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ORIGINAL ARTICLE

Worst Pattern of Invasion as a Predictor of Nodal Metastasis in Early-Stage Oral Squamous Cell Carcinoma

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Abstract

About one-third of early stage oral cancer patients have occult nodal metastasis. High grade worst pattern of invasion (WPOI) is associated with an increased risk of nodal metastasis and poor prognosis. However, it still remains unanswered whether to perform an elective neck dissection for clinically node-negative disease or not. This study aims to evaluate the role of histological parameters including WPOI in predicting nodal metastasis in early-stage oral cancers. This analytical observational study comprised 100 patients of early-stage, node-negative, oral squamous cell carcinoma, admitted in the Surgical Oncology Department from April, 2018 till the sample size was reached. The socio-demographic data, clinical history, and findings of clinical and radiological examination were noted. The association of nodal metastasis with various histological parameters like tumour size, degree of differentiation, depth of invasion (DOI), WPOI, perineural invasion (PNI), lymphovascular invasion (LVI) and lymphocytic response was determined. SPSS 20.0 statistical tool; student's '*t*' test and chi-square tests were applied. While the buccal mucosa was the commonest site, the rate of occult metastasis was highest in the tongue. Nodal metastasis was not significantly associated with age, sex, smoking and primary site. While the nodal positivity was not significantly associated with tumour size, pathological stage, DOI, PNI and lymphocytic response, it was associated with LVI, degree of differentiation and WPOI. Increasing WPOI grade correlated significantly with the nodal stage, LVI and PNI, but not with DOI. WPOI is not only a significant predictor of occult nodal metastasis but can also be a novel therapeutic tool in the management of early-stage oral cancers. In patients with an aggressive WPOI pattern or other high-risk histological parameters, the neck can be addressed with either elective neck dissection or radiotherapy after wide excision of the primary tumor; otherwise, an active surveillance approach can be followed.

Keywords Oral squamous cell carcinoma · Worst pattern of invasion · Nodal metastasis · Prognosis · Histopathological parameters

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Introduction

As per the Global Burden of Disease Study, head and neck cancers represent 5.3% of all cancers, out of which the most common is oral cavity cancer [1]. Cancer of the oral cavity accounts for 2–6% of all cancers and 30% of head-and-neck cancers [2, 3]. Oral cavity cancer is not only the most common overall cancer in Indian males, but also has the highest mortality [4]. Despite several diagnostic and therapeutic advances over the last decades, the rate of mortality and 5-year survival of patients with OSCC has not improved markedly. In developing countries, OSCC is more common and has a higher mortality rate [5–7]. The 5-year survival rate of OSCC patients is relatively low, and especially the patients with recurrence have poor outcomes.

The therapeutic decision-making is based on tumour, node and metastasis (TNM) staging, which is supplemented by various clinicopathological prognostic and predictive factors. Prognosis in oral cancer depends on multiple factors, among which tumour characteristics, nodal involvement and the presence of distant metastasis, affect the survival rates significantly. The presence of lymph nodal metastasis is also considered one of the most important prognostic factors as it not only is a cause of increased locoregional recurrence rates but also poor survival rates. Though the oral cavity is easily accessible for visual examination, about 60% of patients present only at an advanced stage [8]. Most of these patients have nodal metastases at the time of presentation. The reported occult nodal metastasis rate is about 26% in all stages of buccal cancer [9]. Clinical and radiological examinations reveal a sensitivity of 60% to 70% for detecting nodal metastasis [10].

Various clinical and histological parameters are associated with a higher incidence of nodal metastasis in oral cavity cancer. Lymphovascular emboli (LVE) and perineural invasion (PNI) are well-established histological risk factors for nodal metastasis [11]. However, LVE and PNI are difficult to evaluate, especially in small biopsies. Other histological parameters that have been evaluated previously include the degree of tumour histological differentiation, host lymphocyte response (HLR), stromal response and invasive tumour front [12].

