Lymph node ratio as a prognostic marker of oral tongue squamous cell carcinoma: a cohort study

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ABSTRACT

INTRODUCTION Lymph node metastasis is a poor prognostic indicator and is well established in tongue squamous cell carcinoma. Based on the current staging system, accurate risk stratification is difficult. There is thus a need to evaluate an alternate method for predicting recurrence and survival. The objective of the study was to evaluate lymph node ratio as a prognostic marker as compared with N-staging for tongue squamous cell carcinoma.

MATERIALS AND METHODS We conducted a retrospective cohort study with 56 patients with a lymph node ratio greater than 0.012 (exposed) and 74 patients with a lymph node ratio less than 0.012 (unexposed). Overall five-year survival and disease-free survival were assessed. The Cox proportional hazard model was used to analyse lymph node ratio as a predictor of outcome, together with other covariates.

RESULTS A total of 130 patients were included in the study. Patients with lymph node ratio greater than 0.012 had a poor overall five-year (mean survival time 52.1 months vs 38.1 months) and disease-free survival (mean survival time 53.6 months vs 39.2 months). The hazard of death among patients with a lymph node ratio greater than 0.012 was 3.24 times higher than the hazard of death among patients with a lymph node ratio less than 0.012 (95% confidence interval 1.82–5.77).

DISCUSSION Lymph node ratio is a superior prognostic marker compared with the currently used American Joint Committee on Cancer N-staging. Our findings also suggest that the margin status (involved) of the primary tumour resection adversely affects prognosis.

KEYWORDS

Head and neck – Tongue cancer – Oral carcinoma – Lymph node – Lymph node ratio

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Introduction

Oral carcinoma is defined as malignancy of the oral cavity, and is predominantly squamous. There are around 263,900 new cases of oral cavity squamous cell carcinoma diagnosed each year, with around 128,000 deaths per year, making it one of the most common malignancies worldwide.¹ Oral carcinoma is the sixth most common cancer in Asia.¹ The high incidence of oral carcinoma is attributed to some cultural practices, such as the chewing of quid, naswar and tobacco flakes.¹ The risk of developing oral cancer is 11 times higher in people who smoke tobacco compared with those who do not.^{1,2} This, coupled with ancient practices of chewing quid in the form of paan, which contains betel leaf, areca nuts and lime, with or without tobacco predisposes our population to a greater risk of developing oral cancer.^{1,5}

There are around 300 lymph nodes in the neck.⁴ Oral cancer metastasises to these neck nodes, which warrants a neck dissection.⁵ A neck dissection is a surgical procedure whereby neck nodes are excised to achieve regional cancer clearance.⁶ Lymph node metastasis in the neck is considered

as the most important prognostic indicator of adverse outcome and survival in squamous cell carcinoma of the tongue, second only to distant metastasis.⁷ Lymph node ratio is defined as a ratio between the number of affected lymph nodes to the total excised nodes.^{8–12}

South Asia has a high burden of oral cavity squamous cell carcinoma.¹ The absolute number of lymph nodes after neck dissection does not accurately predict survival.⁸ The objective of our study was to determine lymph node ratio as a prognostic marker for tongue squamous cell carcinoma in patients who have undergone treatment at a tertiary care referral centre in a high-burden region.

Material and methods

A retrospective cohort study was conducted at the Aga Khan University Hospital, Karachi, Pakistan from May 2018 to January 2000. The study was approved by the institutional ethical review committee (5150-CHS-ERC-17). The exposure variable was lymph node ratio (> 0.012 exposed) and outcome measure was overall five-year and disease-free

survival rates. Overall survival was measured as deceased or alive after five years or primary treatment (surgery) and disease-free survival as recurrence or no recurrence after five years of the start of treatment.

Sociodemographic, disease and treatment-related variables were collected from medical records and information on survival was collected on telephonic interview. Patients with tongue squamous cell carcinoma treated at the university hospital were included in the study. Exclusions included patients under the age of 18 years, previous history of surgery, previous history of radiation therapy, stage IVb. Patients with distant metastasis (M1) and with missing records were excluded from the study.

