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Original paper

Histopathological grade and cervical nodal involvement in oral squamous cell carcinoma of the gingivobuccal complex: A cross-sectional study

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ABSTRACT

INTRODUCTION: Oral squamous cell carcinoma (OSCC) is the most prevalent malignancy of the oral cavity, carrying a disproportionately high burden in South Asia. Histopathological grade is a recognised prognostic marker, yet its relationship with cervical nodal involvement in OSCC of the gingivobuccal complex has not been adequately characterised in the Pakistani population.

MATERIAL AND METHODS: This descriptive cross-sectional study enrolled 257 consecutive patients with biopsy-confirmed OSCC of the gingivobuccal complex. Histopathological grading was performed by a single accredited laboratory. Cervical nodal status was assessed clinically and by contrast-enhanced computed tomography, since not all patients underwent neck dissection.

RESULTS: Mean age was 48.78 ± 16.62 years; 138 (53.70%) participants were male and 119 (46.30%) female. Clinically and radiologically detected cervical nodal involvement was present in 173 participants (67.32%). Poorly differentiated tumours were most frequent (38.9%), followed by well differentiated (31.5%), moderately differentiated (24.9%), and undifferentiated (4.7%). Nodal involvement was comparable in well and moderately differentiated tumours (58.02% and 53.12%) and rose sharply in poorly differentiated (81.00%) and undifferentiated tumours (91.67%), a difference that was highly statistically significant ($p < 0.001$). Neither age ($p = 0.723$) nor sex ($p = 0.192$) was significantly associated with nodal involvement.

CONCLUSIONS: Histopathological grade showed a strong association with cervical nodal involvement in OSCC of the gingivobuccal complex, whereas age and sex did not. Early diagnosis and grade-informed neck evaluation may help improve outcomes, although prospective multivariable studies are needed before these findings can guide routine practice.

KEYWORDS

lymph nodes, oral squamous cell carcinoma, cervical metastasis, histopathological grading, tumour site

INTRODUCTION

Oral squamous cell carcinoma (OSCC) accounts for 90 to 95% of all oral cavity malignancies and represents one of the leading causes of cancer-related morbidity and mortality worldwide [1,2]. More than 377,000 new cases are recorded annually worldwide, with the highest incidence rates concentrated in South and South-East Asia, where tobacco and betel-quid use are deeply embedded cultural practices. In Pakistan, oral cavity cancer ranks second among all malignancies and constitutes approximately 15% of incident cancer cases, compared with the worldwide average of roughly 3% [3]. This disproportionate burden is largely because of the widespread and heavy use of betel quid, gutka, and tobacco in both smoked and smokeless forms, often initiated

from early adulthood [4,5]. Limited awareness and restricted access to primary care facilities also mean that a large proportion of patients present with locally advanced disease, a pattern that is well documented in low-resource settings and that profoundly affects therapeutic options and the chances of survival [6].

Cervical lymph node involvement remains the single most important prognostic determinant in OSCC, reducing five-year survival by approximately 50% when nodal disease is established [7,8]. Clinical palpation, although widely used as the first-line method of neck assessment, has only modest accuracy, with sensitivity and specificity of around 61.9% and 69.1% respectively reported in one comparative series [9], so imaging with contrast-enhanced computed tomography (CT) is routinely used alongside palpation to strengthen the clinical evaluation. Histopathological grading, described originally by Albert C. Broders and then subsequently refined into the four-tier WHO classification (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), reflects the degree to which tumour cells retain the morphological characteristics of their tissue of origin. Many studies have reported that higher tumour grade correlates with increased risk of regional lymph node spread, perineural invasion, and adverse overall survival, but data from resource-limited South Asian centres remain scarce and are often drawn from retrospective case series with small sample sizes [10].

Characterising how histopathological grade relates to cervical nodal involvement holds practical clinical value. It can guide decisions regarding elective neck dissection, inform the threshold at which prophylactic neck treatment is warranted, and allow surgeons to estimate the probability of occult nodal disease at the time of initial surgical planning. Suresh et al. [11] reported nodal involvement in only 21.2% of well-differentiated OSCC cases, compared with rates exceeding 55% in poorly and moderately differentiated tumours. No comparable prospective series has been published from the Khyber Pakhtunkhwa province of Pakistan. The objective of this study was therefore to characterise the frequency of cervical nodal involvement across histopathological grades of OSCC of the gingivobuccal complex in a cohort from a regional tertiary referral centre.