The invasive tumour front is the interface between the lowest portion of the tumour and the stroma and is defined as the deepest three to six cell layers or detached tumour cell groups at the advancing edge of the tumour. Cancer cells located in the invasive tumour front have been suggested to be more aggressive in terms of metastatic potential and influence prognosis [13]. The worst pattern of invasion (WPOI) refers to how a tumour infiltrates host tissue at the tumour/host interface. The widely dispersed manner of infiltration has been found to be more aggressive than the broad pushing manner of cancer infiltration. The pattern of tumour infiltration at the invasive front has been evaluated in a few previous studies [12, 14]. An invasive pattern of infiltration is associated with a higher risk of LN metastasis and poor disease-free survival [12]. Though the WPOI is a well-established prognostic factor and is mentioned as the required criterion for reporting oral cavity malignancies according to the College of American Pathologists guidelines, it is still not always reported in the pathology reports. This is because of the scarcity of literature available on the invasive tumour front. Histological prognostic factors have been rarely evaluated in Indian patients [11, 15, 16]. The draft proposal for General Rules for Clinical and Pathological Studies on Oral Cancer of the Japan Society for Oral Tumours recommends that the mode of invasion should be recorded as one of the valuable pathologic findings [17].

Bryne et al. have developed a multiparameter histopathological grading system based on the worst pattern of invasion (WPOI), degree of keratinisation, nuclear pleomorphism, and host response for the prognosis of oral cancer [18, 19]. The WPOI was proposed by Brandwein et al. in 2005 [20]. The new version of the AJCC staging system indicates that the WPOI-5 assessed at the advancing tumour edge is an important prognosticator in oral cancer [21]. Despite significant advancement in the multimodality management of oral cavity cancer, locoregional recurrence occurs, and more than half of the patients fail to respond to therapy, so there is a need for a more aggressive and more individualised approach. Histopathological data like WPOI grading is a useful adjunct to predict which low-stage patients are at significant risk for locoregional recurrence, and thus, further adjuvant therapies can be directed for such patients, thus individualising their management.

Also, the controversy still prevails about whether to perform an elective neck dissection for clinically node-negative disease or not. Despite vast technological advances, particularly in the field of imaging such as computed tomography (CT), positron-emission tomography (PET) and magnetic resonance imaging (MRI) scanning, the rate of clinically occult disease in the neck is quite high. This study was conducted to evaluate the role of histological parameters including WPOI to determine the risk of LN metastasis in cases of clinically node-negative OSCC in early-stage (T1/2, N0, M0) OSCC in north Indian patients. Thus, based on this novel approach, it will help to select a subgroup of early-stage high-risk patients who will benefit from adjuvant radiotherapy, who otherwise would be devoid of the traditional indications for any adjuvant therapy. Also, we will study and compare the predictive power of non-aggressive (WPOI

1–3) and aggressive WPOI (WPOI 4, 5) for occult cervical nodal metastasis, which will further help in the better prognostification of the disease.

Methods

This analytical observational study was carried out in the department of Surgical Oncology, Sawai Man Singh Medical College and Hospital, Jaipur, from April 1, 2018, till the sample size was reached. The study included 100 patients of histologically proven early oral cavity squamous cell carcinoma undergoing curative intent surgical excision. Only clinically and radiologically neck node–negative patients were included in the study. All previously operated patients with recurrence, clinically and radiologically neck node-positive patients, patients with verrucous carcinoma and the spindle cell variant of squamous cell carcinoma, patients with prior h/o chemotherapy and/or radiotherapy and patients who did not give informed and written consent were excluded from the study. The patients with verrucous carcinoma and the spindle cell variant of squamous cell carcinoma were excluded from the study because of the very low metastatic potential of these tumours to the regional nodes. Assuming a 73.9% prevalence of node positives among diffuse infiltrative fronts (WPOI), the sample size was calculated at a 95% confidence interval and 80% study power. Seventy-seven patients were required as a sample size, which was further enhanced and rounded off to 100 patients. Subsites of the oral cavity cancer included buccal mucosa, gingivobuccal sulcus, retromolar trigone, palate, alveolus, lips, tongue and floor of mouth carcinoma. Approval was obtained from the institutional ethics committee.

After obtaining written informed consent from patients with suspected oral cavity cancer, the specifics of their case were noted, and a detailed history including symptoms, co-existing comorbid conditions, personal habits such as smoking or alcohol consumption and the presence of risk factors, if any, was taken. The various socio-demographic characteristics were also noted. All patients were subjected to a thorough clinical examination, followed by contrast-enhanced computed tomography (CECT) of the face and neck. After the routine investigations, a punch biopsy of the lesion was taken and sent for histopathological examination. Only after histological confirmation of the malignancy were patients further included in the study. Also, only patients with clinical and radiological node negative necks were further included in the study. On imaging, the neck nodes were considered positive if the size was > 10 mm on the short axis. Clinical staging was done as per the 8th American Joint Committee on Cancer (AJCC) TNM staging system.

