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CORRELATION OF DEPTH OF INVASION OF INCISIONAL BIOPSY SPECIMEN WITH LYMPH NODE STATUS OF ORAL SQUAMOUS CELL CARCINOMA PATIENTS- A RETROSPECTIVE STUDY

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ABSTRACT
Background: Depth of invasion of the tumour (DOI) is an important prognostic factors and elective neck dissection can be made based on the depth of invasion of the primary tumor. Aim of the present study is to scientifically analyse the correlation between DOI of incisional specimen and nodal status.
Materials and methods: n=20 incisional biopsy specimens of oral squamous cell carcinoma cases were included and the histopathological depth of invasion and the lymph node status of the excision biopsy were assessed by two independent pathologists using Magcam vision software and transported to IBM- SPSS for statistical analysis.
Result: Low to moderate depth of invasion was observed in 40% of the cases. Only 20% of the cases showed high(>6mm) depth of invasion. Metastasis was present only in 15% of the cases. The correlation between DOI and lymph node metastasis status was not statistically significant with p value of 0.071(Pearson Chi-square test).
Conclusion: Extensive version of this preliminary study with increased sample size and proper sampling technique will help to analyse this lacuna more precisely. Predicting the possibility of nodal involvement from incisional biopsy depth of invasion can be a great advantage for the better surgical management and prognosis of the patient.

Keywords: Depth of invasion, Incisional biopsy, Lymph node metastasis

INTRODUCTION

According to GLOBOCAN 2020, the number of new cases and death rate due to lip and oral cavity cancer in the world is 377,713 and 177,757 (1). In India, around 77,000 new cases and 52,000 deaths are reported due to oral cancer annually, which is around one-fourth of the global incidence (2). The most common risk factors for developing oral cancer are tobacco chewing and alcohol consumption (3). The incidence of oral cancer in the developing Asian countries like India, Sri Lanka and Thailand are due to the increased rate of tobacco chewing with or without betel quid (4).

Prognosis is the prediction of the course of a disease and it plays a very important role in the survival rate of the patients(5). Several prognostic factors like tumour size, pattern of invasion, depth of invasion and inflammatory cell infiltrate have been used for predicting the outcome of oral squamous cell carcinoma (6). Among which, depth of invasion of the tumour (DOI) is proven to be one of the most important prognostic factors in oral squamous cell carcinoma (OSCC) and it has been included in the American Joint Committee on Cancer staging manual(8th edition) (6). Depth of invasion is the distance from the deepest level of invasion to the basement membrane level of adjacent normal mucosa(7). The recommendation for elective neck dissection can be made based on the depth of invasion(DOI) of the primary tumor (8). Many studies are available in literature, validating depth of invasion as a main prognostic factor and analysing the correlation between nodal status and DOI of the main specimen in OSCC. The depth of invasion is one of the most reliable histopathological parameter which is quantifiable and the inter-observer discrepancy will be considerably minimum when compared to other prognostic parameters like pattern of invasion and tumour budding. Arriving at an idea regarding the lymph node metastasis from the depth of invasion of the incision biopsy specimen can

aid in the treatment planning. The incision biopsy is superficial and does not represent the actual depth of invasion of the tumour in the centre of the lesion. Though the association between nodal status and DOI in excisional specimens is well established, predicting the nodal status based on the depth of invasion of incisional biopsy specimens is a totally new and less explored concept by researchers and can have a great impact on surgical treatment of the patient. Apart from this, the association between nodal status and DOI of incisional specimens has not been proven scientifically. Hence this is the first study of that kind to scientifically analyse the correlation between nodal status and DOI of incisional specimens.

MATERIALS AND METHODS

This study was conducted with approval from the institutional ethical committee and the present study have included n=20 cases of oral squamous cell carcinoma cases reported to the department of oral and maxillofacial pathology who underwent incisional biopsy, excision of the tumour and neck dissection.

The demographic and clinical details of the selected cases were retrieved from the histopathology reports and common clinical database. The sampling method applied for the current study was random sampling. Histopathologically confirmed cases of OSCC were included and cases with questionable and nonspecific histopathological diagnosis were excluded from the present study. H/E slides of the selected cases were retrieved from the archives of the oral pathology department. Histopathological depth of invasion of the incision biopsy and the lymph node status of the excision biopsy were assessed by two independent pathologists using Magcam vision software. Depth of invasion was measured from the basement membrane of the adjacent normal mucosa to the deepest level of invasive front of tumour. The criterias for grading the depth of invasion of OSCC is explained in Table 1 (Table 1).

