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The Correlation between Histopathological Parameters of Oral Squamous Cell Carcinoma and Nodular Metastasis and Consequent Neck Dissection Decision Making

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ABSTRACT

Objectives: The aim of this study was to evaluate neck nodular metastasis and related clinic opathological parameters of primary oral squamous cell carcinoma (OSCC) patients who underwent neck dissections.

Materials and Methods: A descriptive cross-sectional study was conducted compromising 571 records of patients treated at the Oral and Maxillofacial Unit, National Hospital, Galle, Sri Lanka, from 2001 to 2020. Data was analyzed using SPSS-26 statistical software package.

Results: The occurrence of neck positivity was 54.1 %. Stages III and IV cancers (OR = 1.79: 95% CI 1.22- 2.63 (P = 0.003), compared with stages 1 and II and types 3 &4 invasive fronts (OR = 1.8: 95% CI 1.1-2.9) (P = 0.030) compared with types 1 & 2 were significantly associated with neck node metastasis. Depth of invasion types 2, 3, 4 (> 5 mm) *vs.* type 1 (OR = 7.6, 95% CI = 2.5- 13.7) (P = 0.0001) and grade 3 differentiation compared to grade 1 or 2 had significant neck-node metastasis (OR= 2.8, 95% CI, 1.2-6.4) (*p*=0.0001). Palatal (OR = 2.91, 95% CI: 1.40-6.04) (P = 0.004) and tongue lesions (OR=1.50, 95% CI: 1.03-2.19) (P = 0.034) demonstrated higher neck mode metastasis compared to other primary sites.

Conclusions: The results confirm that clinicopathological parameters of primary OSCC could assist rational neck dissection decision. As advanced staged tumors with aggressive biology were more likely to have nodal involvement and radical neck dissections, early detection and prompt treatment of OSCC become important for countries like Sri Lanka.

Keywords: Oral squamous cell carcinoma, Metastasis, Neck dissection, Clinical-pathological parameters.

1. Introduction

As a top cancer among males and females in Sri Lanka, OSCC poses a public health challenge (1). Surgery remains the primary treatment for OSCC, with neck dissections playing a key role in managing lymph node metastasis (2). Some studies advocate watchful waiting for selected cases, offering a cost-effective, less harmful alternative to elective neck dissections (3-5).

Surgical resection followed by radiotherapy, with or without chemotherapy, is commonly used based on clinical and histopathological staging (6-8). Various surgical techniques, including conventional, laser, thermal, and photodynamic therapies, are available for treatment (9).

Tumor resection should be performed with a clinical clearance of 1cm by preserving vital structures whenever it is possible (10). If the tumor margins are not clear, histopathologically at least more than 5mm post-operative radiotherapy is indicated. According to the protocols in western countries, single treatment modality, like surgery or radiotherapy, is indicated for stage-I or II-OSCC, as disease control and five-year survival rate, is similar in both treatment modalities (11). According to the advanced treatment protocols, patients with advance lesion, such as clinical staging of III or IV, require a combination of surgery and radiotherapy with or without chemotherapy (12). This is due to the cervical lymph node metastasis which leads to poor prognosis with a low disease free survival period even though it increases the post-operative complications and morbidity.

The prognosis of OSCC patients is determined using the TNM staging system, a key tool for guiding treatment decisions. Early-stage diseases (Stages I and II) involve small tumors without nodal metastasis, while advanced stages (Stages III and IV) feature larger tumors with potential regional lymph node involvement or invasion of underlying structures (13,14).

The surgical removal of cervical lymph nodes is crucial in managing oral SCC. Factors influencing cervical lymph node metastasis include clinical parameters, like tumor site and staging, as well as histopathological features, such as degree of differentiation, depth of invasion, host response, and invasive tumor front (15,16). The risk of lymph node metastasis in OSCC is influenced by histologic parameters not commonly analyzed in routine pathologic reports. Strong consideration should be given to incorporating these parameters in standard pathology reports. In the same way, care should be taken to prevent surgically undertreating patients with potentially positive lymph nodes (17).

