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Head and Neck Cancer

Clinical, Radiological and Histological Features and Their Association with Extranodal Extension in Buccoalveolar Complex Squamous Cell Carcinoma

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Abstract

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Objectives The study was aimed to (1) evaluate the effectiveness of clinical examination, intraoperative finding, and contrast-enhanced computed tomography (CECT) to detect extranodal extension (ENE) in buccoalveolar complex squamous cell carcinoma (BAOSCC), (2) to know various factors influencing ENE, and (3) to evaluate survival outcome in patients with ENE.

Materials and Methods This was a retrospective cohort study, which included 137 patients with BAOSCC who underwent curative treatment between May 2019 and April 2021. Collaborative findings suggestive of ENE were noted during preoperative clinical examination, CECT, and intraoperatively, and their efficacy was compared with postoperative histopathology. Also, the various factors associated with ENE were evaluated and compared.

Statistical Analysis Univariate and multivariate analysis of parameters was done using multiple logistic regression analysis and significant correlation was determined using chi-square test between ENE positive and negative categories. Analysis of prognosis and survival was done by Kaplan–Meier curve plotting using regression analysis and its significance was compared.

Results The overall prevalence of ENE was 18.98% and that of lymph node involvement was 40.88%. CECT (73.1%) was found to be more sensitive in detecting ENE compared to intraoperative examination (46.2%) and clinical examination (34.6%).In comparison with clinical examination (91.9%) or CECT (78.38%), intraoperative examination (93.7%) showed the highest specificity in detecting ENE. Clinical nodal size $\geq$ 3 cm ($p \leq 0.001$), fixity ($p \leq 0.001$), and clinical number of nodes ($p \leq 0.001$) had significant association with ENE. The presence of thick nodal walls on CECT increased

Keywords

- oral squamous cell carcinoma
- extranodal extension
- contrast-enhanced computed tomography
- prognosis
- oral cancer
- neck metastasis

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the probability of predicting ENE 15 times ($p = 0.180$, confidence interval: 0.3–765.4). After a mean follow-up of 18 months, subjects without nodal positivity had a survival advantage over patients with positive lymph nodes (86.4% vs. 53.3%) and those with ENE (86.4% vs. 23.2%), respectively.

Conclusion The results demonstrated that clinical examination can be used as an adjuvant to radiological imaging for prediction of ENE preoperatively. Clinical finding suggesting size of node ≥ 3 cm and ≥ 2 nodes are strong predictor of ENE, in addition to other known predictors. Patients with ENE had an unfavorable prognosis when compared with subjects with metastatic nodes without ENE. Presence of ENE remains one of the strongest factors predicting recurrence and thus poor prognosis.

Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 350,000 newly diagnosed cases of cancer worldwide annually. It is highly prevalent in developing countries, due to rampant use of tobacco products with buccal mucosa being the most common site.[1,2] In OSCC, neck node involvement plays a significant prognostic role in disease-free survival (DFS) and overall survival (OS) of the patient, and neck node involvement will result in a 50% reduction in OS.[3]

The extranodal extension (ENE) is the spread of cancer cells beyond the capsule of a metastatic lymph node into the surrounding tissues. The importance of ENE has been well documented over the past decade, which led to its inclusion in the current American Joint Committee on Cancer (AJCC) 8th staging system.[4] Three-year OS and DFS drop to 28.9 and 50.4% in patients with OSCC with ENE when compared with 73.4 and 89.3% in patients without ENE, respectively.[5,6]

The criteria for diagnosing node with ENE have been established by AJCC 8th edition, which include clinical, radiological, and pathological determinations.[7] In terms of imaging modalities, contrast-enhanced computed tomography (CECT) remains the gold standard for determining ENE preoperatively.[8] To the best of our knowledge, there are no studies that has evaluated the effectiveness of clinical exam results or intraoperative findings in detecting ENE. Thus, this study was intended to fill the knowledge gap. We have also assessed the various factors predicting ENE and its prognosis, with referral to a specific subsite in oral cavity, that is, buccoalveolar complex (BAC).

Materials and Methods

This was a retrospective cohort study, which included 137 patients diagnosed with BAC OSCC (BAOSCC) who underwent curative surgery in our tertiary care referral hospital between May 2019 and April 2021, after multidisciplinary tumor board discussion. Out of the total 204 diagnosed BAOSCC patients who presented to our institute in the time period, 137 (67%) had a surgically resectable disease at the time of presentation, and were included in the study. Thirty-three patients (16%) had advanced disease who were subsequently referred for palliative care and the rest 34 (17%) patients were unfit for surgery or preferred treatment in outside center. The target sample size was 150 at the beginning of the present study, but since the study was done in the coronavirus disease (COVID) era, we could only achieve a sample size of 137 patients.