For information on survival, patients were contacted three times, after which they were excluded from the study. Purposive sampling technique was used for the selection of patients. Sample size calculated an inflation of 10% in both the groups with a hazard ratio (HR) of 2.3 and standard error of 0.37 to achieve 80% power at a one-tailed level of significance of 5%. Cox regression was expected to have at most an R-squared of 0.7. A total sample size of 242 was calculated with 121 in each arm.

Mean and standard deviation (SD) were reported for continuous normally distributed variables, number and percentages for categorical variables. Mean survival time was computed for disease and treatment related variables. Log-rank test was used for univariate analysis and Cox proportional hazard model was used for multivariable analysis. Kaplan–Meier curves were used to graphically represent survival analysis.

Results

A total of 150 patients were included in the study. Male predominance was seen in our cohort, with 66% men and 34% women. A total of 5541 lymph nodes were evaluated for metastatic deposit; 185 (3.3%) lymph nodes were positive for metastasis. The mean age of the men was 47.32 years (SD 12.2 years) and that of women was 53.58 years (SD 15.75 years). A total of 184 neck dissections were carried out; 120 ipsilateral neck dissections, most of which were modified radical neck dissections ($n = 82$, 68.3%), selective neck dissection ($n = 20$, 16.7%) and radical neck dissections ($n = 18$, 15%). There were 54 neck dissections carried out on the contralateral side. Most contralateral neck dissections were selective neck dissections ($n = 41$, 75.9%), modified radical neck dissections ($n = 12$, 22.2) and radical neck dissections ($n = 1$, 1.85; Tables 1–3).

The Cox proportional hazard model was used for univariate analysis (overall survival). Age, sex, grade of tumour, margin status of tumour, perineural invasion, depth of tumour invasion, pT-stage, pN-stage, overall stage, treatment and lymph node ratio were assessed for significance at p -value less than 0.05. Our main exposure variable, lymph node ratio was significant at a univariate analysis hazard ratio of 3.03 (95% CI 1.72–5.36). Tumour margin status ($p = 0.05$), depth of tumour invasion ($p = 0.02$), pN-stage ($p = 0.003$) and overall stage ($p = 0.003$) were

also significant. All other variables were insignificant at univariate level (Table 4).

Overall survival

The Cox proportional hazard model was used for multivariable analysis. Lymph node ratio and margin status were the only two variables significant in our final model ($p < 0.05$). After adjusting for effects of other covariates we observed that the hazard of death among patients with lymph node ratio greater than 0.012 was 3.24 times higher as compared with patients with lymph node ratio of less than 0.012 (95% CI 1.82–5.77).

Disease-free survival

The Cox proportional hazard model was used for multivariable analysis. After adjusting for the other covariates our final model revealed that the hazard of disease recurrence among patients with lymph node ratio greater than 0.012 was 3.53 times higher as compared with patients with lymph node ratio less than 0.012 (95% CI 1.73–6.24; Table 5).

Discussion

Cancer of the tongue is staged according to the American Joint Committee on Cancer (AJCC) staging system.¹⁵ Surgical excision of tongue cancer is the mainstay of treatment.⁸ Cervical lymph node metastasis can take place with tongue carcinoma, especially in advanced stage disease.^{14,15} Tumour of the tongue has a tendency to metastasise to the opposite side if the tumour is close to the midline.¹⁴ Neck dissection is excision of cervical lymph nodes along with fibrous fatty tissue.¹⁶ Neck dissection is warranted if there is clinical or radiological lymph node metastasis.¹⁷ A 2015 randomised control trial has shown elective neck dissection to be superior to therapeutic neck dissection in patients with oral cavity carcinoma.¹⁸

In our study, lymph node ratio with a cut-off point of 0.012 was significant for overall five-year survival ($p < 0.0001$; Fig 1) and disease-free survival ($p = 0.0004$; Fig 2). Margin status was also significant in our final model. We calculated our own cut-off point (0.012) based on the area under the receiver operating characteristic (ROC) curve

Table 1 Demographics of the study population

Variable	Lymph node ratio	
	< 0.012 ($n = 74$)	> 0.012 ($n = 56$)
Age, years (standard deviation)	50.2 (11.7)	48.3 (14.6)
Sex, n (%):		
Male	53 (71.6%)	34 (60.7%)
Female	21 (28.4%)	22 (39.3%)

(sensitivity 90.91% and specificity 92%; area under the curve 0.90; Fig 3).

