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ORIGINAL ARTICLE

Depth of Invasion, Lymphovascular Invasion, and Perineural Invasion as Predictors of Neck Node Metastasis in Early Oral Cavity Cancers

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Abstract

Aims The present study examines the role of demographic and pathological features of primary tumours in predicting neck metastasis in early oral cavity cancers, which has been a matter of debate.

Methods A single-centre, retrospective, institution review was conducted of all the patients presented to our centre from January 2014 to December 2021. Patient characteristics were compared between the two lymph node groups (lymph node positive and lymph node negative) and significant prognostic factors were determined.

Results A total of 462 oral squamous cell carcinoma (OSCC) patients were included, 407 male and 55 female. Tobacco chewing (59.2%) was a major habit with buccal mucosa (49.5%) and tongue (44.8%) as primary sites. The majority of the patient's histology was of SCC (96.8%) with grade II (moderately differentiated, 74.5%). Univariate logistic regression analysis to predict lymph node metastasis showed pT size (< 0.001), LVI (< 0.001), and PNI (< 0.001) as significant tumor characteristics. On multivariate, pT size (OR-1.58, *P* – 0.0001) and LVI (OR-19.70, *P* – 0.0001) were reported to be statistically significant to predict lymph node metastasis.

Conclusion Reporting and studying the clinico-pathological features of primary tumors can give vital information in predicting the neck node metastasis in OSCC patients.

Keywords Depth of invasion · Lymphovascular invasion · Perineural invasion · Neck node metastasis · Oral cavity cancers

Introduction

Oral cancer of the head and neck is the most common and aggressive form of malignancy with a poor prognosis [1]. The oral squamous cell carcinoma (OSCC) has an especially high propensity for metastasis, so it is often controlled through traditional surgical resection (elective neck dissection - END) or irradiation of the primary tumor, with treatment of the clinically positive neck [2].

The American Joint Committee on Cancer (AJCC)/ International Union Against Cancer (UICC) Tumor-Node-Metastasis (TNM) staging system is the most widely used staging scheme in patients with cancer, defining prognosis, and guiding the most appropriate treatment plans [3]. Recently, AJCC in its 8th edition has proposed to incorporate the depth of invasion (DOI) as a modifier for the T category in the TNM staging [2, 4, 5]. Substantially, histopathologic evidence such as DOI of the primary tumor (thin, ≤ 5 mm,T1; intermediate, > 5 mm and ≤ 10 mm, T2; and thick, > 10 mm, T3/T4) has also identified as a possible predictor of cancer growth beneath the epithelial surface and regional metastasis in OSCC [2, 3]. Apart from DOI, the role of other histological adverse pathological features such as lymphovascular invasion (LVI), perineural invasion (PNI), tumour thickness (TT), and poor differentiation were also incorporated for initial risk group stratification, treatment decision, and to

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predict the need for END based on the tumour behaviour and the risk of recurrence/ occult lymph node metastasis (LNM) [6–10]. Studies have also established these pathological features as poor prognostic factors in many human malignancies [10–12].

LNM tumors occur in about 40% of patients with oral cancer [13]. Among all oral cancers, OSCC and oral tongue have high potential for local invasion and cervical lymph node metastasis. At the time of initial diagnosis, identifying the presence of such node metastasis can play a crucial in patient's treatment planning, prognosis, and survival [14]. LNM is also a well-known and clinically important prognostic factor in head neck cancer patients [15–17].

This retrospective study was aimed to investigate the role of various demographical (age) and pathological features (Grade, LVI, PNI, DOI) of primary tumours of the patients in predicting the neck metastasis in early oral cavity cancers.

Methods

A single-centre, retrospective, institution review was conducted of all the patients presented to our centre from January 2014 to December 2021.

Study Population

Inclusion criteria:

A) Clinically early stage oral cavity cancer.
B) Pathological T (pT) size ≤ 4 cm with SCC histology.
C) With complete histopathological information available.

Exclusion criteria:

A) Presence of a synchronous head and neck SCC.
B) History of head and neck cancer/ or previous resection of an oral cancer.
C) Previous treatment with chemotherapy and/or radiation specifically for head and neck cancer.
D) Distant metastasis at presentation.
E) Histology's other than SCC.
F) Missing histopathological data.

Statistical Analysis

A total of 478 patients were included in this retrospective study. Sixteen of 478 patients were excluded for not meeting the study criterion. All demographic and clinical characteristics were recorded from the case record forms of patients maintained in an electronic database. Data of DOI, tumor characteristics, clinical N-classification, LVI, and PNI were reviewed [7, 8, 10, 18].

