (55%) was the commonly affected site in the oral cavity. Based on the TNM classification, 42.5% of patients were categorized as TNM stage II followed by stage IV (27.5%). Tumor-node-metastasis staging was unknown in 1 (2.5%) patient. All patients underwent surgical resection of the tumor along with SND of level I to level III nodes. Nineteen (47.5%) patients further received adjuvant therapies. The mean LNY in our study was 38.65 \pm 25.41 (range 7-98). We observed recurrence only in 4 (10%) patients. Details of the demographic characteristics, site of tumor, diagnosis, treatment and its outcome are summarized in **Table 1**.

There was no significant difference between the number of LNs retrieved (LNY) during surgery and the recurrence rate ($p=0.892$) (**Table 2**). Factors influencing the LNY and recurrence of OCSCC are summarized in **Table 3**. There was no significant association between LNY with age ($p=0.121$), gender ($p=0.209$), site ($p=0.519$), tumor size ($p=0.416$), and treatment type

Table 1 - Frequency distribution of study variables.

Variables	n	%
<i>Gender</i>		
Male	27	67.5
Female	13	32.5
<i>Sub-site</i>		
Buccal mucosa	4	10.0
Tongue	22	55.0
Floor of the mouth	3	7.5
Alveolus/mandible	4	10.0
Retromolar trigone	3	7.5
Lower lip	1	2.5
Hard palate	2	5.0
Gingiva	1	2.5
<i>Histological code</i>		
Moderately differentiated squamous cell carcinoma	3	7.5
SCC	37	92.5
<i>TNM staging</i>		
Stage I	9	22.5
Stage II	17	42.5
Stage III	2	5.0
Stage IV	11	27.5
unknown	1	2.5
<i>Treatment</i>		
Surgery	21	52.5
Surgery+ chemotherapy	1	2.5
Surgery+ radiotherapy	14	35.0
Surgery+ chemo - radiotherapy	4	10.0
<i>Recurrence</i>		
Yes	4	10.0
No	36	90.0

(0.532). Similarly, age ($p=0.972$), gender ($p=0.284$), site ($p=0.920$), tumor size ($p=0.830$) and treatment type (0.458) had no effect on the recurrence rate.

Discussion. Nodal involvement of the neck in OCSCC increases the risk of recurrence, and poor outcome.⁸ With the limited role of diagnostic imaging, SND with lymphadenectomy remains the gold standard for diagnosing occult metastatic disease and has been recommended as a treatment protocol for cN0 OCSCC patients.⁹ All patients in our study underwent surgical resection of the primary tumor and SND of supramylohyoid lymph nodes (level I to level III). The extent of neck dissection determines the number of dissected LNs and LNY, which influence the survival of head and neck cancer patients.¹⁰ Kuo et al⁶ reported a positive association between meticulous and extensive neck dissection and LNY. However, with no definitive

Table 2 - Effect of lymph node yield on the treatment outcome.

Recurrence	n	Median	Mean rank	Sum of ranks	Mann-Whitney U	Z	P value
Yes	4	35.00	27.25	85.00			
No	36	29.00	20.42	735.00	69.000	-0.135	0.892

Table 3 - Factors influencing the lymph node yield and recurrence rates.

Variable	<31 LNY	>31 LNY	P-value	Recurrence present	Recurrence absent	P-value
<i>Age (in years) (mean±SD)</i>	63±13.77	56.5±11.73	0.121	60.33±9.504	60.05±13.505	0.972
<i>Gender</i>						
Male	13	14	0.209	4	23	0.284
Female	9	4		0	13	
<i>Sites</i>						
Buccal mucosa	2	2	0.519	1	3	0.920
Tongue	12	10		3	19	
Floor of mouth	1	2		0	3	
Alveolus/mandible	1	3		0	4	
Retromolar trigone	3	0		0	3	
Lower lip	1	0		0	1	
Hard palate	1	1		0	2	
Gingiva	1	0		0	1	
<i>T stage</i>						
T1	6	3	0.416	0	9	0.830
T2	11	6		2	15	
T3	1	1		0	2	
T4	4	7		2	9	
T5	0	1		0	1	
<i>Treatment</i>						
Surgery	11	10	0.532	1	20	0.458
Surgery + chemotherapy	0	1		0	1	
Surgery + radiotherapy	9	5		3	11	
Surgery + Chemoradiotherapy	2	3		0	4	

guidelines, the decision on the extent of surgery is dependent on the surgeon's judgment, expertise, and decision-making from previous experience. In our study, the number of LN dissected ranged from 7 to 98 with a mean LNY of 38.65±25.41, which is higher than reported by Muttagi et al¹¹ (21.97±5.57) and Pou et al¹² (21.5±12.9). The difference in the mean LNY and wide range of nodal yield is attributed to the tumor site and lymphatic drainage, surgical technique used, the extent of dissection, and pathological examination.