The chewing of smokeless tobacco is a cultural practice in South East Asia.^{1,3} Oral submucous fibrosis is prevalent among betel nut and quid users.¹⁹ Submucous fibrosis limits the spread of oral cancer because of extensive fibrosis. This and other factors could potentially confound

the disease spread to lymph nodes, giving rise to a different subset of patients whose natural history of disease differs from patients in the West and warrants a separate cut-off point to be computed for our own population. Previous studies have reported cut-off of lymph node ratios ranging from 0.1 to 0.13 by taking the mean or median.^{9,10,20–25} However, reporting mean or median as a cut-off is not a

Table 2 Descriptive statistics of overall five-year survival in patients with lymph node ratio less than 0.012 (unexposed) and greater than 0.012 (exposed)

Variable	Unexposed (<i>n</i> = 74)		Exposed (<i>n</i> = 56)		Mean survival time (SE)
	Event (<i>n</i> = 19)	Censored (<i>n</i> = 55)	Event (<i>n</i> = 32)	Censored (<i>n</i> = 24)	
Grade of tumour, <i>n</i> (%):					
Well differentiated	7 (29.2)	22 (40)	9 (28.1)	7 (36.8)	49.8 (2.4)
Moderately differentiated	17 (70.8)	31 (56.3)	20 (62.5)	12 (63.2)	45.5 (2.3)
Poorly differentiated	–	2 (3.6)	3 (9.4)	–	33.6 (10.9)
Tumour margins, <i>n</i> (%):					
Clear	17 (70.8)	34 (61.8)	15 (46.9)	11 (57.9)	51 (1.8)
Close	7 (29.2)	17 (30.9)	11 (34.4)	6 (31.6)	43 (3.4)
Involved	–	4 (7.3)	6 (18.8)	2 (10.5)	29.3 (6.5)
Perineural invasion, <i>n</i> (%):					
Yes	–	2 (3.6)	31 (96.9)	19 (100)	46.6 (1.7)
Depth of invasion, <i>n</i> (%):					
1–5mm	5 (20.8)	8 (14.5)	4 (12.5)	3 (15.8)	50.8 (3.6)
6–10mm	9 (37.5)	28 (50.9)	8 (25)	5 (26.3)	51.2 (2.3)
>10mm	10 (41.7)	19 (34.5)	20 (62.5)	11 (57.9)	41.6 (2.8)
pT stage, <i>n</i> (%):					
T1	6 (25)	25 (45.5)	9 (28.1)	4 (21.1)	49.7 (2.7)
T2	14 (58.3)	25 (45.5)	18 (56.2)	12 (63.2)	44 (2.6)
T3	3 (12.5)	3 (5.4)	4 (12.5)	1 (5.3)	45.5 (5.1)
T4	1 (4.1)	2 (3.6)	1 (3.1)	2 (10.5)	53.5 (4.7)
pN stage, <i>n</i> (%):					
N0	1 (4.2)	54 (98.2)	5 (15.6)	15 (79)	50.9 (2)
N1	8 (33.3)	–	12 (37.5)	–	40.1 (4.7)
N2	15 (62.5)	1 (1.8)	15 (46.9)	4 (21)	40.6 (3.6)
Overall stage, <i>n</i> (%):					
I	1 (4.2)	25 (45.5)	4 (12.5)	4 (21.1)	52.8 (2.4)
II	2 (8.3)	25 (45.5)	–	10 (52.6)	51.4 (2.8)
III	5 (20.8)	3 (5.4)	13 (40.6)	–	37.3 (4.8)
IVa	16 (66.7)	2 (3.6)	15 (46.9)	5 (26.3)	41.1 (3.5)
Treatment, <i>n</i> (%):					
Surgery	7 (29.2)	22 (40)	13 (40.6)	11 (57.9)	45.7 (2.7)
Surgery + radiotherapy	9 (37.5)	20 (36.4)	9 (28.1)	5 (26.3)	48.5 (2.9)
Surgery + CCRT	8 (33.3)	13 (23.6)	10 (31.2)	3 (15.8)	45.2 (3.6)
CCRT, concurrent chemoradiation therapy; SE, standard error					