DOI	**Interpretation**
Less than 2mm	Low
2-6 mm	Moderate
Greater than 6 mm	High

Table 1 showing criteria of grading of Depth of invasion in OSCC cases.

Depth of invasion of incisional biopsy and the lymph node status of the excisional biopsy were tabulated in MicroSoft Excel sheets and later exported into IBM SPSS software for statistically analysing the data. Pearson Chi-square test was performed to analyse the association between the depth of invasion of incisional biopsy and the lymph node status of excisional biopsy.

RESULT

This preliminary study included 20 oral squamous cell carcinoma cases,in which 80% of the cases were well differentiated squamous cell carcinoma and 20% were moderately differentiated squamous cell carcinoma. 37.8 % of the cases are from right and left buccal mucosa followed by 35 % from gingivobuccal sulcus and 19.8 % from tongue and rest from other sites.

Low(<2mm) (40%) and moderate(2-6mm) (40%) depth of invasion was observed in 80% of the cases. Only 20% of the cases showed high(>6mm) depth of invasion (Figure 1).

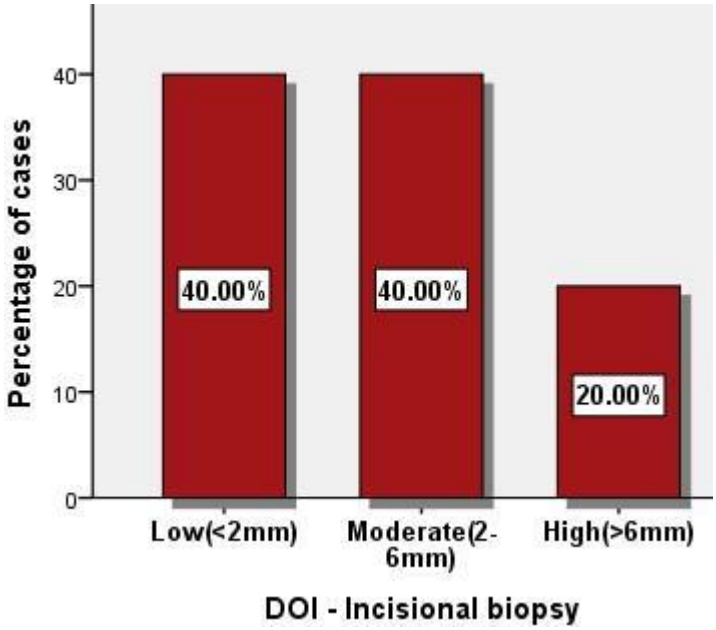

Figure 1: Bar graph showing the distribution of depth of invasion among the selected OSCC cases.

Metastasis was present only in 15% of the cases, with all the cases with positive metastasis, the common site is level1B and in 11% of the cases there was involvement of the level III by skipping levels. (Figure 2).

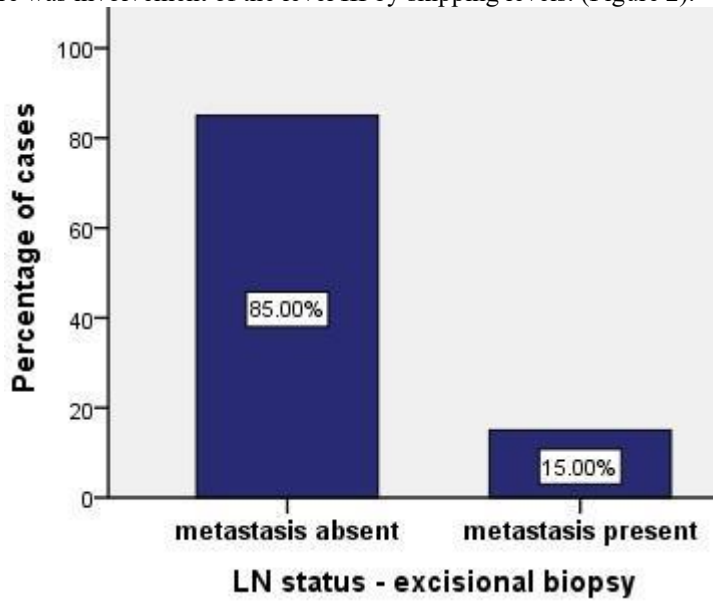

Figure 2: Bar graph showing the percentage of lymph node metastasis among the selected OSCC cases.