Patient characteristics were compared between the two LN groups (lymph node positive and lymph node negative) using Chi-square test for categorical data. A Receiver-Operator-Curve (ROC) analysis was performed to determine the optimal cut-off values of DOI with LN metastases. Univariate logistic regression analysis was used to assess relations between predictor variables (i.e. demographic and all histopathological factors) and lymph node status. A multiple logistic regression model was constructed using forward selection. For all tests, a p-value of <0.05 was considered statistically significant. All statistical data analyses were performed using SPSS (IBM SPSS Statistics version 22.0, IBM Corp., USA).

Results

Over a period of 8 years (January 2014- December 2021), a total of 462 OSCC patients have met all our study criteria and were analysed retrospectively. All demographic and clinical characteristics are summarized in Table 1. Of patients, a distinct male (88.1%) predominance was observed with average age at presentation being 46.5 years (IQR: 21–89 years). Almost 62% of patients were of age < 50 years with no co-morbidities (83.1%) on presentation. Tobacco chewing (59.2%) was a major habit with buccal mucosa (49.5%) and tongue (44.8%) as primary sites. Majority of the patient's histology was of SCC (96.8%) with grade II (moderately differentiated, 74.5%). In 462 patients, 410 patients have undergone surgery/treatment at our centre and the remaining 52 patients were referred to our centre from outside after their surgery for adjuvant treatment (either adjuvant RT or adjuvant CTRT).

More than half of the patient's pathological characteristics such as LVI (21%), PNI (29.7%), LN (33.1%), and margin status (1.9%) were reported to be positive.

A total 153 of 462 patients were LN positive. Most of them were under the age of ≤ 50 years (70%) with grade I/II tumors (86%), size ranging from 2 to 4 cm (72%). On univariate analysis (Table 2), the most significant tumor influencing characteristics between LN negative and LN positive patients were reported to be pT size (< 0.001), LVI (< 0.001), PNI (< 0.001) followed by DOI (0.002), age (0.018), and tumor grade (0.036), respectively. DOI (> 0.5 cm, 78%) was observed to be the most significant factor compared to other pathological parameters and patients with DOI ≤ 0.5 cm (22%). On multivariate analysis of LN positive patients (Table 3), pT size (OR-1.58, P – 0.0001) and LVI (OR-19.70, *P*–0.0001) were reported to be the most statistically significant factors. A proportional increase in LN positivity was reported with increase in

Table 1 Baseline patients and tumour characteristics of the study cohort (n = 462)

Patients characteristics		Number (%)
Age	Median (Range)	46.5 (21–89)
Gender	Male	407 (88.1%)
	Female	55 (11.9%)
Age group	< 30	15 (3.2%)
	31–40	110 (23.8%)
	41–50	160 (34.6%)
	51–60	111 (24%)
	61–70	53 (11.5%)
	> 70	13 (2.8%)
Comorbidities	Hypertension	31 (6.7%)
	DM	31 (6.7%)
	IHD	4 (0.1%)
	Others	12 (2.6%)
	No	384 (83.1%)
Habits	Alcohol + tobacco	42 (9.2%)
	Tobacco	273 (59.2%)
	Bidi/Cigarette smoking	13 (2.8%)
	Others	16 (3.6%)
	No	116 (25.2%)
Primary sites	Lip	9 (1.9%)
	Hard palate	4 (0.9%)
	Alveolus	10 (2.1%)
	Buccal mucosa	228 (49.1%)
	Tongue	207 (44.8%)
	Floor of mouth	3 (4.9%)
Laterality	Right	212 (46%)
	Left	240 (52%)
	Midline	10 (2%)
Tumour characteristics		
Histology	SCC	447 (96.8%)
	Verrucous carcinoma	10 (2.2%)
	Sarcomaoid SCC	5 (1.0%)
Grade	Grade I (WD)	76 (16.5%)
	Grade II (MD)	344 (74.5%)
	Grade III (WD)	42 (9%)
Lympho-vascular invasion	Positive	97 (21%)
	Negative	365 (79%)
Perineural invasion	Positive	137(29.7%)
	Negative	325 (70.3%)
Margin status	Positive	9 (1.9%)
	Close margin	111 (24%)
	Negative	342 (74.1%)
LN status	Positive	153 (33.1%)
	Negative	309 (66.9%)
DOI	< 0.4	109 (23.6%)
	> 0.4	353 (76.4%)

DM Diabetes mellitus, *IHD* Ischemic heart disease, *SCC* Squamous cell carcinoma, *WD* Well differentiated, *MD* Moderately differentiated, *PD* Poorly Differentiated, *LN* Lymph Node, *DOI* Depth of Invasion

DOI (Fig. 1) in LN positive patients. From ROC, the area under ROC (AUROC) was observed to be 0.78 (close to 1, Fig. 1) confirming its accuracy.

