## Original Research Article

# Risk factors in oral carcinoma and the relationship between tumor thickness and regional nodal involvement: a pilot study in a semi urban population in New Delhi, India

## Sujata Jetley[1], Zeeba S. Jairajpuri[1]*, Sama Rizvi[2]

[1]Department of Pathology, [2]MBBS Final Year student, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi,  India

**ABSTRACT**

**Background:** Oral squamous cell carcinoma (OSCC) is a major public health problem worldwide, with approximately 275,000 cases annually and a strong association with risk factors like smoking. It is a subtype of head & neck cancer involving the oral cavity.  The present study evaluated the role of various risk factors in the development of oral carcinoma among our patient population.
**Methods:** A total of 40 cases of oral carcinoma with radical neck dissection were evaluated. Data on the age, personal history and presenting clinical features were analyzed. The depth of the tumor and the maximum tumor thickness were carefully evaluated. Also, pathological T-stage, the presence/absence of vascular and peri-neural infiltration was evaluated in each case. The presence of nodal metastases and the stage of the tumor was assessed. Data was tabulated and correlation of nodal metastasis with tumor thickness, pathological T-stage, vascular invasion, and peri-neural infiltration was evaluated by appropriate statistical analysis method.
**Results:** A total of 40 cases, 82.5% males and 17.5% females, were all smokers with history of consumption of smoking or smokeless or both. Tongue was the most common site of oral carcinoma (37.5%) involvement, histological characterization of all were Squamous cell carcinoma with majority of the patients in pathological stage II. A significant association between the tumor thickness and metastasis was also seen.
**Conclusions:** The tumor thickness of oral squamous cell carcinoma was found to be an important prognostic indicator for the occurrence of metastases to the regional cervical lymph nodes.

**Keywords:** Oral carcinoma, Regional lymph nodes, Risk factors

## INTRODUCTION

Oral cancer is a subtype of head & neck cancer involving the oral cavity. The age-adjusted rate of oral cancer in India has been reported to be 20 per 100,000 population, accounting for over 30% of all cancers in the country.[1] Majority of the oral cancers are squamous cell carcinomas arising from the stratified squamous epithelium, which covers the vascularized connective tissue & is keratinized over the hard palate, lips & gingiva while elsewhere it is non-keratinized. Globally, as of 2010, 124,000 people have died of oral cancer up from 82,000 in 1990. [2] The present study focused on oral squamous cell carcinoma arising from the stratified squamous epithelium covering the vascularized connective tissue and the common sites encountered were the lateral border of tongue, base of tongue, buccal mucosa, hard/ soft palate and tonsils.

Risk factors that predispose to oral cancer have been identified in epidemiological studies. As many as 75 percent of oral cancers are linked to modifiable behaviors such as tobacco use, chewing betel, 'paan' and excessive alcohol consumption.[3] The popularity of addictive habits along with cultural, ethnic and geographic factors have all played a vital role in the high incidence of oral carcinoma in India. In many Asian cultures chewing betel, paan, and areca is known to be a strong risk factor for developing oral cancer. Tumor thickness is also considered to be an important prognostic factor in head and neck cancers and an important parameter in the prediction of nodal metastases in oral squamous cell carcinoma.[4]

The present study evaluated the role of various risk factors in the development of oral carcinoma among our patient population. We also studied the role of tumor thickness or depth of invasion as a prognostic parameter for the development of nodal metastasis for patients with oral squamous cell carcinoma associated with enlarged regional lymph nodes, who have undergone radical neck dissection.

## METHODS

The study was conducted at a tertiary hospital, part of the data (25 cases, collected over three month period from May 2014 to July 2014) was submitted under the STS (Short Term Studentship) program of ICMR 2014. Our hospital caters to a population mostly belonging to a low socioeconomic status residing in the nearby localities. A total of 40 cases of oral carcinoma with radical neck dissection were evaluated, both retrospectively and prospectively. (A) Histologically proven cases of oral carcinoma which had already undergone radical surgery at our Hospital and the specimen sent to the pathology lab for histopathological evaluation, were included in this study as a retrospective analysis, for e.g. specimens such as Glossectomy/ Radical Mandibulectomy with Radical neck dissection.(B) Patients from the ENT OPD and the Tobacco Cessation Clinic presenting with oral ulcer/growth with/ without enlarged cervical lymph nodes who have biopsy proven squamous cell carcinoma and have been taken up for excision of the tumor mass with radical neck dissection were included in this study as a prospective analysis.