The primary objective was to study the effectiveness of clinical examination, intraoperative finding, and CECT to detect ENE in BAOSCC. We also assessed the clinicopathological and radiological factors influencing ENE. Patients who had a second primary, previous neck exploration surgery, recurrent tumors, incomplete charts, and lost to follow-up were excluded from the study. All included patients underwent CECT, in addition to other routine investigations. CECT imaging acquisition was done by a digital online software portal. All patients underwent neck dissection as part of the surgical procedure. All patients with clinical and radiological N0 nodes had an ipsilateral selective neck dissection (SND) of levels 1 to 3 whereas patients with N+ neck or those requiring pectoralis major myocutaneous flap reconstruction had a modified radical neck dissection (MRND). After surgery, radiotherapy or concurrent chemoradiotherapy was offered. As per standard guidelines followed in our institute, candidates with composite pathological stage 1 and 2, with no added risk factors (e.g., close margin, depth < 5 mm, perineural invasion [PNI], lymphovascular emboli (LVE)) were kept under follow-up, while others were offered adjuvant radiotherapy. Patients with ENE/positive surgical margins were offered adjuvant chemoradiotherapy.

Clinical features suggesting ENE includes fixation to adjacent structures, skin infiltration, and nerve paresis.[7] Intraoperative features such as adjacent structure infiltration or fixation either to bone, muscle, or nerve, were considered as features of ENE. CECT features such as size, irregularity of capsule, thick wall of node (enhancing rim of > 1 mm is considered thick rim in lymph nodes) (►Fig. 1), enhancing nodal margin, and adjacent fat or other structure stranding were considered as radiologically positive ENE.[7]

Histopathological ENE was classified as ENEmi (microscopic ENE ≤ 2 mm) or ENEma (major ENE > 2 mm), and both were considered as ENE in the present study as per AJCC 8th edition criteria.[7]

Statistical Analysis

The data was analyzed using IBM SPSS 23.0 version software. The descriptive data for various clinical,

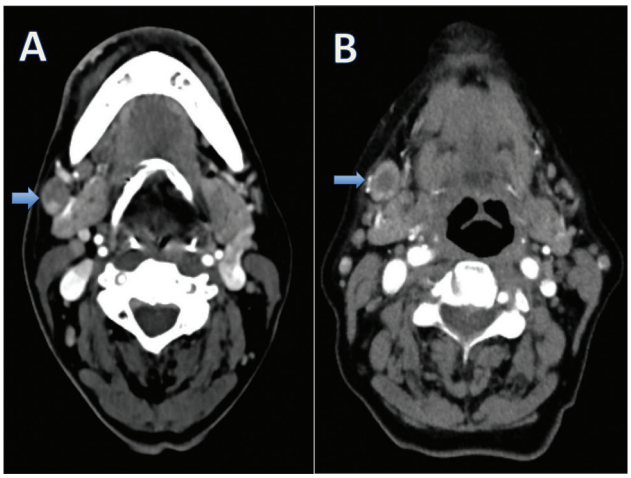

Fig. 1 Contrast-enhanced computed tomography (axial sections) images from two different patients showing necrotic lymph nodes in right level 1b with thick nodular rim enhancement (**A**) and thick rim enhancement (**B**).

radiological, and pathological parameters were expressed as percentages with continuous variables. The univariate and multivariate analysis of various parameters were done using multiple logistic regression analysis and significant correlation was determined using chi-square test between ENE positive and negative categories. A p-value of ≤ 0.05 was considered to be significant in both univariate and multivariate analysis. Analysis of prognosis and survival was done by Kaplan–Meier curve plotting using regression analysis and significance in survival was compared.

Results

The present study involved 137 patients, 108 (78.8%) of whom were males and 29 (21.2%) were females. The mean age of the study population was 51 years. Nineteen (13.9%) of the total cases belonged to early tumor (T1/T2) stage, 118 (86.2%) patients belonged to advanced tumor (T3/T4) category. The overall prevalence of ENE was 18.98% ($n = 26$) and that of lymph node positivity was 40.88% ($n = 56$). Out of total 26 ENE patients, 34.6% (9/26) had ENEmi and 65.4% (17/26) had ENEma. Of the 19 patients with early stage disease, 15.4% (4/19) had ENE positive nodes. A total of 109 (79.6%) patients underwent MRND and 28 (20.4%) patients underwent SND.

The comparison of sensitivity, specificity, and accuracy of various modalities in detecting ENE are shown in ►**Table 1**. Overall, the decreasing order of efficacy of ENE detection by the analyzed modalities is: Sensitivity: Imaging (73.1%) > intraoperative examination (46.2%) > clinical examination (34.6%). Specificity: Intraoperative examination (93.7%) > clinical examination (91.9%) > imaging (78.38%). Negative predictive value (NPV): Imaging (92.6%) > intraoperative examination (88.2%) > clinical examination (88.1%).

