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ORIGINAL ARTICLE

Clinicopathologic Predictive Factors of Extranodal Extension in Oral Squamous Cell Carcinoma – A Retrospective Analysis

Nadimul Hoda[1] · Mainak Ghosh[1] · Aparna Ganesan[1] · K. S. Sabitha[1] · Akshay A. Byadgi[1] · K. P. Amith[1]

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Abstract

The implications of extranodal extension (ENE) in oral carcinoma have been often related to prognosis and survival rates. The clinicopathologic predictive factors of this established prognostic factor were analyzed in this retrospective study. A total of 358 medical records of a single institution were screened. Primary outcome variable was ENE. Predictor variables were clinical tumour (cT) and nodal (cN) staging, tumour subsite, and pathologically tumour size, depth of invasion (DOI), lymph node ratio (LNR), presence, or absence of perineural invasion (PNI), lymphovascular invasion (LVI) and mandibular involvement. After scrutinization, 216 records met the inclusion and exclusion criteria. Presence of ENE was noted in 42.1% (91/216) of patients. In cN0 necks ENE was 34.7% which was statistically significant. The cut-off value for tumour size, DOI and LNR were, 7.28 cm, 9 mm and 0.05 with accuracy rates of 68%, 79% and 94% respectively. The odds of presence ENE were highest with bone involvement (2.91) followed by PNI (2.34) and lastly LVI (2.17). In conclusion, these predictive factors can be used to fortify the pathologic diagnostic criteria of ENE.

Keywords Extranodal extension · Depth of invasion · Lymph node ratio · Oral squamous cell carcinoma

Introduction

Oral squamous cell carcinoma (OSCC) along with oropharyngeal cancers accounts for the sixth most common type of cancers worldwide posing a significant health burden [1]. Cervical lymph node metastasis has been established as the most common form of spread of OSCC which substantially affects the prognosis and treatment outcomes, decreasing the overall survival by 50% [2]. The characteristics of nodal metastasis which specifically influence the prognosis and majorly determine the survival rates are lymph node size, number and extranodal extension (ENE).

ENE is characterized by disruption of lymph node capsule by tumor emboli [3]. ENE was first described by Willis in 1930, and later was ascertained to be associated with worst survival outcomes [4, 5]. Eventually, the importance of ENE as a prognostic marker has been enough extrapolated in the literature. Moreso, in the recent AJCC 8th edition, the presence of ENE has been incorporated in the staging guidelines [3]. ENE is one of the two major adverse pathologic factors that mandates adjuvant chemoradiation, the other being positive margins [6–8]. The presence of ENE challenges adequate surgical clearance, in addition to surging the risk for vascular spread and distant metastasis.

Clinically ENE is characterized by dermal fixation, deep fixity to underlying muscles, or nerve involvement [9]. Radiologically ill-defined nodal borders with invasion into adjacent structures are suggestive of ENE [10, 11]. Initially ENE was considered to occur in nodes > 3 cm, nevertheless, imaging studies have shown ENE in nodes < 1 cm as well [12]. However, the gold standard definition is by pathological assessment which establishes presence of ENE if tumour emboli are found breaching the capsule [13]. Preoperative analyses for ENE comprise of fine needle aspiration (FNA), sentinel node biopsies or imaging. These modalities have their own limitations with low sensitivity and specificity [11]. Lately, molecular markers have been explored to determine the correlation with ENE. These markers are futile due to their unpredictability of results and lack of clinical validation [14]. Thus, at present, detection of ENE mandates histological confirmation augmented with clinical and radiologic evidence. Histologically also controversy exists

✉ Aparna Ganesan
ganesan.aparna@gmail.com

[1] Department of Oral Oncology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India

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with regard to microscopic ENE and considerable inter-observer variability, due to lack of defined guidelines [15]. Unseemly evidence of ENE grounds for undertreatment or overtreatment leading to poor survival rates or increased morbidity respectively. Therefore, there is a felt need to capture the various clinical, radiologic, and pathologic features that predict ENE. Subsequently, assessment and correlation of ENE with adverse clinicopathologic factors may prove beneficial in refining the diagnostic accuracy of ENE. This retrospective analysis aims to correlate the presence of ENE with various clinicopathologic risk factors in OSCC.