MATERIAL AND METHODS

Study design and setting

This was a descriptive cross-sectional study conducted in the Department of Oral and Maxillofacial Surgery, Khyber College of Dentistry, Peshawar, Pakistan, over a twelve-month period from 10 September 2021 to 30 August 2022. The study adhered to the STROBE guidelines for cross-sectional research.

Sample size and sampling technique

Sample size was calculated using the WHO sample size calculator, based on a reported prevalence of 78.8% for absence of cervical nodal involvement in well-differentiated OSCC, a 95% confidence interval, and a 5% margin of error, yielding a minimum of 257 participants. Consecutive (non-probability) sampling was used.

Inclusion and exclusion criteria

Patients aged 20 to 80 years of either sex with histologically confirmed OSCC (incisional or excisional biopsy) and a primary lesion involving the gingivobuccal complex were eligible for inclusion. All eligible patients underwent standardised clinical and radiological assessment of the neck as part of the study protocol, irrespective of baseline nodal status. Cases with lymphadenopathy attributable to active infection or inflammation, malignancies other than squamous cell carcinoma, and tumours arising from the maxilla, mobile tongue, or floor of mouth were excluded.

Operational definitions

OSCC was defined as a malignant neoplasm of squamous epithelium with clinical features of ulceration, induration, hard consistency on palpation, spontaneous bleeding, everted margins, and a history of less than three months, confirmed histologically by a qualified pathologist at an accredited laboratory.

Cervical nodal involvement was defined clinically and radiologically, as a palpable lymph node measuring 1 cm or more in diameter, hard, and non-mobile, or a hyper-dense cervical lymph node of 1 cm or more detected on contrast-enhanced CT. Because nodal status was based on these clinical and radiological criteria rather than histopathological confirmation of neck disease in every case, the term nodal involvement is used throughout this manuscript rather than metastasis, which would require pathological verification.

Histopathological grading followed the four-tier classification: well differentiated (D1, fewer than 25% undifferentiated cells), moderately differentiated (D2, fewer than 50% undifferentiated cells), poorly differentiated (D3, fewer than 75% undifferentiated cells), and undifferentiated (D4, more than 75% undifferentiated cells).

Data collection

Institutional ethical review committee approval was obtained prior to data collection. All participants provided written informed consent after receiving a complete explanation of the study purpose, procedures, potential risks and benefits, and their right to withdraw without affecting clinical care. Confidentiality was ensured throughout.

All biopsies were sent to the same accredited laboratory to minimise inter-observer variability. After histological confirmation, a detailed clinical history was recorded and physical examination of all cervical lymph node levels was performed. Contrast-enhanced CT of the neck was requested for all participants to assess nodal status. Data were collected by the principal investigator and independently verified by a senior consultant who was a Fellow of the College of Physicians and Surgeons Pakistan (FCPS). The exclusion criteria were applied strictly to limit the inclusion of unrelated pathology, although this does not constitute statistical control for confounding, which was not performed in this study.

Statistical analysis

Data were analysed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Frequencies and percentages were calculated for categorical variables (sex, histopathological grade, and cervical nodal involvement). Mean and standard deviation were reported for the continuous variable age. Cervical nodal involvement was stratified by age group, sex, and tumour grade using the Pearson chi-square test; Fisher exact test was applied where cell counts were fewer than five. A p-value of 0.05 or less was considered statistically significant. No multivariable analysis was performed, and the associations reported below should be interpreted as unadjusted.

RESULTS

Two hundred and fifty-seven patients were enrolled. The mean age was 48.78 ± 16.62 years (range 20 to 80 years). Males accounted for 138 participants (53.70%) and females for 119 (46.30%). The most prevalent age group was 31 to 60 years, comprising 140 patients (54.47%), followed by 61 to 80 years (72 patients, 28.02%) and 20 to 30 years (45 patients, 17.51%). Overall, cervical nodal involvement was present in 173 participants (67.32%) and absent in 84 (32.68%). These demographic and outcome data are summarised in Table I.

Table I. Frequency distribution of demographic characteristics and cervical nodal involvement (n = 257)

Variable	Characteristic	n (%)
Sex	Female	119 (46.30)
	Male	138 (53.70)
Age group (years)	20–30	45 (17.51)
	31–60	140 (54.47)
	61–80	72 (28.02)
Cervical nodal involvement	Present	173 (67.32)
	Absent	84 (32.68)

Regarding histopathological grade, poorly differentiated tumours were most common (n = 100, 38.9%), followed by well differentiated (n = 81, 31.5%), moderately differentiated (n = 64, 24.9%), and undifferentiated (n = 12, 4.7%).