Discussion

OSCC was reclassified in AJCC 8th edition by including DOI in the pT staging and clinical management guidelines [9].

The trend of increase in incidence of OSCC has increased many folds over the decades, especially in young males (< 50 years) [19, 20]. Such male preponderance of OSCC over females was quite evident from our study and same pattern was reported earlier in multiple studies [6, 9, 21, 22]. This trend might be due to the high oral habits of Southern Asian and East Asian population compared to West [1, 23]. The primary site was in line with the habits possessed by the patients, where the buccal mucosa and tongue are the most effected [6, 7, 18, 22]. As reported in studies [6, 7, 18, 22, 24], most of the patients with OSCC were also reported to have moderately differentiated tumor characteristics (grade II), strongly predicting the locoregional recurrence and occult metastasis [25, 26].

Node metastasis is another important prognostic factor, influenced by many other factors other than DOI such as LVI, PNI, and LN status. The AJCC 8th edition recommendation was to keep the DOI cut-off for decision making on ENDs at ≥ 4 mm, but the studies published later have showed some large variances in cut-off values. For instance, Tam et al. showed 7.25 mm, Faisal et al. showed 10 mm, Yassine et al. and Lanschot et al. confirmed at 4 mm, Brockhoff et al. calculated the cut-off values based on the sub-sites (i.e., tongue = 2 mm, floor of mouth = 2–3 mm, retromolar trigone/alveolus/hard palate = 3–4 mm, and all sites = 2–4 mm), and Kozak et al. did not specified any DOI cut-off value itself [5–7, 27–29]. Therefore, the cut-off values based on the sub site should be validated in future studies, based on the tumor and its distance from the lymphatic vessels. Such cut-off values will be playing a vital role in metastasis management and prognosis of the patient. Based on the popular reports published after AJCC 8th edition recommendation, we have considered a DOI cut-off of ≥ 4 mm for all ENDs in our patients.

Other than DOI, other tumor and pathological characteristics like pT size, differentiation grade, margin status, LVI, and PNI were also observed to have significant role in LNM. In the present study among all the pathological characteristics, the pT size ($p < 0.001$), differentiation grade ($p < 0.036$), LVI ($p < 0.001$), and PNI ($p < 0.001$) were observed to be the most significant factors compared to others in LNM. Findings from a meta-analysis by Shuojin et al. have also reported the importance of LVI as a prognostic predictor for metastasis and prognosis in patients with OSCC [30]. Mascitti et al. have also conducted a review on clinical and prognostic role of LVI in OSCC and confirmed it as a useful marker to better define the therapeutic strategies in OSCC patients [31]. Wei et al. published the importance of

Table 2 Univariate analysis of tumor characteristics in lymph node negative and lymph node positive patients

Tumour characteristics		Lymph node Negative		Lymph node Positive		*P*-value
		Number (n = 309)	(%)	Number (n = 153)	(%)	
Age (years)	≤ 50	179	58%	106	70%	0.018
	> 50	130	42%	47	30%	
History of addiction	Yes	222	72%	122	80%	0.067
	No	87	28%	31	20%	
pT Size	0–2 cm	169	54%	43	28%	< 0.001
	2–4 cm	140	46%	110	72%	
Subsite*	L/B/A	171	56%	80	53%	0.535
	Tongue / FOM	138	44%	73	47%	
Grades	Grade I / II	287	92%	133	86%	0.036
	Grade III	22	8%	20	14%	
LVI	Positive	15	5%	82	53%	< 0.001
	Negative	294	95%	71	47%	
PNI	Positive	67	21%	70	45%	< 0.001
	Negative	242	79%	83	55%	
DOI (cm)	≤ 0.5	113	36%	34	22%	0.002
	> 0.5	196	64%	119	78%	

pT Tumor size, *DOI* Depth of invasion, *LVI* Lympho vascular invasion, *PNI* Perineural invasion, *LBA* Lip/BM/ Alveolus

*Data is dichotomised in Tongue versus Lip/BM/Alveolus

Data is dichotomised in Positive versus Close and Negative margin

$ Data is dichotomised in Grade III versus Grade I/II

Table 3 Multivariate analysis of prognostic factors in lymph node positive patients