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reliable method. The International Consortium for Outcome Research calculated a cut-off of 0.07 based on analysis of 4,254 patients from 11 centres worldwide.⁸ Gil *et al* analysed oral cavity squamous cell carcinoma and used a cut-off of 0.06.⁹ They concluded that lymph node ratio was a significant marker for prognosis and patients with

higher lymph node ratio fared less well. Sayed *et al* analysed 1,408 oral cavity cancers using a cut-off of 0.088 and found it to be significant compared with N-stage.²⁶

Extracapsular spread significantly affects prognosis and warrants the addition of adjuvant treatment such as radiotherapy and chemotherapy.²⁷ We did not analyse

Table 3 Descriptive statistics of disease-free survival in patients with lymph node ratio 0.012 or less (unexposed) and greater than 0.012 (exposed)					
Variable	Unexposed (<i>n</i> = 74)		Exposed (<i>n</i> = 56)		Mean survival time (SE)
	Event (<i>n</i> = 14)	Censored (<i>n</i> = 16)	Event (<i>n</i> = 26)	Censored (<i>n</i> = 30)	
Grade of tumour, <i>n</i> (%):					
Well differentiated	5 (35.7)	24 (40)	7 (26.9)	9 (30)	51.1 (2.5)
Moderately differentiated	9 (64.3)	34 (56.7)	17 (65.4)	20 (66.7)	45.9 (2.5)
Poorly differentiated	–	2 (3.3)	2 (7.7)	1 (7.3)	37.8 (13.6)
Tumour margins, <i>n</i> (%):					
Clear	7 (50)	38 (63.3)	9 (34.6)	23 (76.7)	52.9 (1.8)
Close	5 (35.7)	18 (30)	11 (42.3)	7 (23.3)	42.4 (3.8)
Involved	2 (14.3)	4 (6.7)	6 (23.1)	–	28.8 (6.9)
Perineural invasion, <i>n</i> (%):					
Yes	1 (7.1)	1 (1.7)	1 (3.9)	–	29 (16.6)
No	13 (92.9)	59 (98.3)	25 (96.2)	30 (100)	47.8 (1.8)
Depth of invasion, <i>n</i> (%):					
1–5mm	3 (21.4)	8 (13.3)	1 (3.9)	8 (26.7)	52.8 (3.7)
6–10mm	4 (28.6)	29 (48.3)	7 (26.9)	10 (33.3)	52 (2.4)
>10mm	7 (50)	23 (38.3)	18 (69.2)	12 (40)	41.8 (3.1)
pT stage, <i>n</i> (%):					
T1	3 (21.4)	26 (43.3)	6 (23.1)	9 (30)	51.3 (2.7)
T2	9 (64.3)	28 (46.7)	14 (53.9)	18 (60)	45.2 (2.7)
T3	1 (7.1)	3 (5)	5 (19.2)	2 (6.7)	43.3 (6.7)
T4	1 (7.1)	3 (5)	1 (3.9)	1 (3.3)	51.3 (7.5)
pN stage, <i>n</i> (%):					
N0	13 (92.9)	56 (93.3)	5 (19.2)	1 (3.3)	51 (2.1)
N1	–	–	6 (23.1)	14 (46.7)	45.9 (5.1)
N2	1 (7.1)	4 (6.7)	15 (57.7)	15 (50)	40.4 (4.1)
Overall stage, <i>n</i> (%):					
I	3 (21.4)	26 (43.3)	2 (7.7)	3 (10)	54.3 (2.5)
II	8 (57.1)	27 (45)	–	2 (6.7)	51.7 (2.9)
III	1 (4.4)	2 (3.3)	8 (30.7)	10 (33.3)	41.4 (5.3)
IVa	2 (14.3)	5 (8.3)	16 (61.5)	15 (50)	40.3 (3.9)
Treatment, <i>n</i> (%):					
Surgery	7 (50)	26 (43.3)	10 (38.5)	10 (33.3)	47.8 (2.8)
Surgery + radiotherapy	4 (28.6)	21 (35)	8 (30.8)	10 (33.3)	47.2 (3.3)
Surgery + CCRT	3 (21.4)	13 (21.7)	8 (30.7)	10 (33.3)	46.9 (3.7)

CCRT, concurrent chemoradiation therapy; SE, standard error

extracapsular spread as information was not available to us for all the cases.