The survey of factors predicting ENE is elaborated in ►**Tables 2** and **3**. The demographic factors were comparable among those with and without ENE.

There were occult nodal metastases in 14.8% (12/81 patients) of patients and occult ENE positive nodes in 7.7% (2/26 patients) of patients. Among the 25 patents who had clinical node size ≥3cm, 18 (72%) patients had ENE ($p \leq 0.001$, hazard ratio [HR]: 75.8, confidence interval [CI]: 14.4–398.1). Fifty percent of patients who had ≥ 2 nodes on clinical palpation had ENE ($p \leq 0.001$, HR: 29.5, CI: 5.1–170.8). Fixity of node to underlying structure was associated with ENE in 57% of subjects ($p \leq 0.001$, HR: 7.8, CI: 2.4–25.1).

Clinical nodal size ≥ 3 cm and clinical neck stage were not included in multivariate analysis due to very high association. On multivariate analysis, none of the other clinical factors were significantly associated with ENE as illustrated in ►**Table 4**.

On radiological assessment, 28 (20.4%) patients belonged to the early stage (T1/T2) category and 109 (79.6%) patients belonged to the advanced (T3/T4) category. Radiologically, 67

Table 1 Comparison of efficacy of clinical examination, cross-sectional imaging, and intraoperative finding in detection of ENE and lymph nodes in buccoalveolar complex oral squamous cell carcinoma

		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	Positive likelihood ratio	Negative likelihood ratio
Extranodal extension	Clinical examination	34.62	91.89	50	85.71	81.02	4.27	0.71
	Cross-section imaging (CT)	73.08	78.38	44.19	92.55	77.37	3.38	0.34
	Intraoperative examination	46.15	93.69	63.16	88.14	84.67	7.32	0.57
Metastatic lymph nodes	Clinical examination	78.57	60.49	57.89	80.33	67.88	1.99	0.35
	Cross-section imaging (CT)	87.50	22.22	43.75	72	48.91	1.12	0.56
	Intraoperative examination	94.64	56.79	60.23	93.88	72.26	2.19	0.09

Abbreviations: CT, computed tomography; ENE, extranodal extension.

Table 2 Univariate analysis of demographic and clinical factors influencing extranodal extension in final histopathology specimen in 137 patients with buccoalveolar complex oral squamous cell carcinoma

Serial no.	Parameter	Variable	Number of patients ($N = 137$) (%)	ENE positive ($n = 26$) (%)	ENE negative ($n = 111$) (%)	*p*-Value (chi-square test)
1	Age	< 45 y	46 (33.6)	11 (23.9)	35 (76.1)	0.295
		≥ 45 y	91 (66.4)	15 (16.5)	76 (83.5)	
2	Sex	Male	108 (78.8)	23 (21.3)	85 (78.7)	0.285
		Female	29 (21.2)	3 (10.3)	26 (89.7)	
3	Site	Alveolus	17 (12.4)	4 (23.5)	13 (76.5)	0.680
		Buccoalveolar sulcus	37 (27)	8 (21.6)	29 (78.4)	
		Buccal mucosa	72 (52.6)	11 (15.3)	61 (84.7)	
		Retromolar trigone	11 (8)	3 (27.3)	8 (72.7)	
4	Habit	Yes - Single	76 (55.5)	13 (17.1)	63 (82.9)	0.799
		Yes - Multiple	50 (36.5)	11 (22)	39 (78)	
		No	11 (8)	2 (18.2)	9 (81.8)	
5	Clinical tumour staging	c T1/ cT2	19 (13.9)	4 (21.1)	15 (78.9)	0.912
		cT3/c T4	118 (86.2)	22 (18.6)	96 (81.4)	
6	Clinical skin invasion of primary tumour	Yes	53 (38.7)	13 (24.5)	40 (75.5)	0.188
		No	84 (61.3)	13 (15.5)	71 (84.5)	
7	Clinical neck levels involved	No nodes	61 (44.5)	2 (3.3)	59 (96.7)	< **0.001**
		Isolated IB	63 (46)	16 (25.4)	46 (74.6)	
		IB+ spread	10 (7.3)	5 (50)	5 (50)	
		Other levels	3 (2.2)	2 (66.7)	1 (33.3)	
8	Clinical size of nodes	No nodes	61 (44.5)	2 (3.3)	59 (96.7)	< **0.001**
		< 3	51 (37.2)	6 (11.8)	45 (88.3)	
		≥ 3	25 (18.3)	18 (72)	7 (28)	
9	Clinical neck stage	0	61 (44.6)	2 (3.3)	59 (96.7)	< **0.001**
		1	50 (36.5)	10 (20)	40 (80)	
		2	11 (8)	5 (45.5)	6 (54.6)	
		3	15 (10.9)	9 (60)	6 (40)	
10	Clinical fixity	Yes	14 (10.2)	8 (57.1)	6 (42.9)	< **0.001**
		No	123 (89.8)	18 14.6)	105 (85.4)	
11	Clinical number of nodes	0	61 (44.5)	2 (3.3)	59 (96.7)	< **0.001**
		1	62 (45.3)	17 (27.4)	45 (72.6)	
		2	11 (8)	4 (36.4)	7 (63.7)	
		> 2	3 (2.2)	3 (100)	0 (0)	