Prognostic factors		Lymph node Positive			
		Odds ratio (OR)	95% CI		*p* - value
Age (years)	< 50 (Ref)	1.58	0.95	2.62	0.076
	> 50				
pT (cm)	2–4 (Ref)	2.75	1.59	4.75	< 0.0001
	≤ 2				
Grade	Grade III (Ref)	1.38	0.60	3.14	0.44
	Grade I / II				
DOI (cm)	> 0.5	0.98	0.54	1.78	0.95
	≤ 0.5				
LVI	Present	19.70	10.31	37.63	< 0.0001
	Absent				
PNI	Present	1.23	0.70	2.16	0.46
	Absent				

pT Tumor size, *DOI* Depth of Invasion, *LVE* Lympho vascular invasion, *PNI* Perineural Invasion

investigated features such as margin status, PNI, LVI, and DOI in patients with a pN0 status. The incidence of PNI in wide variety of head-and-neck malignancies ranges from 2.5 to 5.0% [32]. In our study, the incidence of PNI (29.7%) was high compared to existing literature. However, in some exceptional studies the percentage of PNI was observed to be as high as 45.27% [33].

On univariate and multivariate analysis, the strongest prognostic predictor in both the LN negative and LN positive patients leading to their poor prognosis and survival was reported to be pT size and LVI. On multivariate analysis of their retrospective data, Larson et al.[34] have also reported a strong prediction of recurrence and poor survival in the patients with two or more prognostic factors in the tumor such as the DOI > 4 mm and LVI. With increase in DOI, the proportionality for LN positivity and metastasis was also observed to be increasing and it was proven by literature [6, 7, 24, 29].

Altogether, timing chosen to evaluate the pathological features were proven to be of greater value. Earlier, all the evaluations were usually done post-surgical leading to re-exploration in exceptional cases based on the final report. To avoid such circumstances, in identifying such occult LNM. At present, performing of pre-operative MRI or intra-operative assessments or sentinel lymph node biopsies (SLNB) were highly encouraged.[29, 35] The intra-operative assessment of resection margins (i.e. frozen section analysis) is also now recommended as a standard of care by the AJCC 8th edition. Brockhoff et al. have also reported the success of such intra-operative

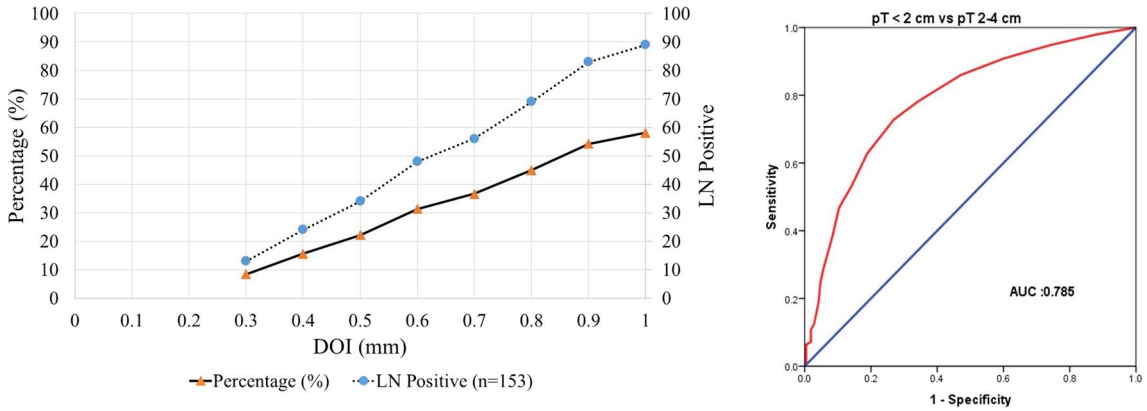

Fig. 1 Significance of depth of invasion on lymph node positivity (on left). Receiver operator characteristic curve (ROC) for differentiating depth of Invasion among the defined groups of oral squamous cell carcinoma based on pT < 2 cm and pT 2–4 cm (on right)

assessments and Tim et al. also proven the high sensitivity (95%) of SLNB supporting its role in the diagnostic work-up of OSCC [29, 35]. Like studies conducted by Barroso et al. and Santos et al., recently Lanschot et al. are also investigating the use Raman spectroscopic method pre-operatively to discriminate the OSCC from surrounding healthy tissues.[7, 36,37] The strength of the present study includes its large number of patient population and robust data for analysis. However, the major limitation of this study is its retrospective study design.

Conclusion

Overall results from our study confirms that these clinical and pathological features of primary tumours can give a vital information in predicting the neck node metastasis in OSCC patients.

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Data Availability The data analysed during the current study are not publicly available. They are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent for Publication All the authors have given their consent for publication.

Ethics Approval The manuscript has got an ethical review exemption from the Ethical review committee of our hospital as retrospective studies are exempted from review according to our ERC's policy.

Informed Consent Written informed consent was obtained from all the participants.

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