Following a thorough pre-anaesthetic examination, all patients underwent fibreoptic nasotracheal intubation and were given general anaesthesia. For all the patients, transoral wide excision of the lesion along with ipsilateral selective neck dissection was done. After the procedure, the resected specimen was sent for histopathological examination. All the slides were retrieved from the archive and reviewed by investigators who were blinded to the clinical data. All specimens were analysed by two pathologists, and their pathological parameters were checked. The size of the tumour was noted from the surgical pathology report, and the pT stage was determined accordingly. The histological parameters evaluated in each patient consisted of the degree of differentiation, depth of invasion, a worst pattern of invasion (WPOI), perineural invasion (PNI), lymphovascular invasion (LVI) and host lymphocytic response (HLR). The tumours were graded histologically into well, moderately and poorly differentiated according to their degree of differentiation. Perineural invasion was determined as a nerve being surrounded or infiltrated by the tumour. Tumour invasion within arterial, venous or lymphatic channels is qualified for LVI. Host lymphocyte response was evaluated at the invasive tumour front. The host lymphocyte response was graded as strong, intermediate or weak. The depth of invasion was measured from the basement membrane of the adjacent normal mucosa to the deepest level of invasion of the tumour. The depth was measured in millimetres using a slide calliper, and it was graded as D1 (≤ 5 mm), D2 (> 5 mm, ≤ 10 mm) and D3 (> 10 mm) as per of the 8th AJCC TNM staging system. The invasive tumour front was evaluated for WPOI. The WPOI was determined and classified into 5 patterns that depict the infiltrative manner of cancer at the tumour–host interface (Table 1). If there are multiple patterns of invasion, the score was determined by the highest pattern present. Among these 5 patterns, WPOI 4 and 5 were classified as invasive patterns, whereas WPOI 1 to 3 were cohesive patterns [22, 23].

A note of any mortality that occurred during the hospital stay was made. Statistical analysis was done using SPPS 20.0 statistical software. The student's *t* test and the chi-square test were applied to determine the association.

Table 1 Types of worst pattern of invasion at the tumour-host interface

WPOI 1	Pushing border
WPOI 2	Finger-like growth
WPOI 3	Large tumour islands (> 15 cancer cells)
WPOI 4	Small tumour islands (≤ 15 cancer cells)
WPOI 5	Tumour satellites which lie 1 mm or more away from the main tumour mass or the nearest satellite (under 20 × magnification)

Results

A total of 100 patients of histologically proven early oral cavity squamous cell carcinoma undergoing curative intent surgical excision were included in this prospective study. The mean age of presentation was 47.6 ± 17.31 years, with the range being 25–75 years. The difference between the mean age of node-positive and node-negative cases was statistically insignificant (p-value = 0.081). Out of 100 patients, 75 were males of which 22 were node-positive and 25 females out of which 13 were positive for nodal metastasis. Both age and sex were not associated with the risk of occult cervical nodal metastasis (p-value = 0.069). This showed the similarity and comparability of subjects in both groups. As shown in the Fig. 1, buccal mucosa was the most common site (n = 38), which was followed by the tongue (n = 27) and gingivobuccal sulcus (n = 19). It was interesting to note that 48% of the tongue cases had occult LN metastasis while only 25% of buccal mucosa cases had occult lymph nodal metastasis. However, on applying the chi-square statistical test, no significant association was found between the site of the primary and the nodal metastasis (p value = 0.389).