Abbreviation: ENE, extranodal extension. *p*-Values which are significant are boldfaced.

(48.9%) had subcentimetric (< 1 cm) but suspicious nodal metastasis, 41 (29.9%) had 1 to 2 cm nodal metastasis, and 4 (2.9%) had ≥ 2 cm node involvement. All patients who had radiological nodal size of > 2 cm had ENE. Among the radiological parameters, thick nodal wall ($p \leq 0.001$, HR: 18.6, CI: 6.6–51.8), enhancing margin ($p \leq 0.001$, HR: 11.3, CI: 4.2–30), adjacent fat stranding ($p \leq 0.001$, HR: 7.1, CI: 2.5–20), and surrounding structure involvement ($p \leq 0.001$, HR: 8.1, CI: 3.1–20.9) were significant predictors of ENE. However, on multivariate analysis none of the factors predicted ENE. Presence of thick nodal walls was 15 times more likely to predict ENE than those without thick walls ($p = 0.180$, HR: 14.8, CI: 0.3–765.4). Intraoperatively, bone adhesion was noted in 13 (9.5%) patients of whom ENE was positive in 8 (61.5%) ($p \leq 0.001$, HR: 9.4, CI: 2.8–32).

ENE positivity was noted in 18/26 (69.2%) patients with depth of invasion (DOI) > 10 mm, which was significant with a *p*-value of 0.045 (HR: 2.5, CI: 1–6.4). ENE was observed in 29.6% of patients with positive lymphovascular invasion and 27.7% of patients with positive PNI. The majority of patients with

Table 3 Distribution of patients in extranodal positive and negative categories and logistic regression analysis on radiological, intraoperative, and postoperative histopathological factors predicting extranodal in buccoalveolar complex oral squamous cell carcinoma

Feature	Parameter	Variable	Number of patients ($N = 137$)	ENE positive ($n = 26$) (%)	ENE negative ($n = 111$) (%)	*p*-Value (chi-square test)
Radiological	Radiological bone involvement of primary tumour	Yes	71 (51.8)	12 (16.9)	59 (83.1)	0.520
		No	66 (48.2)	14 (21.2)	52 (78.8)	
	Neck levels involved	No nodes	94 (68.6)	7 (7.5)	87 (92.6)	< **0.001**
		Isolated IB	35 (25.6)	13 37.1)	22 (62.9)	
		IB+ other neck levels	5 (3.7)	4 (80)	1 (20)	
		Other levels	3 (2)	2 (66.7)	1 (33.3)	
	Size of nodes (cm)	No nodes	25 (18.2)	2 (8)	23 (92)	**0.015**
		< 10	67 (48.9)	7 (10.5)	60 (89.6)	
		10–20	41 (29.9)	13 (31.7)	28 (68.3)	
		> 20	4 (2.9)	4 (100)	0 (0)	
	Irregularity of capsule	Yes	20 (14.6)	10 (50)	10 (50)	< **0.001**
		No	117 (85.4)	16 (13.7)	101 (86.3)	
	Thick wall of node	Yes	30 (21.9)	18 (60)	12 (40)	< **0.001**
		No	107 (78.1)	8 (7.5)	99 (92.5)	
	Enhancing nodal margin	Yes	27 (19.7)	15 (55.6)	12 (44.4)	< **0.001**
		No	110 (80.3)	11 (10)	99 (90)	
	Adjacent fat stranding	Yes	19 (13.9)	10 (52.6)	9 (47.4)	**0.001**
		No	118 (86.1)	16 (13.6)	102 (86.4)	
	Surrounding structure involvement	Yes	28 (20.4)	14 (50)	14 (50)	< **0.001**
		No	109 (79.6)	12 (11)	97 (89)	
	Radiological number of nodes	0	25 (18.3)	2 (8)	23 (92)	0.129
		1	31 (22.6)	6 (19.4)	25 (80.7)	
		2–5	62 (45.3)	11 (17.7)	51 (82.3)	
		> 5	19 (13.9)	7 (36.8)	12 (63.2)	
Intraoperative examination	Intraoperative neck levels involved	No nodes	49 (35.8)	1 (2.1)	48 (97.9)	< **0.001**
		Isolated IB	35 (25.6)	5 (14.4)	30 (85.7)	
		IB+ spread	43 (31.4)	19 (44.2)	24 (55.8)	
		Other levels	10 (7.3)	1 (10)	9 (90)	
	Bone adhesion	Yes	13 (9.5)	8 (61.5)	5 (38.7)	< **0.001**
		No	124 (90.5)	18 (14.5)	106 (85.5)	
Postoperative histopathology	Tumor size	≤ 2 cm	30 (21.9)	5 (16.7)	25 (83.3)	0.730
		> 2 cm and < 4 cm	59 (43.1)	13 (22)	46 (77.9)	
		≥ 4 cm	48 (35)	8 (16.7)	40 (83.3)	
	Depth of invasion	< 5	24 (17.5)	1 (4.2)	23 (95.8)	**0.044**
		5–10	43 (31.4)	7 (16.3)	36 (83.7)	
		> 10	70 (51.1)	18 (25.7)	52 (74.3)	
	Histological grading	Well differentiated	30 (21.9)	3 (10)	27 (90)	0.185