A radical neck dissection (RND) is the gold standard for metastatic neck. First RND was carried out by George Washington Crile in 1906, but with anatomical and functional disadvantages (18). Nowadays, selective neck dissection, such as supra-omohyoid neck dissection, is recommended for patients with N0 necks, as lymph node levels I-III are considered sentinel or first-echelon lymph nodes for oral cancer (18). Since these are first levels of lymph nodes, they are expected to have metastatic deposits, and this well- accepted concept is the basis for prophylactic neck dissections in patients with clinically negative necks with the likelihood of occult disease exceeding 20% (19). Patients with N0 neck do not undergo RND due to functional morbidity, such as shoulder syndrome.

Radical neck dissection (RND) is advised for patients with N+ necks. Selective neck dissection is also appropriate for patients with low-volume nodal disease (N1) in the upper neck, provided that post-operative radiation therapy is included as part of the treatment plan (20).

The management of clinically negative necks in early OSCC remains contentious. Recent evidence supports elective neck dissection even for tumors with a depth of invasion under 4 mm (21). A direct meta-analysis indicated that Elective Neck Dissection (END) is more effective than Total Neck Dissection (TND) and similar to Sentinel Lymph Node Biopsy (SLNB). END is likely the best option for enhancing overall survival and disease specific survival and minimizing nodal recurrence in early-stage OSCC, followed by SLNB and TND (22).

Pre-operative assessment using clinical and histopathological parameters can guide the severity of the disease, enable tailored neck dissection plans, streamline intra-operative and post-operative protocols, and facilitate informed patient consent.

This study highlights the importance of guiding patient management in OSCC based on clinical and histopathological evidence to minimize oncological risks and improve personalized treatment planning. It emphasizes the socio-economic impact of OSCC and its treatments, which significantly affect patients' quality of life, impose high costs on families, and burden the healthcare system. Pre-treatment planning is crucial for optimizing treatment, avoiding unnecessary procedures, reducing costs, and improving survival outcomes. The study evaluates neck-node metastasis and related clinic pathological factors in OSCC patients treated over 19 years at the Oral and Maxillofacial Unit, National Hospital, Galle, Sri Lanka.

2. Materials and Methods

2.1 Study Design

The present study was a descriptive cross- sectional study with an analytical component. A set of secondary data was used for the study. Patients were not followed up prospectively or retrospectively.

2.2 Study Setting

Data was extracted from an electronic database comprising 571 patients with histopathologically confirmed diagnosis of OSCC who underwent neck dissections at the Oral and Maxillofacial Unit, National Hospital, Galle, Sri Lanka, over a period of 19 years, from January 2001 to December 2020.

2.3 Study Population

Records of patients confirmed OSCC histopathologically and managed with a neck dissection at the above study setting were taken as the study population. Moreover, those patients were presented with clinically/radiologically positive or negative neck nodes. Clinical data was extracted from an electronic patients' data base with evaluation of respective biopsy reports. However, the patients presented with recurrent diseases, had primary lesions in any other site of the body in addition to oral cavity or oropharynx, had other histological types of oral cancers, and those who obtained neoadjuvent radiotherapy or chemotherapy were excluded. Selection criteria were strictly followed, and because the outcome of interest was not the original reason for the data to be collected, bias was minimized. The study was conducted in accordance with the ethical principles mentioned in the Declaration of Helsinski (2013) and in accordance with institutional and international standards (Ethics Review Committee, Ref. 2021, P.014).

2.4 Sample Size Calculation

Sample size was calculated using the formula introduced by Lwanga and Lemeshow in 1991; $N = Z^2 P [1-p)/d^2$ with an anticipated overall estimated percentage of patients with neck metastasis of 30%. To accommodate non-respondents/missing data, the sample size was increased by 10. The final sample size calculated was 356. However, the total number of patient records available in the data base was taken as the study sample.

2.5 Study Instrument

An Excel data sheet was used to record extracted data. Data, such as date of the surgery, demographic data, primary site of the lesion, clinical staging, type of treatment, and histopathological findings, was recorded in the Excel data sheet. Confidentiality and security of data were maintained throughout this process. Data extraction was carried out by a single investigator and double checked during each entry. Clinical and histopathological parameters were assessed in this study to see the associations with positive nodal metastasis.