Lymph node metastases were absent in cases with low(<2mm) depth of invasion (Figure 3). Out of the 40% of cases with moderate depth of invasion (Figure 4), 5% of the cases showed lymph node involvement. Among 20% of cases with high depth of invasion (Figure 5),10% showed lymph node involvement The correlation between DOI and lymph node metastasis status was not statistically significant with p value of 0.071(Figure 6).

Figure 3: Photomicrograph showing OSCC case with depth of invasion less than 2mm measured using Magcam software (H and E staining, 10 X magnification)

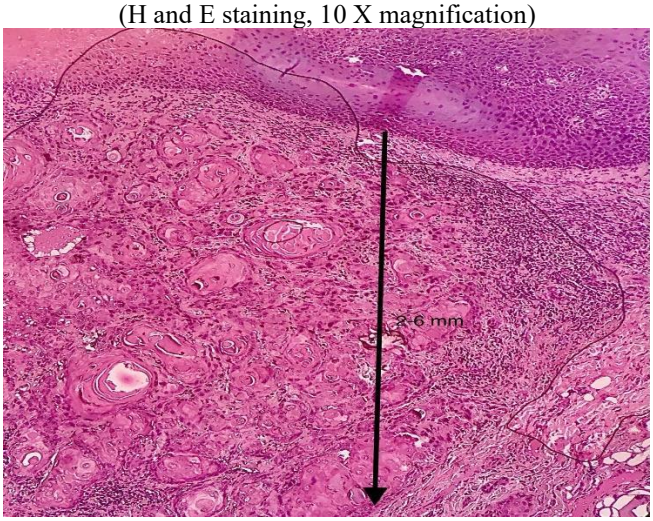

Figure 4: Photomicrograph showing OSCC case with depth of invasion 2-6 mm measured using Magcam software (H and E staining, 10 X magnification)

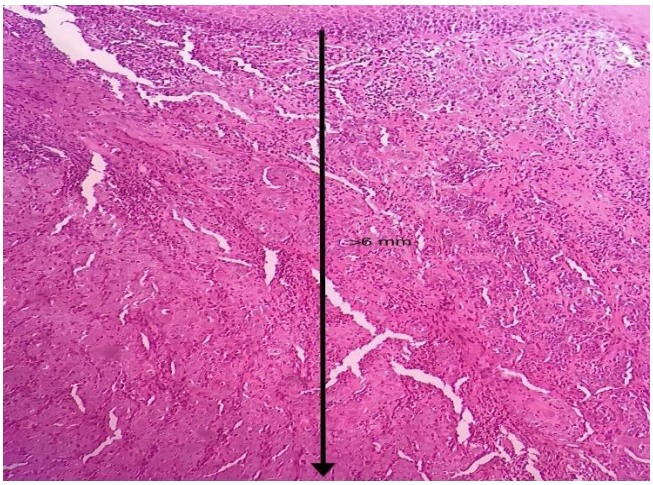

Figure 5: Photomicrograph showing OSCC case with depth of invasion more than 6 mm measured using Magcam software (H and E staining, 10 X magnification)

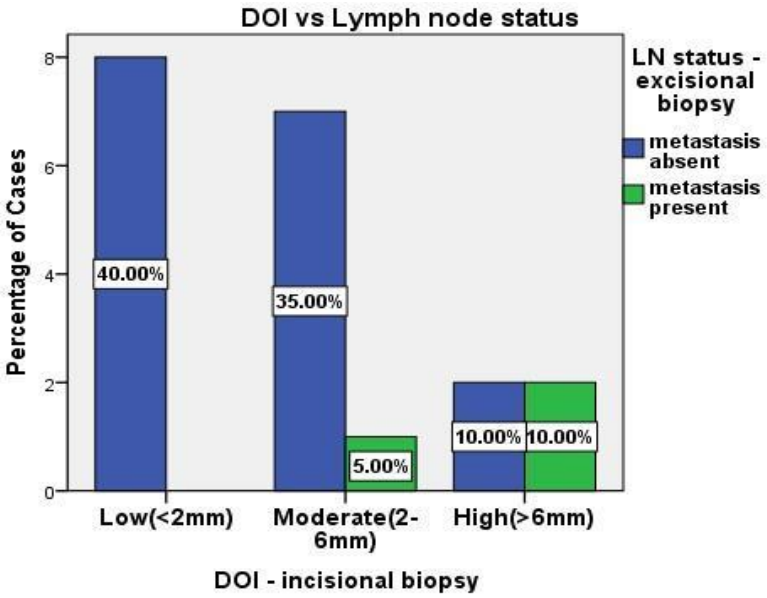

Figure 6: Bar graph showing association between DOI and Lymph node metastasis among selected OSCC cases. The percentage of lymph node metastasis is higher in cases with High depth of invasion. Chi-square test (p= 0.071).