(*Continued*)

Table 3 (*Continued*)

Feature	Parameter	Variable	Number of patients ($N = 137$)	ENE positive ($n = 26$) (%)	ENE negative ($n = 111$) (%)	*p*-Value (chi-square test)
		Moderately differentiated	101 (73.7)	23 (22.8)	78 (77.2)	
		Poorly differentiated	6 (4.4)	0 (0)	6 (100)	
	Lymphovascular invasion	Absent	110 (80.3)	18 (16.4)	92 (83.6)	0.115
		Present	27 (19.7)	8 (29.6)	19 (70.4)	
	Neural invasion	Absent	90 (65.7)	13 (14.5)	77 (85.6)	0.061
		Present	47 (34.3)	13 (27.7)	34 (72.3)	
	Margin	Free	83 (60.6)	13 (15.7)	70 (84.3)	0.130
		Close	50 (36.5)	11 (22)	39 (78)	
		Involved	4 (2.9)	2 (50)	2 (50)	
	Adjacent dysplasia	Yes	9 (6.6)	3 (33.3)	6 (66.8)	0.371
		No	128 (93.4)	23 (18)	105 (82)	
	Bone involvement	Yes	50 (36.5)	15 (30)	35 (70)	**0.015**
		No	87 (63.5)	11 (12.6)	76 (87.4)	
	Skin invasion	Yes	39 (28.5)	13 (33.3)	26 (66.7)	**0.009**
		No	98 (71.5)	13 (13.3)	85 (86.7)	
	WPOI	1–3	51 (37.2)	3 (5.9)	48 (94.1)	**0.006**
		4–5	86 (62.8)	23 (26.7)	63 (73.3)	
	Pathological number of nodes	0	81 (59.1)	0 (0)	81 (100)	**0.028**
		< 3	24 (17.5)	7 (29.2)	17 (70.8)	
		≥ 3	32 (23.4)	19 (59.4)	13 (40.6)	
	Neck levels involved	No nodes	81 (59.1)	0 (0)	81 (100)	$<$ **0.001**
		Isolated IB	22 (16.1)	8 (36.4)	14 (63.6)	
		IB+ spread	31 (22.6)	18 (58.1)	13 (41.9)	
		Other levels	3 (2.2)	0 (0)	3 (100)	
	Tumour deposit in node	0	81 (59.1)	0 (0)	81 (100)	**0.017**
		≤ 1 cm	27 (19.7)	8 (29.6)	19 (70.4)	
		> 1 cm	29 (21.2)	18 (62.1)	11 (37.9)	

Abbreviations: ENE, extranodal extension; WPOI, worst pattern of invasion. *p*-Value which are significant are boldfaced.

pathological bone invasion (58%) ($p = 0.015$) and skin involvement (50%) ($p = 0.009$) had ENE. Eighty-nine percent of ENE positive patients had a worst pattern of invasion (WPOI) grades 4 or 5 ($p = 0.006$, HR: 5.8, CI: 1.6–20.6). On pathological nodal analysis, candidates with ≥ 3 positive nodes (19/32 patients, 59.38%) and a tumor deposit of > 1 cm (18/29, 62%) had significant association with ENE (►Table 4). Thirty percent (8/26) patients had ENE positive nodes in isolated level IB and 69.2% (18/26) had metastatic nodes with ENE in other levels in addition to level IB. No skip metastasis was noted directly to other levels in analysis of ENE positive nodes.