2.6 Statistical Methods

The extracted data was entered and analyzed using SPSS-26 statistical software package. Neck-node metastasis was determined clinically and by radiological investigations (Ultrasound scan/Computed tomography/Magnetic-resonance imaging). The occurrence of positive neck nodal metastasis was described as the percentage of patients with positive neck nodes among all the OSCC patients included, managed with a neck dissection. Uni-variate analysis was conducted using chi-square test of statistical significance to compare the group differences in positive neck-node status by selected clinical and histopathological parameters. The clinical parameters were primary site and staging of the OSCC, whilst the histopathological parameters consisted of degree of differentiation, type of invasive front, lymphocytic host response, and depth of invasion, assessed according to the American Joint Committee on Cancer 8^{th} Edition (23), a detailed description of which is published at https://acsjournals.onlinelibrary.wiley.com/doi/pdf/10.3322/caac.21388.

Elective neck dissections were performed for sites assumed to have a high risk of neck metastasis, taking into consideration the size of the lesion along with the histopathological parameters in incisional biopsy reports. The level of significance was set at $P < 0.05$. Multi-variate binary logistic regression analysis was conducted to determine the independent clinical and histopathological parameters that increased the risk of neck-node metastasis among OSCC patients. Dependent variable was neck-node status, categorized as 'positive' and 'negative'.

3. Results

Males dominated the sample (80.7%). The mean age was 59.24 years (95% CI 58.24-60.25). The most common primary site was buccal mucosa (31.7%), followed by tongue (26.8%) and mandible (21.5%).

Further, 46.5% of OSCCs belonged to stage IV, while 29.0% were in stage II and 20.5% in stage III. Moderately differentiated OSCC dominated (47.3%).

Tongue, maxilla, floor of the mouth and combined sites and Stage IV and III OSCCs demonstrated significantly higher probability of neck-node positivity compared to lip, buccal mucosa and mandible and Stages I and II OSCCs (Table 1).

Table 1: Comparison of neck-node status of OSCC patients by selected clinical parameters

Parameter	Node Positive Patients N	(%)	Node Negative Patients N	(%)	Chi-square Value (df)	P-value
Primary Site					25.9 (6)	**0.0001**
Lip	3	(50.0)	3	(50.0)		
Tongue	94	(61.4)	59	(38.6)		
Palate	32	(66.2)	10	(23.8)		
Floor of the mouth	28	(62.2)	17	(37.8)		
Buccal mucosa	89	(49.2)	92	(50.8)		
Mandible	49	(39.8)	74	(60.2)		
Other	14	(66.7)	7	(33.3)		
Total	309	(54.1)	262	(45.9)		
Clinical Stage					10.45 (3)	**0.015**
Stage I	8	(42.1)	11	(57.9)		
Stage II	62	(44.3)	78	(55.7)		
Stage III	53	(53.6)	46	(46.5)		
Stage IV	136	(60.7)	88	(39.2)		
Total*	259	(53.7)	223	(46.3)		

*<571 due to missing data.

Patients with poorly and moderately differentiated OSCC showed significantly higher neck-node positivity compared to patients with well-differentiated OSCC (P =0.0001). Patients with type-4 invasive front demonstrated a significantly higher neck-node positivity compared to other types (P=0.01). The majority of patients with T3 depth of invasion demonstrated a significantly higher probability of neck-node positivity compared to patients with T1 & T2 (P =0.0001) depths of invasion (Table 2).

Table 2: Comparison of neck-node status of OSCC patients by selected histopathological parameters

Variable	Neck Positive N	(%)	Neck Negative N	(%)	Chi-square Value (df)	P-value
Degree of Differentiation						
Well	103	(43.4)	140	(57.6%)	31.1 (4)	**0.0001**
Moderate	167	(61.9)	103	(38.2%)		
Poor	25	(80.6)	6	(19.4%)		
Anaplastic	0	(0)	1	(100%)		
Not determined	0	(0)	1	(100%)		
Total*	295	(54.0)	251	(46.0)		
Invasive front						
Type 1	4	(33.3%)	8	(66.6%)	11.2 (3)	**0.01**
Type 2	36	(50.7%)	35	(49.3%)		
Type 3	79	(56%)	62	(43.9%)		
Type 4	66	(70.9%)	27	(29%)		
Total*	185	(58.4)	132	(41.6)		
Host immune response						
Dense	22	(45.8%)	26	(54.1%)	5.24 (2)	**0.07**
Moderate	70	(56%)	55	(44%)		
Light	83	(64.3%)	46	(35.6%)		
Total*	175	(57.9)	127	(42.1)		

Depth of Invasion						
T1	5	(22.7)	17	(77.3%)	16.86 (3)	**0.0001**
T2	16	(61.2%)	10	(38.5%)		
T3	29	(74.4%)	10	(25.6%)		
T4	1	(100%)	0	(0%)		
Total*	50	(56.8)	38	(43.2)		

* Total < 571 due to missing data.