Table 2 shows the association of different clinical and histological parameters with lymph nodal metastasis. Out of the total 100 patients, 39.7% of the smokers and 28.6% of non-smokers were found to have occult nodal metastasis. The association between the history of smoking and the presence of nodal metastasis was found to be insignificant (p-value = 0.350). The mean tumour size was 2.38 cm. While 66 patients had a tumour size of between 2 and 4 cm, only 34 patients had a tumour size of less than 2 cm. There was a trend towards increased nodal positivity for metastasis in the 2–4-cm tumour size group, but the association was not significant (p value = 0.859). Similarly, though the node positivity rate was higher in the pathological stage II group, a significant association between the pathological stage of the disease and the presence of nodal metastasis was not found. A significant association was found between the grade of differentiation and the nodal positivity rate. The majority of the study population had well-differentiated malignancies (72%), followed by moderately differentiated carcinomas (25%), and only 3% had poorly differentiated histopathology. The well-differentiated histology also included two patients with verrucous SCC, as these are also a variety of highly differentiated squamous cell carcinoma. Only one histology revealed a spindle cell tumour which was included in the poorly differentiated category as these are aggressive tumours with a predilection for higher rates of recurrence and metastasis. The presence of nodal metastasis was not significantly associated with either the depth of invasion or the presence of perineural invasion. The mean DOI was 6.83 mm. Only 29 patients out of a total of 79 patients who had DOI between 5 and 10 mm were found to be positive for lymph nodal metastasis (36.7%). In the majority of the study population, there was no perineural invasion. Though there was a trend towards increased nodal positivity in patients with perineural invasion, the association was statistically insignificant (p-value = 0.086). In the majority of the study population, there was a strong lymphocytic response (52%). However, there was no association found between lymphocytic response and occult lymph node positivity (p-value = 0.069). In the majority of the study population, there was no lymphovascular invasion (n = 81). There was a significant association found between lymphovascular invasion and occult lymph node positivity (p value = 0.04).

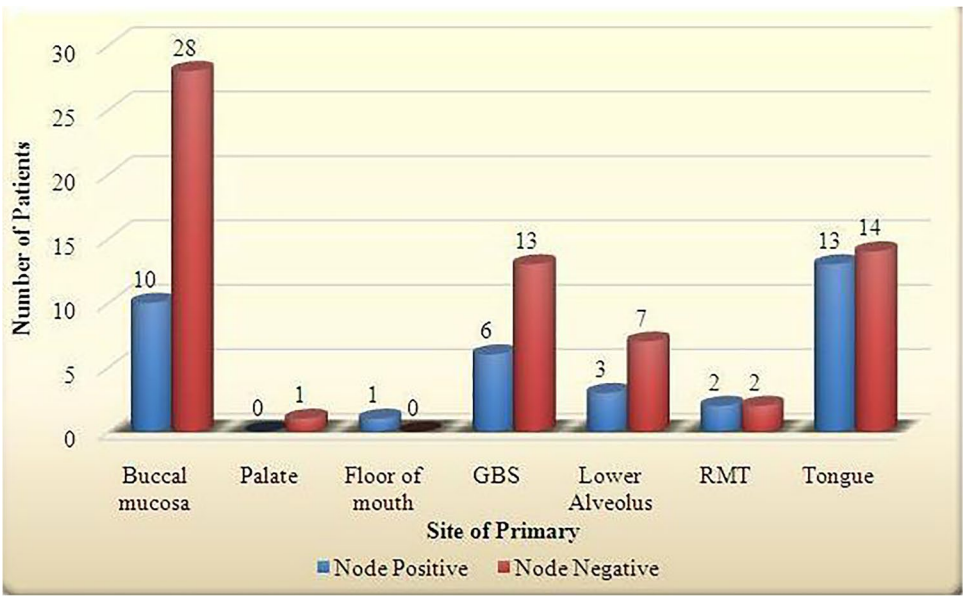

Fig. 1 Distribution of patients according to the site of primary

Table 2 Association of different clinico-histological parameters with lymph nodal metastasis

	Node negative ($n=65$), n (%)	Node positive ($n=35$), n (%)	p value
Mean age(years)	51.6 ± 19.9	44.01 ± 16.3	0.081
Sex			
Male	53 (81.5%)	22 (62.9%)	0.069
Female	12 (18.5%)	13 (37.1%)	
Smoking			
Present	35 (53.9%)	23 (65.7%)	0.350
Absent	30 (46.1%)	12 (34.3%)	
Tumour size			
≤ 2 cm	23 (35.4%)	11 (31.4%)	0.859
2–4 cm	42 (64.6%)	24 (68.6%)	
Pathological T stage			
Stage I	14 (21.9%)	5 (13.9%)	0.544
Stage II	50 (78.1%)	31 (86.1%)	
Differentiation			
Well differentiated	52 (80%)	20 (57.1%)	0.039
Moderately differentiated	11 (16.9%)	14 (40%)	
Poorly differentiated	2 (3.1%)	1 (2.9%)	
POI score			
Non aggressive (WPOI 1–3)	34 (52.3%)	9 (25.7%)	0.019
Aggressive (WPOI 4–5)	31 (47.7%)	26 (74.3%)	
Depth of invasion			
≤ 5 mm	15 (23.1%)	6 (17.1%)	0.662
5–10 mm	50 (76.9%)	29 (82.9%)	
Lymphovascular invasion			
Present	8 (12.3%)	11 (31.4%)	0.040
Absent	57 (87.7%)	24 (68.6%)	
Perineural invasion			
Present	7 (10.8%)	8 (22.9%)	0.086
Absent	58 (89.2%)	27 (77.1%)	
Lymphocytic response			
Weak	21 (32.3%)	4 (11.4%)	0.069
Moderate	14 (21.5%)	9 (25.7%)	
Strong	30 (46.2%)	22 (62.9%)	