Materials & Methods

A retrospective single center cohort study was designed in accordance with the Declaration of Helsinki, strictly abiding by the STROBE Guidelines after obtaining institutional ethical clearance. Medical records of all the patients with histopathologically proven oral squamous cell carcinoma from a period of January 2019 to May 2023, who underwent surgery at a tertiary oncology centre were scrutinised. Patients who underwent neoadjuvant treatment prior to surgery, those who presented with upfront metastatic disease, patients operated for second primary tumours or recurrences, previous history of other malignancies and unretrievable records were excluded from the study.

Clinical staging of tumour was done according to the AJCC 8th edition TNM classification after appropriate imaging and histopathological aids. All the patients underwent resection of primary tumour, neck dissection and suitable reconstruction as per requirement. Subsequently, histopathological analysis was performed to analyse the various adverse histological features, nodal status, and the margins. All the demographic, clinical, radiographic, and histopathological data were retrieved from the medical records of the institution.

Primary outcome variable was ENE. Predictor variables included clinical tumour stage (cT), clinical nodal status (cN0 vs. cN+), and histologic adverse features comprising of depth of invasion (DOI), worst pattern of invasion (WPOI), lymphovascular invasion (LVI), perineural invasion (PNI), lymph node ratio (LNR) and bone involvement.

Table 1 Demographic details and tumour characteristics of study population

Variable	Subcategory	*N*(%)
Gender	Male	100 (46.3)
	Female	116 (53.7)
Tumour subsite	Tongue	52 (24.1)
	Buccal mucosa	60 (27.8)
	Lower GBS	101 (46.8)
	Upper GBS	3 (1.4)
Clinical T stage (cT)	cT1	62 (28.7)
	cT2	102 (47.2)
	cT3	18 (8.3)
	cT4a	30 (13.9)
	cT4b	4 (1.9)
Clinical N stage (cN)	cN0	101 (46.8)
	cN+	115 (53.2)
WPOI	1	2 (0.9)
	3	3 (1.4)
	4	173 (80.1)
	5	38 (17.6)
LVI	Present	91 (42.1)
	Absent	125 (57.9)
PNI	Present	58 (26.9)
	Absent	158 (73.1)
Bone involvement	Present	52 (24.1)
	Absent	164 (75.9)
ENE	Present	49 (22.7)
	Absent	167 (77.3)
		Mean (SD)
DOI (mm)		10.1 (7.2)
LNR		0.06 (0.13)
Tumour size (cm)		12.3 (20.1)

GBS – gingivobuccal sulcus, WPOI – worst pattern of invasion, LVI – lymphovascular invasion, PNI – perineural invasion, ENE – extranodal extension, DOI – depth of invasion, LNR – lymph node ratio

Statistical Analysis

The statistical analysis was done with SPSS (Version 22.0, Armonk, NY: IBM Corp.)

Descriptive analysis of the explanatory and outcome parameters was done using frequency and proportions for categorical variables, and in terms of mean & standard deviation for continuous variables. Chi Square Test was applied to evaluate the presence of ENE based on age & gender of the study subjects, cT, cN, tumour subsite, and histopathological parameters of OSCC. Mann Whitney Test was used to compare the tumour Size, DOI & LNR based on the presence of ENE.

ROC Curve analysis was performed with respect to study parameters in predicting the ENE among the study subjects. Binary logistic regression analysis was carried out estimate the risk of ENE based on the various histopathological parameters of the OSCC. A p-value of < 0.05 was considered to be statistically significant.