Adjuvant chemoradiotherapy (trimodality treatment) was offered to 28 (20.4%) patients, 90 (65.7%) patients had adjuvant radiotherapy, and 19 (13.9%) patients were kept under follow-up. We had postsurgical complications in 29 (21%) patients of which 9 (31%) patients had partial flap necrosis, 8 (28%) had surgical site infection, 3 (10%) had postoperative hematoma, and the rest (31%) belonged to other minor complications like sialocele, seroma, and chyle leak. No patient in the current study group had delay in adjuvant treatment because of surgical complications.

Analysis of Prognosis

The overall DFS with a mean follow-up of 18 months without metastatic nodes was 86.4%, with positive metastatic nodes it was 53.3%, and with ENE it was 23.1%. The follow-up of patients for the present study ranges from 6 to 30 months with a mean follow-up of 18 months. The overall recurrence rate was 32.85% (45/137 patients). The recurrence rate for patients without nodal metastasis was 13.6% (11/81), with nodal metastasis was 46.7% (14/30), and with ENE was 76.9%

Table 4 Logistic regression multivariate analysis of factors predicting extranodal which for the significant parameters on univariate analysis

Modality	Parameter	Variable	Number of patients ($N = 137$)	*n* (%)	Univariate analysis		Multivariate analysis	
					OR (95% CI)	*p*-Value	aOR (95% CI)	*p*-Value
Clinical	Clinical size of nodes	No nodes	61	44.53	–			
		< 3	51	37.23	3.9 (0.75, 20.4)	0.103		
		≥ 3	25	18.25	75.8 (14.4, 398.1)	< **0.001**		
	Clinical neck stage	0	61	44.53	–			
		1	50	36.5	7.4 (1.5, 35.5)	**0.013**		
		2	11	8.03	24.6 (3.9, 155.2)	**0.001**		
		3	15	10.95	44.3 (7.7, 253.9)	< **0.001**		
	Clinical fixity	Yes	14	10.22	7.8 (2.4, 25.1)	**0.001**	0.7 (0.1, 12.1)	0.815
		No	123	89.78	–			
	Clinical number of nodes	0	61	44.5	–		–	
		1	62	45.3	11.1 (2.4, 50.7)	**0.002**	3.4 (0.3, 45.9)	0.358
		2	11	8	29.5 (5.1, 170.8)	< **0.001**	8.9 (0.3, 233.7)	0.189
		> 2	3	2.2				
Radiological	Size of nodes	No nodes	25	18.2	–		–	
		< 10	67	48.9	1.3 (0.3, 6.9)	0.726	2.1 (0.1, 41.9)	0.635
		10–20	41	29.9	6.9 (0.6, 33.4)	**0.015**	2.8 (0.1, 72.9)	0.529
		> 20	4	2.9				
	Irregularity of capsule	Yes	20	14.6	6.3 (2.3, 17.6)	< **0.001**	2.8 (0.1, 72.1)	0.640
		No	117	85.4	–			
	Thick wall of node	Yes	30	21.9	18.6 (6.6, 51.8)	< **0.001**	14.8 (0.3, 765.4)	0.180
		No	107	78.1	–			
	Enhancing nodal margin	Yes	27	19.7	11.3 (4.2, 30.0)	< **0.001**	0.1 (0.0, 6.0)	0.269
		No	110	80.3	–			
	Adjacent fat stranding	Yes	19	13.9	7.1 (2.5, 20.1)	< **0.001**	1.1 (0.1, 11.1)	0.941
		No	118	86.1	–			
	Surrounding structure involvement	Yes	28	20.4	8.1 (3.1, 20.9)	< **0.001**	0.2 (0.0, 2.9)	0.239
		No	109	79.6	–			
Intraoperative	Bone adhesion	Yes	13	9.5	9.4 (2.8, 32.0)	< **0.001**	12.6 (0.4, 2.9)	0.137
		No	124	90.5	–			
Postoperative	Depth of invasion	< 5	24	17.5	–			
		5–10	43	31.4				
		> 10	70	51.1	2.5 (1.0, 6.4)	**0.044**	0.5 (0.1, 3.3)	0.509
	Bone involvement	Yes	50	36.5	2.9 (1.2, 7.1)	**0.015**	2.8 (0.3, 21.9)	0.339
		No	87	63.5	–			
	Skin invasion	Yes	39	28.5	3.3 (1.3, 7.9)	**0.009**	2.1 (0.2, 19.2)	0.499
		No	98	71.5	–			
	WPOI	1–3	51	37.2	–			
		4–5	86	62.8	5.8 (1.6, 20.6)	**0.006**	3.4 (0.4, 28.1)	0.261
	Pathological number of nodes	0	81	59.1	–			
		≤ 3	24	17.5	–			
		> 3	32	23.4	3.5 (1.1, 10.9)	**0.028**	1.9 (0.2, 16.3)	0.524
	Tumor deposit in node	0	81	59.1	–			
		≤ 1 cm	27	19.7	–			
		> 1 cm	29	21.2	3.9 (1.3, 11.9)	**0.017**	1.3 (0.2, 7.1)	0.734

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; WPOI, worst pattern of invasion. *p*-Value which are significant are boldfaced.