In the retrospective analyses, data on the age, personal history and presenting clinical features were retrieved from the accompanying laboratory request forms, or patients records wherever available. The depth of the tumor and the maximum tumor thickness was ascertained by retrieving the histopathology slides of the tumor and also by re-examination of the preserved specimen wherever necessary/possible. The tumor thickness was measured in all cases by measuring from the surface of the tumor to the deepest point of invasion. Also clinical T-stage, pathological T-stage, the presence/absence of vascular and peri-neural infiltration was evaluated in each

case. The presence of nodal metastases and the stage of the tumor were assessed. All the above data was tabulated and correlation of nodal metastasis with tumor thickness, clinical T-stage, pathological T-stage, vascular invasion, and peri-neural infiltration was evaluated by appropriate statistical analysis method.

## RESULTS

A total of 40 patients of oral carcinoma who had undergone radical surgery with resection of the regional cervical lymph nodes were the subjects of this study. Among these, 33(82.5%) patients were males and 7 (17.5%) patients were females. A total of 22 patients (55%), were in the age range of 31 to 50 years (Figure 1), and the mean age at presentation was 46.07± 12.71years. The youngest patient was 27 years while eldest was 75 years old.
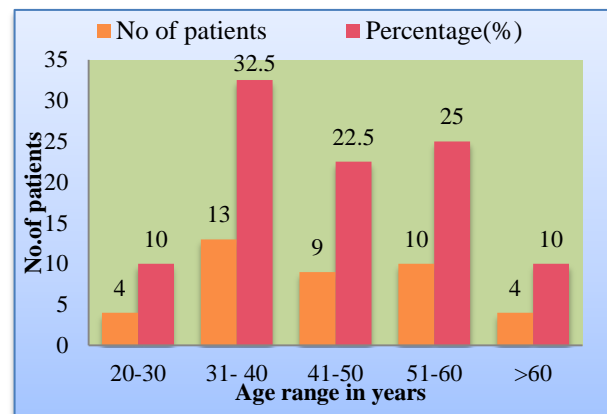


**Figure 1: Age-wise distribution of cases.**

A detailed history was elicited from the patients, who were mostly young adults with a long term history of tobacco usage, regarding the type of tobacco used & the duration of usage.

**Table 1: Distribution of cases according to site of lesion.**

| Site of lesion | No. of cases | | | Percentage (%) |
|---|---|---|---|---|
| | **Right** | **Left** | **Total** | |
| Lateral margin tongue | 5 | 10 | 15 | 37.5 |
| Gingivobuccal Sulcus | 4 | 7 | 11 | 27.5 |
| Retromolar Trigone | - | 5 | 5 | 12.5 |
| Buccal mucosa | 2 | 6 | 8 | 20 |
| Tonsil | - | 1 | 1 | 2.5 |

The lesions were localized to various regions of the oral cavity (Table 1 )with tongue being the most common site of oral carcinoma involvement (15 cases), followed by gingivobuccal sulcus, the lesions being confined more to

the left than right. Consumption of tobacco was seen in all the patients with history of either smoking or smokeless or both (Figure 2).
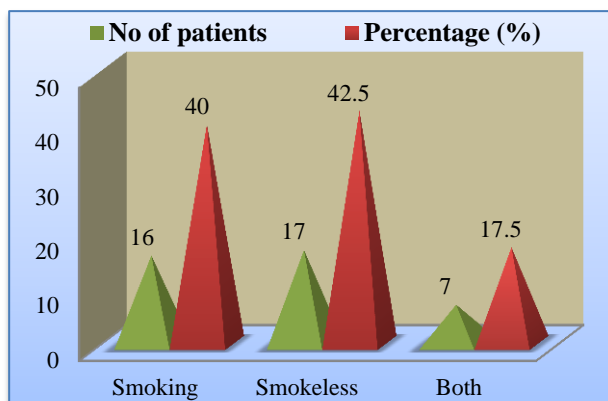


**Figure 2: Distribution of cases according to type of tobacco consumption.**

We also analyzed the duration of usage by the patients, it varied from a minimum of 4years to a maximum of 50years with a mean duration of 16.32±9.70 years. 40% of the patients had history of tobacco abuse between 11-20years. As regards intake of smoking and smokeless tobacco we found an average intake of smoking tobacco was 32.21±11.59/day and smokeless of 5.54±1.17 packets/day.

We also analyzed the type of tobacco consumption and its relation to site of lesion (Table 2), in both smokers and those using smokeless tobacco, maximum number were localized to the lateral margins of tongue.