In a study conducted by Suslu *et al*, median lymph node count was reported and was taken as a cut-off point for lymph node ratio.²⁵ Tumours at all subsites of the head and neck were incorporated in the analysis. Given the small sample size and lack of subgroup analysis, the results may be skewed with uneven distribution of subsites. Gil *et al* also used a mean cut-off point of 0.06 to stratify their cohort.⁹ The area under the ROC curve was not reported.

Median lymph node count could potentially differ with a change in sample size, and so is an unreliable method to consider for a cut-off point. The largest study was conducted by International Consortium for Outcome Research. It suggested a cut-off point of 0.07 based on pooled analysis.⁸ However, the study failed to elaborate on the methods used to achieve that sample size. Moreover, N-stage was significant in its analysis. They further added

the use of lymph node ratio (lymph node density) in conjunction with the already proposed system. Lieng *et al* analysed data from 72 patients with tongue squamous cell

Table 4 Mean survival times for overall five-year and disease-free survival rates for the main exposure variable (lymph node ratio)

Survival rate	Lymph node ratio (%)		Mean survival time (SE)	
	≤0.012	> 0.012	≤0.012	> 0.012
Five-year	74 (56.9)	56 (43.1)	52.1 (1.72)	38.1 (2.96)
Disease-free	74 (56.9)	56 (43.1)	53.6 (1.76)	39.2 (3.25)

Table 5 Multivariable analysis of individual factors affecting overall and disease-free survival rates at ratio cut off 0.012 (*p*-value 0.05)

Survival rate	Adjusted hazard ratio	95% confidence interval
<i>Overall</i>		
Lymph node ratio:		
≤0.012	1	–
> 0.012	3.33	1.73–6.24
Tumour margins:		
Clear	1	–
Close	2.34	1.17–4.68
Involved	5.33	2.24–12.68
<i>Disease-free</i>		
Lymph node ratio:		
≤0.012	1	–
> 0.012	3.24	1.82–5.77
Tumour margins:		
Clear	1	–
Close	1.45	0.78–2.97
Involved	3.94	1.72–8.90

Figure 1 Kaplan–Meier curve of overall survival stratified on lymph node ratio (0.012). Patients with lymph node ratio less than 0.012 had a mean survival time 52.1 (1.72) and 38.1 (2.96) compared with lymph node ratio greater than 0.012 (*p* < 0.0001)

carcinoma but excluded patients who had no nodal metastasis.²⁸ We feel that as lymph node ratio is derived from N-staging and N0 nodal metastasis would fall under the lower cut-off (less than 0.012) these patients should be considered for establishing a cut-off point.

Limitations and strengths

There were limitations to our study. The study was retrospective. Selection bias is an inherent property of a retrospective study and we minimised it by taking all patients with tongue squamous cell carcinoma. Recall bias

was reduced by allowing patients to recollect information on the date of recurrence or death of the patient (information taken from spouse). We were not able to achieve our target sample size owing to time limitations, but we plan to continue the study until we are able to achieve our targeted sample size. Extracapsular spread (extranodal extension), which is an important prognostic indicator, could not be assessed as it was not reported for all patients. Given the retrospective nature of the study, additions and comorbid conditions were missing from the dataset, so could not be evaluated in the study.

To the best of our knowledge, there has been only one study conducted to determine lymph node ratio including tongue as the subsite.²⁹ This is the first report from our population. We were able to establish our own cut-off points by robust statistical methods.

Conclusion

Our study shows that lymph node ratio is a significant prognostic marker of tongue squamous cell carcinoma. Lymph node ratio is a superior prognostic marker as compared with current N-staging of the AJCC. Patients with high lymph node ratio would fare worse and would require postoperative adjuvant treatment. Moreover, our finding suggests that the tumour resection margin status of the primary tumour resection affects the prognosis.

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