Results

A total of 358 records were screened out of which 216 patients met the inclusion criteria. The mean age of presentation was 52.9 years (29–80 years) comprising of 100 males and 116 females. Table 1 represents the demographic

Table 2 Association of ENE with tumour size, DOI and LNR

Parameters	ENE	*N*	Mean	SD	Mean Diff	*p*-value
Tumour size (cm)	Absent	167	9.13	14.429	-13.821	< 0.001*
	Present	49	22.95	30.729		
DOI (mm)	Absent	167	8.43	5.776	-7.43	< 0.001*
	Present	49	15.86	8.597		
LNR	Absent	167	0.023	0.066	-0.159	< 0.001*
	Present	49	0.182	0.194		

* - Statistically Significant

DOI – depth of invasion, LNR – lymph node ratio, SD- standard deviation, ENE – extranodal extension

Table 3 ROC curve analysis for predicting ENE

Parameter	AUC	Std. Error	95% Conf. Interval		*p*-value	Cut off	Sensitivity (%)	Specificity (%)
			Lower	Upper				
Tumour Size (in cm)	0.68	0.04	0.61	0.74	< 0.001*	> 7.28	63.27	64.67
DOI (in mm)	0.79	0.04	0.73	0.84	< 0.001*	> 9.0	81.63	67.07
LNR	0.94	0.02	0.90	0.97	< 0.001*	> 0.05	97.96	83.23

* - Statistically Significant

DOI – depth of invasion, LNR – lymph node ratio, AUC- area under the curve

data of the study population, clinic-radiologic and histopathological characteristics of the tumour.

Lymph node positivity was observed in 42.1% and ENE was noted in 22.7% of the whole cohort. The presence of ENE with respect to age, gender, or clinical tumour stage (cT) was not found to be statistically significant. However, it differed significantly with clinical nodal status (cN), tumour size, tumour subsite, DOI, LNR, PNI, LVI and mandibular involvement as shown in Table 2 & Supplementary Table 1.

As presented in Table 3, ROC curve analysis for predicting the ENE suggested AUC of 0.68 with cut-off value of 7.28 cm (p value < 0.001) for tumour size (Fig. 1). The AUC of DOI based on ENE was 0.79 with cut-off value of 9 mm (p value < 0.001) and that of LNR was 0.94 with cut-off value of 0.05 (p value < 0.001) (Figs. 2 and 3).

Binary logistic regression analysis estimated the risk of ENE with an odds ratio (OR) of 2.17, 2.34, 2.91 for LVI, PNI and bone involvement respectively (Supplementary Table 2).

Discussion

The present retrospective study assessed the factors predicting ENE in patients surgically treated for OSCC. The association of ENE with cN stage was statistically significant, which confirmed the presence of ENE in 34.7% of cN0 neck, 65.3% of cN+necks. In the relevant literature, ENE has been noted in 60–100% of > 3 cm lymph nodes, 39–59% in < 3 cm nodes and 23% in nodes < 1 cm. In the cN0 neck, the reported incidence of ENE is 10–25% [16]. The presence of ENE is cN0 neck in this study was 34.7% which an alarming finding.

Pertaining to the histopathologic features, the tumour size, DOI, LNR and presence of PNI and LVI were associated with ENE, which was statistically significant. Predictability of ENE was further confirmed by the ROC curve analysis. Tumour size of > 7.28 cm (sensitivity = 63.27%, specificity = 64.67%, AUC = 0.68) and DOI of > 9 mm (sensitivity = 81.83%, specificity = 67.07%, AUC = 0.79) were associated with ENE. LNR was found to have the highest predictability (AUC = 0.94) among the histopathological adverse features with a sensitivity of 97.96% and specificity of 82.23%. Similar results have been reported in previous studies. Mair et al. [17] stated that DOI > 5 mm and lymph node size > 15 mm primarily predicted ENE, whereas, Liao et al. in 2018 suggested that DOI > 25 mm predicted ENE and poor overall survival [18] Tandon S et al. reported a mean LNR of 0.06, along with an insignificant association with ENE [16] However, the present study found a statistically significant association of LNR with ENE with a cut-off value of > 0.05. In the existing literature, LNR has always been directly associated survival rates and less frequently associated with predictability of ENE.