When cervical nodal involvement was stratified by sex, the frequency was 88 (63.77%) in males and 85 (71.43%) in females, although this difference was not statistically significant (p = 0.192; Table II). Stratification by age group similarly showed no significant difference in nodal involvement across the three age strata (p = 0.723; Table III).

Table II. Cervical nodal involvement stratified by sex

Cervical nodal involvement	Female (n = 119) n (%)	Male (n = 138) n (%)	p-value
Present	85 (71.43)	88 (63.77)	0.192
Absent	34 (28.57)	50 (36.23)	

Pearson chi-square test

Table III. Cervical nodal involvement stratified by age group

Age group (years)	Present n (%)	Absent n (%)	p-value
20–30	28 (16.18)	17 (20.24)	0.723
31–60	96 (55.49)	44 (52.38)	
61–80	49 (28.32)	23 (27.38)	

Pearson chi-square test

By contrast, the relationship between histopathological grade and cervical nodal involvement was highly significant (p < 0.001; Table IV). Nodal involvement was present in 47 of 81 well differentiated tumours (58.02%) and 34 of 64 moderately differentiated tumours (53.12%), rates that were broadly similar to one another. Involvement then rose markedly in poorly differentiated tumours (81 of 100, 81.00%) and undifferentiated tumours (11 of 12, 91.67%). Rather than a strictly graded increase across all four categories, this pattern suggests a threshold effect, with a marked rise in nodal involvement once tumours became poorly differentiated or undifferentiated.

Table IV. Cervical nodal involvement stratified by histopathological tumour grade

Tumour grade	Present n (%)	Absent n (%)	p-value
Well differentiated	47 (58.02)	34 (41.98)	< 0.001
Moderately differentiated	34 (53.12)	30 (46.88)	
Poorly differentiated	81 (81.00)	19 (19.00)	
Undifferentiated	11 (91.67)	1 (8.33)	

Fisher exact test

DISCUSSION

This study examined 257 patients with biopsy-confirmed OSCC of the gingivobuccal complex treated at a tertiary dental institution in north-western Pakistan. The central finding was that histopathological grade showed a strong association with cervical nodal involvement, with comparable rates in well and moderately differentiated tumours (58.02% and 53.12%) followed by a marked rise in poorly differentiated and undifferentiated tumours (81.00% and 91.67%, $p < 0.001$). Neither age nor sex was significantly associated with nodal involvement in this cohort. As no multivariable analysis was performed, these findings indicate an association rather than an independent or causal relationship and should be interpreted accordingly.

The male-to-female ratio in this series was 1.16:1, broadly consistent with the 1.2:1 ratio described by Pinholt et al. [12] in a Danish retrospective cohort. A higher male predominance of 4.18:1 was reported by Shenoi et al. [13] in an Indian population, and a substantially elevated ratio of 9.2:1 by Antoniades et al. [14] in northern Greece. The relatively narrow sex gap in our cohort is consistent with broader epidemiological trends within Pakistan, where the prevalence of betel-quid and smokeless tobacco use has risen among women, particularly in peri-urban and rural communities, slowly eroding the historically marked male preponderance.

The mean age of 48.78 ± 16.62 years aligns with the Indian series reported by Shenoi et al. [13] (mean 52 years) and with an institutional series from the Armed Forces Institute of Dentistry, Islamabad [15]. This relatively young mean age, compared with Western cohorts in which OSCC predominantly affects patients in the seventh and eighth decades, reflects both the earlier onset of carcinogen exposure through betel-quid initiation in adolescence and the genetic susceptibility profiles documented in South Asian populations. The 20-to-30-year age stratum accounted for 17.51% of cases, a proportion that echoes the increasing incidence of OSCC in young adults observed across South and South-East Asia over the past two decades.

The overall rate of cervical nodal involvement of 67.32% in this series is higher than the 35.3% to 60% range reported in previous literature for general OSCC cohorts [16], and higher than the 27% occult metastasis rate described by Haseeb et al. [17] in a Pakistani series of 100 patients. This discrepancy most plausibly reflects late presentation, since patients in our setting typically seek care only when disease has become locally advanced, by which time regional nodal involvement is substantially more likely. It may also partly reflect our reliance on clinical and radiological rather than histopathological criteria for nodal status, which can overestimate true pathological involvement relative to series that use neck dissection specimens as the reference standard. The anatomical distribution of metastasis reported in the literature ranges from 37 to 55% for tongue

primaries, 11 to 50% for mandibular gingival lesions, and 24 to 75% for buccal mucosa, underscoring that primary site itself modulates nodal risk and should be factored into neck management decisions alongside histopathological grade [17,18].