Most of the cases had WPOI 5 ($n=32$), followed by WPOI 4 ($n=25$) and WPOI 1 ($n=25$), as shown in Fig. 2. In all WPOI groups, node-negative cases were more than node-positive cases except in WPOI 5 in which node-positive cases ($n=17$, 53.1%) were more than node-negative cases ($n=15$, 46.9%). On statistical evaluation, a significant association was found between WPOI and node positivity (p-value = 0.01). A total of 43 patients belonged to the non-aggressive WPOI group (WPOI 1–3), while 57 belonged to the aggressive WPOI group (WPOI 4–5). Node positivity rate in the non-aggressive and aggressive WPOI group was 20.9% and 45.6% respectively. The correlation between the aggressive WPOI group and the presence of occult node positivity was found to be significant, p-value = 0.019 (Table 2).

Table 3 shows the association of WPOI grade with various histological parameters. Thirty-nine patients were found to have node positivity on final histopathological examination, out of which 24 patients had N1 as the pathological stage (61.5%). Out of the 39 neck node-positive patients, 29 belonged to the aggressive WPOI group. A total of 29 patients out of 57 patients belonging to the aggressive WPOI group (50.9%) were found to be positive for nodal metastasis. A significant association was found (p value = 0.031), and hence, it was concluded that WPOI is not only related to node positivity but also related to N staging. Also, a significant correlation was found between the WPOI grade and the presence of lymphovascular invasion (p value = 0.029). Similarly, a significant association was found between the grade of WPOI and the presence of perineural invasion (p-value = 0.043). Of patients with LVI and PNI, respectively, 63.2% and 73.3% belonged to the aggressive WPOI group. However, no significant association was found between the WPOI grading and the depth of invasion.

Discussion

The lymph nodal metastasis is considered an independent poor prognostic factor for oral SCC. Histological examination of the excised cervical LNs is the gold standard to detect the presence of LN metastasis [24]. Clinically, the determination of nodal metastasis is done by both clinical examination and imaging modalities such as computed tomography scans, but the sensitivity is variable. However, in clinically and radiographically negative lymph nodes (cN0), almost one-third of the patients were reported by Thiagarajan et al. to have occult nodal metastasis on histopathological examination of dissected nodes [25]. Previous studies have evaluated various histological parameters that can predict cervical LN metastasis in OSCC. Recently, the invasive tumour front has become an area of interest in understanding the biology and clinical presentation of oral SCC. Invasive POI is a good predictor of the risk of occult LN metastasis [26]. As the WPOI grading increases, so does the risk of cervical nodal metastasis. In a large cohort of cT1-2 N0M0 patients with no clinical and radiological evidence of metastatic neck nodes, it was found that the presence of WPOI is significantly associated with occult nodal metastasis [11]. In our study, we also found a significant correlation between neck node positivity and the WPOI grading.

In our study, no correlation was found between neck node positivity and either age or sex. Consistent with the findings in our study, Chatterjee et al. and De Silva et al. also found no significant association between the presence of occult nodal metastasis and either age or sex [24, 27]. In our study,