**Table 2: Distribution of cases according to type of tobacco intake and site of lesion.**

| Site of lesion | No. of cases | | | |
| --- | --- | --- | --- | --- |
| | Smoking | Smokeless | Both | Total |
| Lateral margin tongue | 5 | 7 | 3 | 15 |
| Gingivo-buccal sulcus | 4 | 6 | 1 | 11 |
| Retromolar trigone | 4 | - | 1 | 5 |
| Buccal mucosa | 3 | 3 | 2 | 8 |
| Tonsil | - | 1 | - | 1 |
| Total | 16 | 17 | 7 | 40 |

In all the 40 cases , the gross specimens were carefully examined, tumor dimensions alongwith the maximum tumor thickness was measured. The tumor thickness was obtained by measuring from the surface of the tumor to the deepest point of invasion. Microscopic examination of these 40 cases was done and all of them were

diagnosed as Squamous cell carcinoma, 23cases (57.5%) were well differentiated squamous cell carcinomas with well formed keratin pearls. The histological characterization of the 40 cases and their distribution is depicted at Table 3.

**Table 3: Histological characterization of the cases and their distribution.**

| Type of squamous cell carcinoma (Grade) | No. of cases | Percentage (%) |
| --- | --- | --- |
| Well differentiated (G1) | 23 | 57.5 |
| Moderately differentiated (G2) | 15 | 37.5 |
| Poorly differentiated (G3) | 2 | 5 |

The presence of nodal metastases and the stage of the tumor was assessed in all the cases (Table 4). We found that a maximum number of patients in this study (i.e.25 (62.5%) cases) were in pathologic stage T2, with a tumor size more than 2 cm but not more than 4 cm in greatest dimension.

**Table 4: Distribution of cases according to pathological stage.**

| Pathological stage | No. of patients | Percentage (%) |
| --- | --- | --- |
| pT1N0 | 6 | 15 |
| pT1N1 | 4 | 10 |
| pT1N2 | 2 | 5 |
| pT2N0 | 3 | 7.5 |
| pT2N1 | 7 | 17.5 |
| pT2N2a | 5 | 12.5 |
| pT2N2b | 10 | 25 |
| pT4aN2a | 1 | 2.5 |
| pT4aN2b | 2 | 5 |

The presence/absence of vascular and peri-neural infiltration was evaluated in each case. We found lymphovascular invasion in 8 cases & peri-neural invasion in only 6 cases.

Since our sample size was small and these findings were seen in only 8/40 (20%) and 6/40 (15%) cases, no definitive conclusions could be drawn. The above data was tabulated and correlation of nodal metastasis with tumor thickness was evaluated by the Fisher's exact test method to ascertain the p value of significance. The Fisher's exact test, testing the significance of tumor thickness and metastasis yielded a p-value < 0.05 (p value of 0.0001) (Table 5).

Thus, in this study of oral carcinoma we found that a cut-off of Tumor Thickness of 0.6 cm or greater was associated with regional lymph node metastases, hence indicating that increasing tumor thickness correlates well with increased probability of risk of metastasis to regional lymph nodes.

**Table 5: Distribution of cases according to tumor thickness and metastatic lymph nodes.**

| Tumor thickness (cm) | No. of patients | Cases with metastatic lymph nodes |
|---|---|---|
| 0.5 or less | 5 | 0 |
| 0.6-1.0 | 12 | 10 |
| 1.1-1.5 | 10 | 9 |
| 1.6-2.0 | 7 | 7 |
| 2.1-2.5 | 3 | 3 |
| 2.6-3.0 | 1 | 1 |
| 3.0-3.5 | 2 | 2 |

## DISCUSSION

Oral squamous cell carcinoma (OSCC) is a major public health problem worldwide, with approximately 275,000 cases annually and a strong association with risk factors like smoking.[5-7] Age-adjusted rates of oral cancer in India are high, i.e, 20 per 100,000 population and account for over 30% of all cancers in the country.[1,8] Tobacco use, and in particular smoking, is the largest cause of preventable death among adults in India, as it is globally. Bidi, an indigenous, leaf-rolled cigarette made from coarse sun-cured tobacco, tied with a string at one end, is the dominant form among all smoked products. More than eight to ten bidis are consumed for every cigarette in India. Jha et al in their study estimated that at least 930,000 adult deaths in India could be attributed to smoking in the year 2010 alone and that this figure would continue to rise annually.[9]