Patients with palatal (OR = 2.91, 95% CI: 1.40-6.04) (P=0.004) and tongue lesions (OR=1.50, 95% CI: 1.03-2.19) (P=0.03) demonstrated higher neck-node metastasis compared to other primary sites. Patients with stages IV and III cancers demonstrated increased neck-node metastasis compared with patients with stages 1 and II cancers (OR = 1.79: 95% CI 1.22- 2.63 (P= 0.003) (Table 3).

Table 3: Independent associations between neck status & clinical parameters

Variable	**Neck status**						**P value**	**Odds ratio (95% CI)**
	Positive		**Negative**		**Total**			
	No	**%**	**No**	**%**	**No**	**%**		
Primary site								
Other sites*	281	53.4	245	46.6	526	100	.258	1.00
Floor of the mouth	28	62.2	17	37.8	45	100		1.44 (0.76-2.68)
Other sites*	277	52.4	252	47.6	529	100	**.004**	1.00
Palate	32	76.2	10	23.8	42	100		2.91 (1.40-6.04)
Other sites*	215	51.4	203	48.6	418	100	**.034**	1.00
Tongue	94	61.4	59	38.6	153	100		1.50 (1.03- 2.19)
Stage of cancer								
Stages I & II	70	44	89	56	159	100	**.003**	1.00
Stages III & IV	189	58.5	134	41.5	323	100		1.79 (1.22-2.63)

* buccal mucosa, commissures, alveolus, retromolar area and all sites other than palate, tongue and floor of the mouth.

Depth of invasion, degree of differentiation and type of invasive front increased the occurrence of neck-node metastasis among OSCC patients (Table 4).

Table 4: Independent association between histopathological parameters and neck-node metastasis

Variable	**Neck status**		**P-value**	**Odds ratio (95%CI)**
	Positive Number (%)	**Negative Number (%)**		
Depth of invasion				
T1	5 (22.7)	17 (77.3)	**0.000**	1.00
T2,T3,T4	45 (77.3)	20 (30.8)		7.6 (2.5-13.7)
Degree of differentiation				
Grade1 & II	270 (52.6)	243 (47.4)	**0.013**	1.00
Grade III	25 (75.8)	8 (24.2)		2.8 (1.2-6.4)
Host immune response				
Dense	22 (45.8)	26 (54.2)		1.00
Moderate	70 (56.0)	55 (44.0)	0.23	1.5 (0.8-2.9)
Light	83 (64.3)	46 (35.7)	0.27	2.1 (1.1-4.2)
Invasive front				
Types 1&2	40 (51.8)	43 (48.2)	**0.030**	1.00
Types 3&4	145 (38.0)	89 (62.0)		1.8 (1.1-2.9)

4. Discussion

Given the occurrence of occult regional lymph node metastasis among >20% patients with cN0, the question of how to manage necks of those patients with primary OSCC lesions remains controversial and a complex challenge (24). We studied neck-node metastasis and associated clinic-pathological risk factors among 571 OSCC patients with (cN+) or without (cN0) clinically/radiologically detectable neck nodes who underwent neck dissections. For the best of our knowledge, this is the first analysis in this regard with a large cohort over a long period on patients' records in Sri Lanka.

Given the well-known evidence on less aggressiveness of palatal/maxillary lesions, we performed therapeutic neck dissection (TND) only to manage those patients with clinically or radiologically positive neck nodes. Therefore, it is more justifiable to get a higher percentage of positive nodal metastasis (66.2%) histopathologically when compared to other sites which were differently managed. Elective neck dissection (END) should be carried out for high-risk cases by site (tongue), size (T3/T4), invasive front 3/4 and depth of invasion more than 5mm. Except for the depth of invasion, all the other parameters were possible to assess clinically and histopathologically by utilizing the findings of incisional biopsy. Primary OSCC cases of buccal mucosa/mandible/lip were managed by TND or END, I-III levels of neck nodes. For tongue/floor of the mouth OSCC with TND or END, I-IV levels of neck nodes.