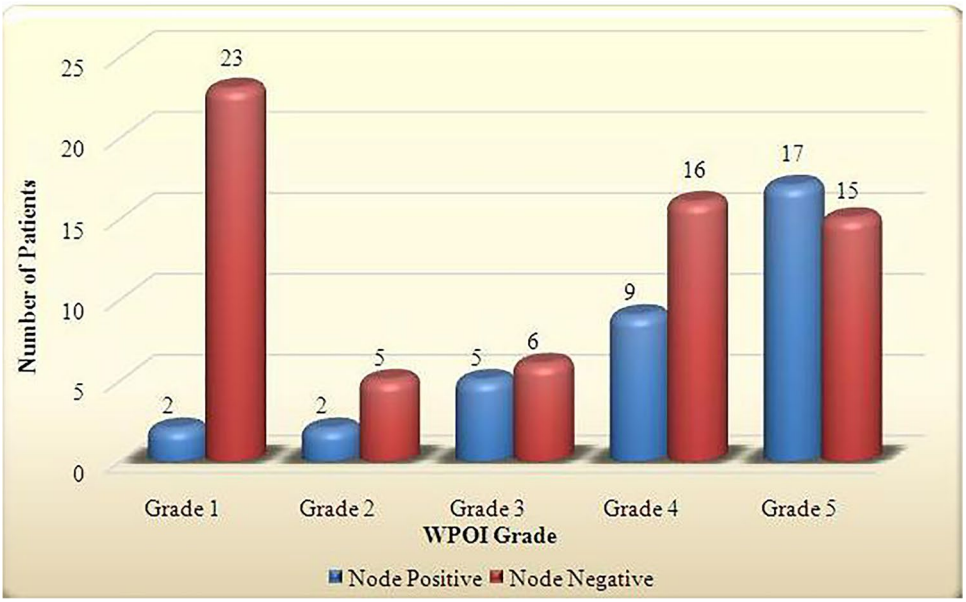

Fig. 2 Distribution of patients according to WPOI grade

the buccal mucosa was the most common site of the primary tumour, followed by the tongue. However, when it comes to the rate of occult neck node positivity, the tongue superseded the buccal mucosa as the most common site. We found no significant association between the history of smoking and nodal positivity. De Silva et al., in their retrospective study of 623 patients with oral and tongue cancers, found that the tongue was the most common site involved and also that when it comes to occult nodal positivity; the rate was much higher in the primary of the tongue than in the buccal mucosa [27]. The reason for the same can be explained by the fact that the tongue has a rich supply of lymphatics, owing to its anatomical position at the floor of the mouth, and thus, the nodal spread occurs early and rapidly.

Various histological parameters such as tumour size, tumour stage, grade of differentiation, DOI, LVE and PNI are well-known prognostic factors for OSCC in all stages and are mandatory parts of the standard histological reporting format. In our study, we found a significant association of LVE and the grade of differentiation with the risk of nodal metastasis but failed to show any significant association of PNI, tumour size, lymphocytic response or depth of invasion with the risk of lymph node metastasis. In a prospective analysis by Manjula et al. on 33 patients of gingivo-buccal complex SCC, they also found that neither the tumour size nor the pathological T stage was significantly associated with the risk of cervical nodal metastasis [15]. While Almangush et al. [17], in their multicentre study on 479 patients of early-stage tongue cancer, found DOI to be a significant predictor of cervical nodal metastasis, several other studies are in agreement with the findings in our study, that increasing DOI does increase the risk of occult nodal positivity but the association is not significant [15, 24]. Though Chatterjee et al. [24] found a significant association between the presence of perineural invasion and cervical nodal metastasis, several studies, in line with our study, found no significant association between the two [14, 15]. Almangush et al. and Chatterjee et al. found no significant correlation between lymphocytic response and cervical nodal metastasis, which is consistent with our findings [14, 24]. While the results by Chatterjee et al. [24] are consistent with those in our study, several other studies [14, 15] found the contrasting fact that there is no significant association between the grade of differentiation and nodal metastasis. The rate of neck node positivity almost doubled with the presence of lymphovascular invasion, the association confirmed to be significant statistically. The correlation of LVI with the presence of nodal metastasis can be explained by the fact that the invasion of the lymphatics by the tumour emboli will surely put the draining nodal stations at a higher risk of having metastasis. This finding was also found to be true in other studies [24, 28, 29]. While 20.9% of non-aggressive WPOI (WPOI 1–3) patients had occult cervical nodal metastasis, 45.6% of aggressive WPOI (WPOI 4, 5) patients had nodal positivity. An increase in the grade of the WPOI means an increase in the aggressiveness of the tumour biology and hence the higher risk of the tumour dissemination to the cervical nodal basins. There is strong literary evidence available in support of our findings. Brandwein et al. in 2005 gave a risk scoring model and found a strong association between the aggressive pattern of invasion and the metastasis in the cervical lymph nodes [20]. The risk model was later validated by them in 2010 with a different group of cohorts [30]. Dissanayaka et al. in 2012 [31] discovered not only a strong association between WPOI grade and nodal metastasis but also that the risk was higher with WPOI 3 and WPOI 4 than with WPOI 1 and WPOI 2. In their study, Yue et al. reported a significantly