The qualitative histopathological variables were analysed using binary logistic regression to estimate the OR. LVI, PNI and mandibular involvement significantly predicted ENE with an OR of 2.17, 2.34 and 2.91 respectively. Current evidence on the correlation between these factors and ENE remains hazy. Few authors have found a significant positive correlation between ENE and LVI and PNI, while a few others have found nil correlation.

LVI is known to be a prognostic indicator and its occurrence indicates initial stages of nodal metastasis. Rajappa et al. [13] found a significant association of ENE with LVI with an OR of 1.53 (p = 0.053), whereas Adel et al. [19] reported an OR of 1.83 (p = 0.007). Pertaining to PNI, Tandon et al. [16]

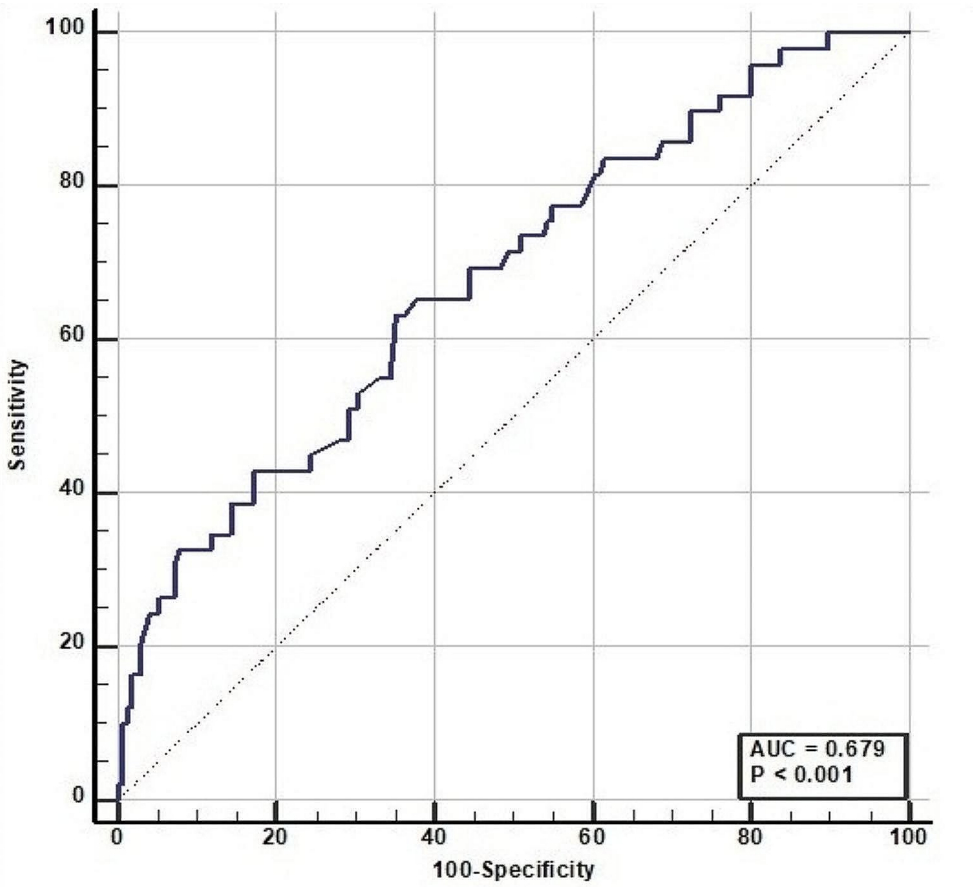

Fig. 1 ROC curve for mean tumour size (cm) predicting ENE

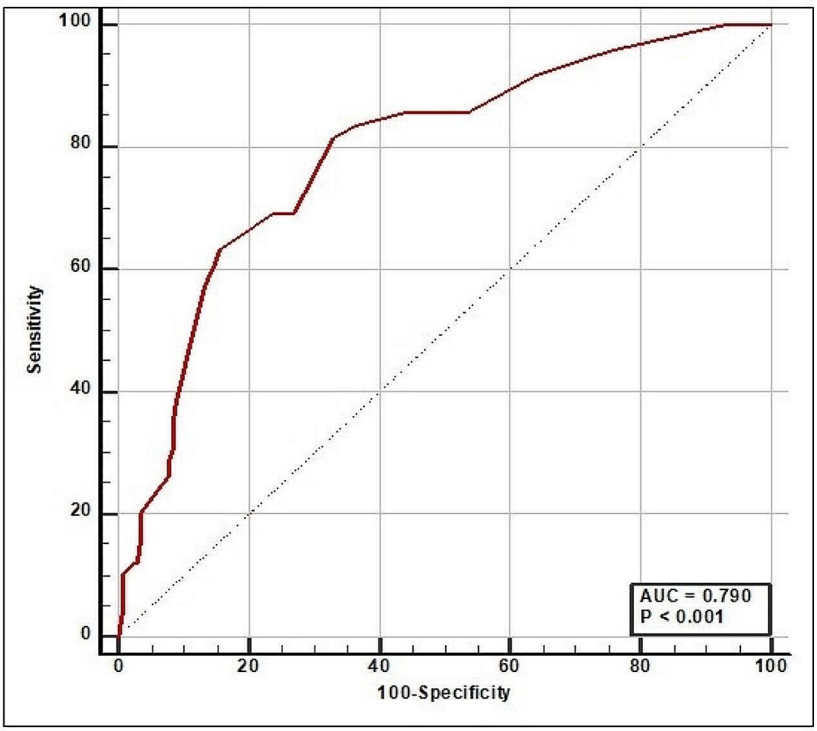

Fig. 2 ROC curve for DOI (mm) predicting ENE

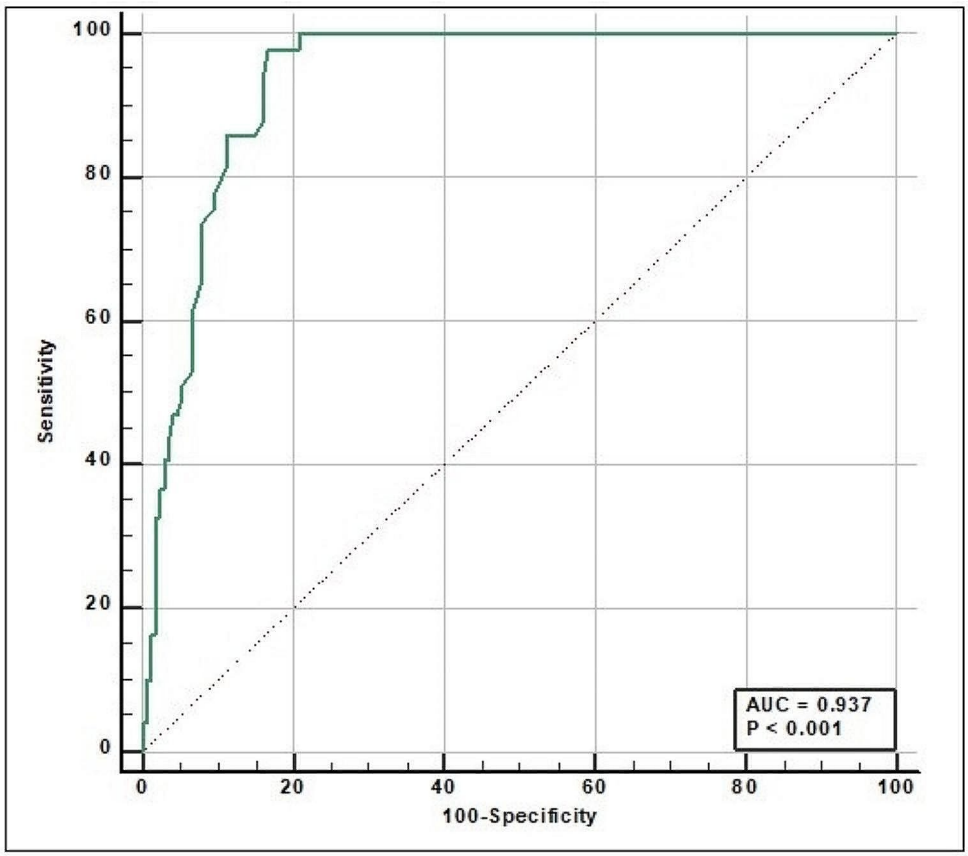

Fig. 3 ROC curve for LNR predicting ENE

found a significant association with occurrence of ENE only in tumours of tongue, while Rajappa et al. estimated the OR to be 1.4, which was statistically insignificant.

The presence of mandibular involvement as a direct predictor of ENE has not been reported in the literature until date. In the present study, 40.8% (9.3% of the whole cohort) of the patients with mandibular involvement were found to have ENE, which was also statistically significant ($p=0.002$) with an OR of 2.91. Besides, ENE presentation was highest in the lower gingivobuccal sulcus subsite which is associated with increased chances of bone involvement as compared to other tumour subsites, which suggests an inter-relationship between tumour subsite, bone involvement and ENE.