In a meta-analysis of 10 OCSCC studies, de Kort et al¹³ conferred an improved overall survival of cancer patients associated with higher LNY. Higher LNY has advantages in the diagnostic, therapeutic front. Firstly, higher LNY acts as a diagnostic aid for the accurate

pathological staging of the neck, which subsequently impacts the treatment plan thereafter.^{4,5} Secondly, higher LNY increases the likelihood of removing the occult metastatic disease. Finally, higher LNY reflects on the quality care of the surgeon and the institution, resulting in an improved outcome.⁶ On the other hand, decreased survival in patients with low LNY implicates the undertreatment of occult neck disease resulting in regional failure. Despite the known advantage of LNY, there is no consensus with the minimal LNY for OCSCC. While Bottcher et al¹⁴ reported decreased survival rate and increased risk of locoregional recurrence with <18 LNY, Kuo et al⁸ and Lemieux et al¹⁵ observed increased survival in cN0 patients with >16 LNY and >21 LNY, respectively. Arun et al⁵ did not observe a significant

difference in risk of recurrence and improved outcome with a median cut-off of 36 nodes. In our study cohort, the overall LNY did not affect the recurrence rate.

Following the initial treatment, Chow et al⁹ reported 23.1% local recurrence, 12.8% regional recurrence and 7.7% distant metastasis in OCSCC patients. In our study, the recurrence was comparatively less, with a frequency of 10%. Gender, oral sub-sites including oral tongue and floor of the mouth, TNM stage, increased tumor thickness, skin invasion, LNY, type of initial treatment, and postoperative adjuvant therapy are the prognostic indicators of oral cancer.^{2,5,9} In our study, recurrence was present only in male patients, of whom 3 patients had tongue cancer, and one had cancer in the buccal mucosa. Recurrence was noted in patients with stages T2 and T4 and 3 patients who underwent radiotherapy. However, there was no significant association between patient, tumor characteristics, adjuvant therapy and recurrence.

Factors such as patient's age, immunological response, primary tumor size, TNM stage, anatomic location, presence of oral potentially malignant disorder, prior history of radiation therapy, delay in surgery following diagnosis influence the LNY. Moreover, LN hypertrophy is influenced by many physiological and pathological factors, and it differs among individuals.¹⁰ More importantly, the extent of training and experience of the surgeon, surgical technique used, duration of formalin fixation and method of handling the specimen, the pathologist's experience in harvesting the LNs, different reporting techniques followed influence the overall LNY.¹³ Muttagi et al¹¹ observed higher LNY in patients who delayed surgery after the initial diagnosis, suggesting disease progression during the waiting period. Also, the presence of oral potentially malignant disorder increased LNY. Increased LNY could be due to the inflammatory response to the non-healing ulcer and its related symptoms, including trismus and poor oral hygiene.

The findings of our study imply that a good neck dissection and thorough sampling of LN increases the prognosis of patients. Survival depends on the quality of dissection, rather than the quantity of LNY. Despite the absence of specific guidelines concerning the optimal number of sampled LNs, SND with a good quality will no doubt impact the treatment outcome and thus can be used as a tool to assess the quality of operative techniques and pathological examinations, which further provide insights on ways to improve the quality of care.

Study limitations. Our sample size was limited as we used only node-negative samples with different oral

cavity subsites. The study's retrospective nature was another limitation, as the retrospective collection of information may have diverse and variable information due to the difference in the data collection methods used by different clinicians. Although all patients underwent supramylohyoid neck dissection as per the guidelines, we could not control the surgeon and pathologist counting the LNY and relied on the pathology reports. Histologic depth of invasion also plays a vital role in cancer recurrence, and the same was not considered.

Further large-scale prospective studies including multicentered data or nationwide databases are warranted to understand the implications of the extent of SND and LNY on the treatment outcome of OCSCC. Additionally, minimal LNY required for specific sub-sites of OCSCC also needs to be assessed due to variable lymphatic drainage, especially for the tumors involving the tongue and floor of the mouth, as they are more liable for LN metastasis. Furthermore, guidelines must be established for surgical dissection, minimal LNY needed to identify occult metastasis for individual sites of the oral cavity and different tumor stages, and pathological interpretation of neck samples.

In conclusion, there is no significant correlation between LNY and recurrence in cN0 OCSCC patients. The findings suggest that an LNY obtained from a meticulous neck dissection and a thorough pathologic sectioning and interpretation of samples are the basis for an adequate cancer staging. This further improves the quality of care and the clinical outcome. However, it is essential to develop specific guidelines to aid the surgeons and pathologists to identify an adequate number of LNs from the neck to minimize the risk of leaving the occult nodal metastasis.

Received 19th July 2021. Accepted 1st September 2021.

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