Table 3 Association of WPOI with various histological parameters

	WPOI 1–3 ($n=43$), n (%)	WPOI 4–5 ($n=57$), n (%)	p-value
Pathological N staging			
N0	33 (76.7%)	28 (49.1%)	0.031
N1	4 (9.3%)	20 (35.1%)	
N2a	2 (4.7%)	3 (5.3%)	
N2b	4 (9.3%)	6 (10.5%)	
Depth of invasion			
≤5 mm	10 (23.3%)	11 (19.3%)	0.891
>5 mm	33 (76.7%)	46 (80.7%)	
Lymphovascular invasion			
Present	7 (16.3%)	12 (21.1%)	0.029
Absent	36 (83.7%)	45 (78.9%)	
Perineural invasion			
Present	4 (9.3%)	11 (19.3%)	0.043
Absent	39 (90.7%)	46 (80.7%)	

higher incidence of bone involvement in aggressive WPOI as compared to non-aggressive WPOI [32]. Similar findings have also been found in other studies, thus validating the association further [10, 14, 15, 26, 27].

While some of the pathological risk factors might not be independent predictors of nodal metastasis, they might be high-risk factors and might indicate a predilection towards nodal metastasis. Therefore, we also studied the association between the grade of WPOI and various other histological parameters. In our study, depth of invasion was not found to be significantly associated with the grade of WPOI. However, it was noted that the depth of invasion was greater in the aggressive WPOI group than in the non-aggressive group. Pathological N staging was found to be correlated with the WPOI grade significantly. There was an increase in the pathological N stage as the grade of WPOI increased. WPOI grade was also found to be statistically associated, both with the presence of LVI and PNI. Out of the total 57 patients of aggressive WPOI grade, LVI and PNI were present in 12 and 11 patients respectively. After an extensive literature search, we could only find two such studies which aimed at analysing the inter-correlation of various histological factors. Nanda et al. [33] studied the association of WPOI with other histopathological parameters in 70 patients with oral cavity cancer and concluded that aggressive WPOI grade (WPOI 4/5) is associated significantly with PNI and infiltrative pattern of invasion. Similarly, Ahlawat et al. [34], in their retrospective study on 202 patients of oral tongue SCC, WPOI was found to be significantly correlated with pathological T and N stage, DOI, PNI and LVI. However, WPOI was not found to be associated with either tumour thickness or the grade of differentiation. Though not many studies have been done which analyse the inter-correlation of the various histological factors, doing so might help in the identification of high risk factors for nodal metastasis, which otherwise might not be independent predictors. These high-risk factors, if present, might have an impact on the overall prognosis of the disease.

Researchers and clinicians have advocated a threshold of 15% possibility of cervical metastasis as the indication for elective neck dissection in patients with SCC of the head and neck [22]. A decision-tree analysis was created by Weiss et al. [35], and they concluded that observation is the preferred option when the probability of occult metastasis is less than 20%, and elective neck treatment (irradiation or dissection) is preferred if the probability of occult metastasis is greater than 20%. However, recent randomized trials have reported in the favour of doing elective nodal dissection because of a high rate of occult nodal metastasis. As the rate of occult cervical nodal metastasis is about 30%, any histological parameter that can predict nodal positivity in clinico-radiological neck node–negative patients will not only aid in decision-making, but also the prognostification of the disease.

Conclusion

The presence of WPOI, LVI and poor differentiation is an independent predictor of cervical nodal metastasis in early-stage oral cavity cancers. Identification of these histological parameters can help in the clinical decision-making and also prognostification of the disease. Also, the inter-correlation analysis among different histological parameters can help in the identification of some high-risk factors, which otherwise might not predict nodal metastasis independently, but might have a significant effect on the outcome, survival and overall prognosis of the disease. Our study, whilst offering innovative lines of enquiry, creates a paradigm for future insight on this topic.

Author Contribution KKL: concept; analysis and/or interpretation.
YN: design; literature search; writing.
PM: concept; design.
RJ: concept; design; literature search; writing.
PP: analysis and/or interpretation.
SS: supervision; critical review.
AH: analysis and/or interpretation; literature search.
RGS: critical review; supervision.

Declarations

Ethics Approval and Consent to Participate The research involved human participants and a well informed consent was taken from each individual.

Also, approval was taken from the institutional ethical committee.

Conflict of Interest The authors declare no competing interests.

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