Substantial discussion on the predictive factors of ENE is noteworthy. This can be attributed to its prognostic importance which is reflected by the survival rates in ENE positive patients. Some authors have highlighted the difference in survival rates for patients with microscopic and macroscopic ENE [15, 20, 21]. This raises an inquest upon stratification of patients presenting with ENE, thus complicating the diagnostic criteria. Clinical and radiological assessments are insufficient, with low sensitivity. Although, the aid of artificial intelligence and automated detection algorithms did improve the accuracy of clinic-radiologic assessments [15]. Pathologic diagnosis remains the most reliable until time. However, institutional protocols vary remarkably in the pathologic assessment of ENE. It has been proven that the intra- and inter-rater reliability for ENE assessment is poor and intricated in certain circumstances [22]. These include nodes with a deficient capsule, nodes with tumour infiltrating the hilum, presence of a second capsular layer, desmoplastic reaction. Therefore, robust histopathological criteria are required to confirm ENE [15]. More recently, Noda et al. have recognised tumour budding, tumour infiltrating lymphocytes and desmoplastic reactions as potential predictors of ENE in OSCC [14]. Yet, these are highly subjective features and require suitable expertise.

Our study presented cut-off values of DOI, LNR and tumour size through ROC curve analysis, above which the presence of ENE is likely. The AUC signifies the accuracy of these parameters in predicting ENE. It was found that tumour size was the least accurate, followed by DOI and the LNR being the most accurate for envisaging the presence of ENE. These findings and values can assist the pathologist to establish the diagnosis of ENE in borderline cases or complex scenarios as stated previously. Moreso, these values can be implemented in the institutional protocols, curbing the intra- and inter-rater variability.

This study had a few drawbacks. The retrospective study design had inherent biases and detection of ENE was not done by a single pathologist. Since, it is a single-institution study, the results may lack generalisability. The study included a limited

sample size, and we could not perform survival analysis as patients were lost to follow up at varied intervals.

However, this study analysed the predictability of ENE with respect to various histopathologic parameters. This can form a backbone to frame additional histopathologic criteria aimed at refining the diagnostic accuracy of ENE.

Thus, this retrospective analysis highlights the predictors of ENE in OSCC which can hint towards the need for intensifying the adjuvant therapies to yield better survival rates. The authors believe that there is scope for further retrospective studies with multicentric larger samples to augment the results obtained. In future, a systematic consensus can be arrived at for unambiguous diagnosis of ENE, thereby offering prompt management strategies to patients.

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Declarations

Conflict of Interest None.

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