Our hospital mostly caters to the residents of the nearby slums and adjoining areas. In the present study of 40 cases, the favored smoking method was bidi and 14 patients were bidi smokers whereas only 2 patient gave a history of cigarette smoking. All the smokers were males. The preferred form of smokeless tobacco was gutka, which was consumed by 17 patients in this study. 15 were gutka (smokeless tobacco) users, of which 9 were males & 6 were females, two males gave history of khaini/surti consumption. Seven patients, 6 males and 1 female respectively gave a history of both smoking & smokeless tobacco use. Hence, we observed a larger number of male smokeless tobacco users in our study. In contrast. a large population based study among tobacco users in Mumbai in which house to house surveys were carried out using voter's lists noted that smokeless tobacco users were mostly women.[10] A study based in Southern India provided strong evidence that smoking bidi is more hazardous than cigarette smoking. Low educational attainment, occupation as a farmer or manual worker and various indicators of poor oral hygiene were associated with significantly increased risk. The study found that among men, 35% of oral cancer was attributable to the combination of smoking and alcohol drinking and 49% to pan-tobacco chewing, whereas among women, chewing and poor oral hygiene explained 95% of oral cancer.[11]

The incidence of occult lymph-node metastasis in early-stage tumors (primary site T-categorization T1 or T2) has been reported to be between 27%- 40%.[12] Also, generally speaking, elective neck dissection (END) is advocated in cases of oral carcinoma when the risk of cervical lymph-node involvement is greater than 15%-20%.[13] Therefore, in any surgical practice there will always be a significant number of patients who having undergone elective neck dissection and will suffer the morbidity of a neck dissection but will be free of nodal metastases. Hence there were a number of studies with the aim of identifying a reliable parameter that would predict regional nodal involvement.

Tumor thickness or depth of invasion was first reported as a prognostic factor in cutaneous melanoma in 1970 by pathologist Alexander Breslow at George Washington University. He established a relationship between the depth of invasion of tumor and the number of lymph nodes being affected with the increase in the depth of the tumor.[14] Tumor thickness (TT) has also been found to be an important prognostic factor in head and neck cancers and an important parameter in the prediction of nodal metastases in oral squamous cell carcinoma. It is now accepted that tumor thickness is a more accurate predictor of nodal metastasis, local recurrence, and survival than tumor size/diameter.[15]

Subsequently there were a number of studies where the concept of tumor thickness was applied to oral carcinoma and tumor thickness has been shown to be a strong independent predictor of cervical lymph node metastases.[16,17] O-charoenrat et al found that tumor thickness above 5 mm is a strong predictor of occult nodal metastases and should indicate an elective neck dissection.[16] Gonzalez-Moles et al, in a similar study evaluated the influence of some clinical and pathologic parameters on survival and suggested that tumor thickness may exercise more influence on the survival rates than factors such as clinical and pathologic staging.[17]

Discrepancy exists over the optimal cutoff point for TT to predict clinical risk of cervical lymph-node involvement. Previous studies have suggested a cutoff point of between 3 mm to 6 mm. Although most studies have confirmed a link between TT and cervical lymph-node involvement, the strength of the association appears to be variable among individual studies. In the present study of 40 cases of Oral Squamous cell carcinoma a cut-off of Tumor Thickness of 0.6 cm or greater was noted to be associated with cervical lymph node metastases.

Differences in results could be attributable to the imprecise definition of TT used between studies. Several ways of defining TT have been used in the previous studies and summarized by Pentenero et al as follows: a) from surface/base of the ulcer to deepest point of invasion; b) from adjacent intact mucosa to deepest point of invasion; c) from basal membrane to deepest point of

invasion.[18] Moore et al found that survival correlated better with TT when measured from a theoretical construction of a basement membrane through the tumor than from the surface of the tumor.[19,20] In a study originating from Tata Memorial Hospital, Mumbai, Kane et al compared depths measured from the surface of a tumor versus from adjacent normal mucosa and concluded that the latter (referred to as microscopic depth) had a stronger correlation with the risk of lymph-node involvement.[20] This was the method adopted in our study for estimation of tumor thickness. It has been suggested that the optimal cutoff point is better determined based on the findings from multiple investigations with a larger cohort.[21] As well, there is significant variation in the selection of subsites of the oral cavity included in the studies. The relationship of lymph-node involvement as a function of TT may vary between subsites because of either potential differences in biologic behavior or the ease with which depth can be determined pathologically between subsites. Limitation of the sample size in this study has restricted us from performing a subanalysis on subsites.