The incidence of positive neck-node metastasis was as high as 54.1% in our study. This could be plausibly attributed to a significantly higher presentation of stage-IV OSCC which is a common phenomenon in Sri Lanka as well as having more cases of moderately differentiated carcinomas with depths of invasion >5 mm that could give rise to more c N+ cases (1-6). The extent of neck-node metastasis has been extensively investigated across the world with regard to neck-dissection types. One study that employed END reported a comparatively lower incidence of neck-node metastasis that ranged from 4% for cN0 early stages maxillary gingival OSCC (25). Therefore, the stage of the disease, cN+, neck dissection type and sub-site seemed to be among the contributing factors for differences in the findings on the incidence of neck-node metastasis in OSCC patients. A previous Sri Lankan multi-centre study on incidence of neck-node metastasis among OSCC patients found the majority to have level-I and level-II nodal involvement, reported as 58.3% and 56.1%, respectively (26). The detected level-III nodal positivity was 40.1%, whereas level-IV positivity was 27.3%. However, level-V positivity was as minimal as 6.4% (26). Thereby, the findings indicated that the higher the nodal level, the lower the percentage of positivity. This provides an alternative explanation for our findings.

Our findings suggested a significantly higher risk of primary lesions of OSCC of palate and tongue for node metastasis compared to other sub-sites. This was supported by other studies, especially for T3 and T4 cases. Greater propensity for occult metastasis in tongue OSCC is well known (27-30). Our data predominantly included patients with maxilla/palatal lesions with clinically/ radiologically positive neck nodes that were exclusively managed by therapeutic neck dissections, which could have probably reduced the prominence of floor of the mouth and mandible, showing an increased risk for neck metastasis in logistic regression analysis. Histopathological parameters emerged as the significant risk factors for neck-node metastasis in our study, thus corroborating the findings of similar studies; however, in contrast to findings of other studies, lymphoid response did not appear as a significant risk factor (6,7,8,31). Further post-operative adjuvant therapy is a collective decision taken by considering the closed margin, involved margin of the tumor resection, positive lymph node metastasis, and degree of differentiation, invasive front, depth of invasion, as well as the size and site of the primary lesion. The findings of this study will significantly contribute to future decision-making regarding adjuvant radiotherapy.

For extensive neck dissections carried out for such patients with late stages, biologically aggressive tumors are not only costly to the public health system, but also do not guarantee recurrence free survival and quality of life of the affected patients (32). Hence, early detection, early referral and prompt treatment for oral cancers are essential with strategic oral cancer prevention and control activities. Moreover, rigorous research is warranted on innovative management of neck-node metastasis, especially neck-node negative oral cancer patients with early stages less biologically aggressive tumours. Previous research reported significant reduction in nodal recurrence and five-year-combined recurrence free survival of a group of tongue and buccal squamous cell carcinoma patients treated with herbal regimens that consisted of *Emblica officinalis* and *Tinospora cordifolia* compared to a placebo group, after subjection to conventional treatment (33).

We have used broad inclusion criteria, so that our study population resembles real-life patients more closely. This was carried out to increase the external validity of our study. However, lack of data for certain parameters for the sample of 571 patients due to incomplete histopathological reports was a limitation of our study. However, it is noteworthy that pathology reporting was conducted by several pathologists. Additionally, neck dissections were performed by both a consultant oral and maxillofacial surgeon and post-graduate trainees. The insufficient data available hindered our ability to analyze the specific levels of neck-node metastasis in relation to particular clinical and histopathological parameters. Despite these limitations, we have made every effort to present the findings as accurately as possible. Further research with a more comprehensive dataset is necessary to address these limitations and provide more comprehensive insights.

5. Conclusions

In our retrospective cohort study involving 571 OSCC patients (cN0 and cN+), the incidence of neck-node metastasis was as high as 54.1%, which could be explained by the higher presentation of stage-IV and moderately differentiated OSCCs, which agrees with previous studies.

Our findings confirm that patients with tumors of advanced stages with aggressive biology are more likely to have nodal involvement and radical neck dissections. The results confirm that clinicopathological parameters of primary OSCC could assist rational neck-dissection decisions. Therefore, this study, conducted over a period of 19 years, represents a significant contribution to the understanding of clinical and histopathological parameters of OSCC that could guide rational neck-dissection decisions. Notably, it is the only study of its kind conducted within this province in Sri Lanka, providing unique insights and valuable data that can inform future research and healthcare interventions in the region.

Conflict of Interests

There is no actual or potential conflict of interests to be declared by the authors regarding the present manuscript.

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