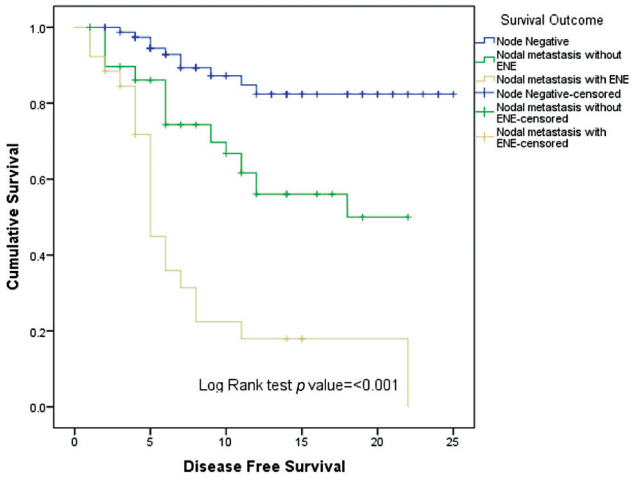

Fig. 2 Kaplan–Meier survival curves for disease-free survival (DFS) in relation to nodal status.

(20/26 patients). Of the patients with ENE who had recurrence, 45% (9/20) had distant metastasis, 35% (7/20) had local recurrence, and 20% (4/20) had regional recurrence in the neck. On Kaplan–Meier analysis (►**Fig. 2**), patients who had nodal metastasis and ENE had statistically significant decreased survival when compared with patients without nodal metastasis with HR of 1.5 (CI: 10.4–16.4) and 1.46 (CI: 5.3–11), respectively. On analysis of pathological ENEmi and ENEma categories, 66.7% (6/9) patients with ENEmi and 82.4% (14/17) patients with ENEma had recurrence, respectively. Pathological nodal stage had strong correlation with recurrence ($r = 0.545$; $p < 0.001$) and margin status had no correlation ($p = 0.687$).

Discussion

The concept of ENE, previously termed extracapsular extension, was put forward first by Willis in 1930.[9] The College of American Pathologists define ENE as presence of metastatic tumour, within the lymph node, extension through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction.[7] Despite the intensification of postoperative adjuvant therapy by including chemotherapy in patients with ENE to potentiate better prognosis, the overall outcome remains bleak.[10,11] Thus, it is important to identify ENE preoperatively in order to plan better treatment including adjuvant therapy and also for prognostication of the patient.

The frequency of lymph node metastasis (LNM) varies from 28 to 52.7% in OSCC[12–14] and that of ENE is around 15.3%.[14] The prevalence of ENE in the present study with respect to BAC subsite was 18.98% and that of metastatic lymph nodes was 41%.

The accuracy of detecting LNM clinically is vital especially in a resource-constrained setting. Although a handful of studies in literature have put forward the detection rates of cervical lymph nodes by palpation, details of precise accuracy of detection of ENE by clinical palpation is sparse. Following are the studies that were done for detecting nodal metastases by palpation. A study done by Anand et al[15] showed that clinical palpation has a sensitivity, specificity, and NPV of 67.4, 90.1, and 62.3%, respectively. Shetty et al[16] noted similar findings with a sensitivity, specificity, and NPV of 36.6, 86.61, and 77.6%, respectively. Prospective study by Jhony et al showed clinical palpation has a sensitivity, specificity, and NPV of 61.9, 69.1, and 82.6%, respectively, to detect significant neck node.[17] In the present study, the sensitivity, specificity, and NPV for detection of lymph nodes by clinical examination are 78.6, 60.5, and 80.3% and for ENE positive nodes are 34.6, 91.9, and 85.7%, respectively. Despite the low sensitivity of detecting ENE when compared to detecting lymph nodes, the specificity, accuracy, and NPV of detecting ENE clinically are higher. We believe that the low sensitivity rate for detection of ENE may also be related to ENEmi, which is difficult to assess clinically, which accounted for about 65% (17/26) of the cases in our study.

Seven out of 14 patients (50%) with ≥ 2 clinically palpable nodes had ENE increasing the probability of detection by nine times. Similarly, clinical size of node $\geq$ 3 cm was associated with 75.8 times risk of harboring ENE. Multivariate analysis could not be used for the latter factor because of its high association.