The finding that poorly differentiated and undifferentiated tumours carry the highest rates of nodal involvement aligns with the mechanistic understanding of tumour biology. Loss of intercellular adhesion molecules, dysregulation of matrix metalloproteinases, and epithelial-to-mesenchymal transition all intensify with declining differentiation, facilitating lymphovascular invasion. Suresh et al. [11] reported nodal involvement in only 21.2% of well-differentiated OSCC, compared with rates exceeding 55% in moderately and poorly differentiated tumours combined. Our data broadly align with this pattern, although our absolute rates are higher, consistent with the late-presentation pattern of our patient population. Yasin et al. [19] reported a predominance of moderately differentiated OSCC (76.5%) in a Pakistani cohort, with lower rates of poorly differentiated tumours than we observed. The proportionally higher poorly differentiated rate (38.9%) in our series may reflect referral bias, as our centre receives tertiary cases from a wide catchment area in Khyber Pakhtunkhwa, where advanced disease at first presentation is the norm [20].

The absence of a significant association between age or sex and cervical nodal involvement in our cohort suggests that neither variable, on its own, is a strong indicator for guiding neck management, whereas tumour grade showed a clear and statistically significant association. This grade-related pattern, if confirmed in future studies with multivariable adjustment, could have implications for surgical decision making. Poorly differentiated and undifferentiated OSCC of the gingivobuccal complex might warrant closer consideration for elective neck dissection, given that the observed rates of nodal involvement in these groups are well above the 20% threshold commonly cited as an indication for prophylactic neck treatment [8]. This observation, however, is hypothesis-generating rather than a basis for a firm treatment recommendation, for the reasons discussed below.

This study has several limitations that should be noted. The cross-sectional design precludes inference about causal direction or temporal sequence, and the analysis was based on chi-square and Fisher exact tests without multivariable adjustment, so grade cannot be described as an independent predictor of nodal involvement in this dataset. Nodal status was determined clinically and radiologically rather than histopathologically for all patients, since not all underwent neck dissection, so some degree of misclassification relative to true pathological nodal status cannot be excluded. Tumours of the mobile tongue, floor of mouth, and maxilla were excluded, which limits

the generalisability of findings to the gingivobuccal complex specifically and does not allow direct comparison with studies encompassing the full oral cavity. The absence of a standardised imaging protocol before enrolment and the use of clinical palpation alongside CT, rather than PET-CT or sentinel lymph node biopsy, may have resulted in some misestimation of true nodal involvement rates in either direction. Additionally, follow-up data were not collected, so survival and recurrence outcomes could not be evaluated. Future work should include multi-centre prospective studies covering all primary oral cavity subsites, with multivariable analysis and sentinel lymph node biopsy or neck dissection histopathology as the reference standard for nodal staging.

CONCLUSIONS

Histopathological tumour grade showed a strong association with cervical nodal involvement in OSCC of the gingivobuccal complex, with undifferentiated and poorly differentiated tumours showing involvement rates of 91.67% and 81.00% respectively, compared with 58.02% and 53.12% in well and moderately differentiated tumours. Age and sex were not significantly associated with nodal involvement in this population. Given the frequency of late presentation in the study setting and the high overall rate of nodal involvement of 67.32%, these findings suggest a possible role for tumour grade in informing neck management decisions in OSCC of the gingivobuccal complex, particularly for poorly differentiated and undifferentiated tumours. However, because this was a single-centre, cross-sectional study without multivariable analysis or universal histopathological confirmation of nodal status, this observation should be treated as hypothesis-generating, and prospective multivariable studies are needed before grade alone can be used to guide routine neck management. Systematic early-detection programmes and public health campaigns targeting tobacco and betel-quid cessation remain essential to reducing the incidence and stage at presentation of this disease in Pakistan.

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Conflict of interest

The authors declare no conflict of interest.

Authors' contribution

Study design – U. Noreen, I. Alam

Data collection – U. Noreen, I. Alam, F. Yahya

Data interpretation – U. Noreen, F. Yahya, Q.J. Hayat

Statistical analysis – I. Alam, F. Yahya, Q.J. Hayat

Manuscript preparation – U. Noreen, Q.J. Hayat

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