DISCUSSION

Oral squamous cell carcinoma (OSCC) is the 6th most common cancer and accounts for approximately 5% of all types of malignancies(9).Oral squamous cell carcinoma (OSCC) is frequently associated with poor prognosis and despite all the advancements in treatment, the 5 year survival rate of the patients affected with OSCC is approximately 50%(10, 11).The common site for metastasis in OSCC is cervical lymph nodes and each type of primary squamous cell carcinoma of the oral cavity commonly metastasizes to a particular group of cervical lymph nodes(12). Several studies from literature showed that the occurrence of lymph node metastasis in patients with OSCC can be a reason for reduction of the survival rate (7,14,15). The surgical decision on neck dissection is dependent on the primary tumour site and various prognostic factors like pattern of invasion, tumour budding and depth of invasion(7,13).

Literature review showed the differences in primary tumour site is also an important factor which determines the DOI and tumour metastasis to lymph nodes(14). Several other studies have also suggested that the clinically less aggressive T1 and T2 lesions of OSCC also carries a high risk of cervical lymph node metastasis. Some selective studies have showed the histopathological involvement of multiple lymph nodes in cases with no clinical lymph node involvement(15). Hence the management of oral cancer remains controversial even in the current era. However several researches have been conducted in the area of histopathological assessment of primary oral cancer and its various prognostic factors like DOI, pattern of invasion, tumour budding and inflammatory cell infiltrate(16, 17).

According to the American Joint Committee on Cancer Classification (AJCC) 8th edition, DOI is measured from a plane at the level of the basement membrane of the adjacent normal mucosa to the deepest point of tumour invasion in the connective tissue(18). According to the National Comprehensive Cancer Network (NCCN) guidelines, the neck dissection is performed along with the excision of the primary tumour if the DOI is greater than or equal to 4 mm(19). Significant studies on DOI and its prognostic importance in oral cancer are limited due to improper histopathological measuring methods and hence the lack of a precise reference level of DOI for predicting the need for surgical neck dissection is also diminished (19).

In the present study, the depth of invasion in the incisional biopsy specimen of primary tumour and the nodal metastasis status of the same patient after excisional biopsy of primary tumour and neck dissection has been compared. However, there are several studies evaluating the association of depth of invasion of primary tumour in excision biopsy specimen and nodal metastasis, the present study is unique in such a way that it analyses the association between incisional biopsy depth of invasion and nodal metastasis status. Among the selected cases lymph node metastasis was present in 15 % of the cases and this could be attributed to the random sampling method. The combined percentage of cases with DOI less than 2mm and 2-6mm was 80% and DOI more than 6mm were found in 20% of the cases only. This could be due to the early detection and commencement of treatment in most of the oral cancer cases and random sampling technique used.

Lymph node metastasis was more commonly seen in cases with increased depth of invasion when compared to low depth of invasion. Even though this association was not statistically significant(p=0.071), similar observations were also reported by van Lanschot et al, Brockhoff HC et al and Melchers LJ et al (19, 20, 21). Increased depth of invasion in cases with positive lymph node involvement can be explained by several other factors. One of the most studied reason is he conversion of fibroblasts to myofibroblasts (22). CAF-mediated ECM remodelling provides a supportive microenvironment for tumour cell migration and dissemination (22). Li Y Y et al established that the increased depth of invasion is associated with increased distribution of CAF in the stroma (23). This could be attributed to CAF induced remodelling of extracellular matrix, epithelial mesenchymal transition (EMT) and induction of motile phenotypes

(22). The extracellular matrix factors, Hyaluronic acid (HA) produced by CAF, plays a significant role in the migratory interactions of CAFs and inducing motile phenotypes in tumour cells and this further helps in dissemination of tumour cells (23).

However, limited sample size, random sampling and less representation of the precise depth of invasion in incisional biopsy, subjective errors in measuring depth of invasion are the main limitations of the current study.

CONCLUSION

The present study couldn't establish a statistically significant correlation between the incisional biopsy DOI and lymph node metastasis status. However, an extensive version of this study with increased sample size and proper sampling technique will help to analyse these lacunae more precisely. Accurately predicting the possibility of nodal involvement from incisional biopsy depth of invasion can be a great advantage for the better surgical management and prognosis of the patient.

CONFLICT OF INTEREST

None declared

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