Multiple studies have evaluated the efficacy of diagnosing ENE preoperatively using CECT. The sensitivity, specificity, and accuracy of CECT imaging in diagnosing ENE in various studies are 65 to 90%, 73 to 91%, and 75 to 86%, respectively.[18–22] Similar finding was noted in our study group, with sensitivity, specificity, and accuracy by CECT for detecting ENE to be 73.1, 73.4, and 77.4%, respectively.

Prospective study by Hao and Ng compared magnetic resonance imaging (MRI) versus clinical palpation in detecting ENE. In their study, done in 2000, MRI did not significantly improve detection of ENE, and 43.5% of the ENEs could be predicted using either method.[23] We found that CECT had higher sensitivity to detect ENE (73.1%) when compared with clinical (34.6%) or intraoperative (46.2%) examination. But clinical and intraoperative examination had high specificity of 91.89 and 93.69%, respectively, when compared to CECT (78.38%). Further using clinical examination in parallel with CECT we could increase the NPV to 94%, also having a high sensitivity of 82.4%.

In a meta-analysis by Su et al comparing the efficacy of different parameters used for diagnosis of ENE, it was found that size of the nodal metastasis with short-axis diameter $>$ 15 mm had the highest sensitivity of 0.93.[5] We noted that, ENE was positive in all patients with radiological nodal size $>$ 2 cm. Other independent factors that could predict ENE include irregularity of capsule, thick wall of node, enhancing nodal margin, adjacent fat stranding, and involvement of surrounding structure. Among them, ENE was 18 times more likely to occur when there is a thick nodal wall.

In a retrospective study of 354 patients with early OSCC, Mair et al[14] noted that the DOI $>$5 mm and metastatic nodal size of $>$ 15 mm were significantly found to be associated with ENE. Our study showed 96% of ENE patients had a DOI $>$ 5 mm, 50% had skin involvement, 58% had bone

invasion, and 89% had a WPOI > 3. The nodal characteristics in histopathology reveal that 73% of patients with ENE have more than 2 nodes and 69% have > 1 cm of tumour deposit in node. Nevertheless, none of these factors were statistically significant on multivariate analysis.

ENE is considered as a poor prognostic factor for which trimodality treatment is considered. According to a study by Rajappa et al 5-year DFS and OS for patients with ENE positive and negative nodes were 63.8 versus 56% and 87.2 versus 70.7%, respectively.[12] Overall as per previous literature, the 3-year DFS averages of around 45 to 57% in candidates with ENE.[14,24] In the present study, the DFS rate for patients without nodal metastasis, with nodal metastasis, and with ENE are 86.4, 53.3, and 23.1% showing significant correlation for poor prognostic outcome in ENE patients with logistic regression analysis ($p < 0.001$). The reason behind the poor prognostic outcome in our patients with ENE might be due to two reasons: We have included specifically BAC subsite which is well known for its poor prognosis and also high number of patients with advanced tumour stage in our cohort (86.4%), could have contributed to the high recurrence rate. High number of patients in advanced stage was partly attributed to inclusion of patient during COVID-19 pandemic.

AJCC 8th edition has included both ENEmi and ENEma qualify for the inclusion criteria for ENE.[7] But the prognostic inference of this classification still remains a debate whether to consider ENEmi same as ENEma in terms of prognosis.[25,26] Wreesmann et al in his study, concluded that tumour at a distance of 1.7 mm beyond the capsule of the node has poor prognostic value.[27] We noted that DFS in patients ENEma (17.6%) was poor than those with ENEmi (33.3%). ENEmi definitely has worse prognosis when compared to metastatic nodes without ENE (53.3%).

The strength of our study is that this was the first study to the best of our knowledge to analyze the efficacy of clinical examination/intraoperative/CECT finding in predicting ENE in OSCC. The study was confined only to BAOSCC, so the predictors are better analyzed. The limitations of the study being the retrospective nature and most of the cases were in advanced stage. Future studies including other subsites in OSCC with a large cohort group in a prospective manner may be considered for further research.

Conclusion

The clinical examination and intraoperative assessment have lower sensitivity than CECT when it comes to detecting ENE but are equally accurate and specific. CECT in conjunction with clinical examination will aid in detecting ENE. In addition to other known parameters, the size of the node ≥ 3 cm and ≥ 2 significant nodes on clinical examination might serve as a predictor to clinically categorizing ENE. Thick nodal wall in CECT is more specific for predicting ENE. DFS of patients with ENE fell nearly to half when compared with no ENE, but nodal metastasis. Patients with ENEma had a 50% poor favorable outcome as compared with patients with ENEmi.

Ethical Approval

The study is approved by the Institutional Review Board of Christian Medical College, Vellore, Tamil Nadu, India (IRB No: 12886).

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None.

Conflict of Interest

None declared.

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