Lastly, while studies may vary according to T and N categories, most are confined to T1 and/or T2 cases. However, considering the impact of various imaging modalities and technical advances over time, we believed limiting the inclusion criteria to early stage clinical N0 cases might introduce bias on the studies reported from different institutions or over different time periods; therefore, we included all clinical T and N categories in this study.

## CONCLUSION

The present pilot study of 40 cases has shown that tobacco addiction, either as a smoking habit or the chewing of smokeless tobacco over a long period of time (ranging from 4 years to 50 years) was associated with the development of Oral Carcinoma. All the 40 cases in this initial study, on histological examination were noted to be Squamous Cell Carcinomas arising in the oral cavity. The tongue was the most common site for the development of squamous carcinoma in those patients who gave a history of smoking as well as tobacco chewing. The buccal mucosa, gingivo-buccal sulcus & the retromolar trigone were the common sites of development of squamous carcinoma among the smokers.

The tumor thickness of Oral Squamous Cell Carcinoma was found to be an important prognostic indicator for the occurrence of metastases to the regional cervical lymph nodes. In the present study, a tumor thickness of 0.6 cm or more was found to be significantly associated with regional lymph involvement by the oral squamous cell carcinoma. Ongoing studies at our centre on oral carcinoma on a larger sample size are underway which will give us a better insight into the pathogenesis of this disease and its relation to risk factors.

## REFERENCES

1. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. The Lancet 2005;365:1927-33.
2. Lozano, R. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. The Lancet. 2012;380(9859): 2095-128.
3. Byakodi R, Byakodi S, Hiremath S, Byakodi J, Adaki S, Marathe K et al. Oral cancer in India: an epidemiologic and clinical review. J Community Health. 2012;37:316-9.
4. Omar EA. The outline of prognosis and new advances in diagnosis of oral squamous cell carcinoma (OSCC): review of the literature. J Oral Oncol. 2013;2013:Article ID 519312.
5. Oliveira AMLC, Wagner VP, Filho MS, Carrard VC, Hugo FN, Martins MD. A 10-year analysis of the oral squamous cell carcinoma profile in patients from public health centers in Uruguay. Braz Oral Res [online]. 2015;29:1-8
6. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45:309-16.
7. International Agency for Research on Cancer. Tobacco smoke and involuntary smoking. IARC Monographs on the evaluation of carcinogenic risk to humans, Lyon, IARC, France 2004;83:53.
8. Coelho BKR. Challenges of the Oral Cancer Burden in India. J Cancer Epidemiol. 2012, Article ID 701932.
9. Jha P, Jacob B, Gajalakshmi V, Gupta PC, Dhingra N, Kumar R et al. A nationally representative case-control study of smoking and death in India. N. Engl. J. Med. 2008;358:1137-47.
10. Gupta PC, Mehta HC. Cohort study of all-cause mortality among tobacco users in Mumbai, India. Bulletin of the World Health Organization. 2000;78(7):877-83.
11. Balaram, P, Sridhar. H, Rajkumar, T, Vaccarella S, Herrero R, Nandakumar A, et al. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int. J. Cancer. 2002;98:440-5.

12. Keski-Santti H, Atula T, Tornwall J, Koivunen P, Makitie A. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. Oral Oncol. 2006;42:96-101.
13. Kowalski LP, Medina JE. Nodal metastases: predictive factors. Otolaryngol Clin North Am. 1998;31:621-637.
14. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Annals Surg. 1970;172:902-8.
15. J A Woolgar. Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. Oral Oncol.2006;42:229-39.
16. O-charoenrat P, Pillai G, Patel S, Ficher C, Archer D, Eccles S, et al. Tumor thickness predicts cervical nodal metastases and survival in early oral tongue cancer. Oral Oncol. 2003;39:386-90.
17. Gonzales-Moles MA, Esteban F, Rodriguez-Archilla A, Ruiz- Avila I, Gonzales-Moles S. Importance of tumour thickness measurement in prognosis of tongue cancer. Oral Oncol. 2002;38:394-7.
18. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck. 2005;27:1080-91.
19. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. Arch Surg. 1986;121:1410-14.
20. Kane SV, Gupta M, Kakade AC, D'Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. Eur J Surg Oncol. 2006;32:795-803.
21. Buettner P, Garbe C, Guggenmoos-Holzmann I. Problems in defining cutoff points of continuous prognostic factors: example of tumor thickness in primary cutaneous melanoma. J Clin Epidemiol. 1997;50:1201-10.