

Histopathological evaluation of the correlation of depth of invasion and the nodal metastasis – A pilot study in south indian population

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ABSTRACT

Introduction: Oral squamous cell carcinoma (OSCC) is unpredictable lesion and thus has a marked variation in prognosis, which is probably due to the function of many variables related to biological behaviors of primary lesion. **Aim:** The aim of the study was to find the correlation between the depth of invasion (DOI) and the nodal metastasis and to explore the risk of occult neck nodal metastasis and local recurrence in relation to depth in early stage squamous cell carcinoma of tongue. **Materials and Methods:** We have retrieved records of the OSCC patients retrospectively for the past 2 years. The DOI for 30 excision specimens was measured using the magna software. Measurement was done by experienced pathologists in millimeters. **Results:** In our study, we have found that DOI above 6 mm was established in 80% and developed nodal metastasis with 13.33% had recurrence. **Conclusion:** DOI is studied in a smaller number of Indian studies, but with the increase in the multifactorial etiology in the Indian population, we suggest that there is a discerning point at 5 mm of tumor depth at which cervical metastasis is probable. Therefore, the DOI is found to be an important prognostic marker in OSCC.

KEY WORDS: Depth of invasion, Oral cancer, Prognosis, Squamous cell carcinoma

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a complex malignancy, in which genetic alterations, environmental factors, and other risks extensively interact and thus lead to the neoplastic condition.^[1] Malignant potential of OSCC is closely associated with local expansion and lymph node metastasis.^[2]

Neck metastasis is the most important prognostic factor in head and neck SCC.^[3,4] Classically, neck dissection has been divided into therapeutic, when it treats lymph node metastases found during physical examination or imaging studies opportune, when the approach for exposure and resection of a malignant primary tumor is through the neck; elective, when lymph node compromise is not found clinically or by imaging, but the risk of microscopic metastases is higher than the risk associated with addition of a surgical procedure and its morbidity.^[5]

If the probability of neck metastases is low or nil, neck dissection simply acts as an overtreatment, where the morbidity of the neck procedure only offers a decrease in quality of life and functional deficits. In principle, the indication of neck dissection in oral cancer is a problem of risk-benefit evaluation between the probability of neck metastases, the probability of complications associated with neck dissection, and the possible prognostic influence of late diagnosis of metastasis during follow-up.^[6,7] Recently, it has been found that mode of invasion, pattern of invasion (POI), and tumor budding also plays an important role as a predictive marker for nodal metastasis.^[8]

The tumor, node, and metastasis (TNM) classification of OSCC provides a reliable basis for patient prognosis and therapeutic planning, but it does not completely efficient, many patients die despite the fact that their primary neoplasms were considered clinically to be detected or small undetectable or early cases (Stage I or Stage II) and were treated accordingly.^[9,10] Several studies had shown that the TNM staging system is not

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a sensitive indicator for the occurrence of lymph node involvement in OSCC.^[11-15]

To identify patients who are likely to have nodal metastases, several parameters such as tumor differentiation, perineural invasion, lymphovascular invasion, POI, and depth of invasion (DOI) have been previously studied.^[16,17] According to previous studies on OSCC, it has been shown that POI, tumor size (T), and stage are important parameters in predicting nodal metastasis.^[18]

DOI is considered as an objective parameter and has been evaluated by several investigators for OSCC. Although most authors substantially agree that DOI is an important parameter for nodal metastasis and survival, the results vary in the literature and there is no cutoff point to prompt neck dissection.^[19]

The aim of the study is to find the correlation between the DOI and the nodal metastasis and to explore the risk of occult neck nodal metastasis and local recurrence in relation to depth in OSCC.

MATERIALS AND METHODS

Thirty formalin fixed paraffin embedded tissue blocks of the core specimen of excision specimens were obtained from the archives of the department of oral and maxillofacial pathology. The inclusion criteria of the study included cases of excision cases of OSCC and cases with excision of the lymph nodes.

Staining Protocol

The sections were deparaffinized using Xylene for 20 min and rehydration was done using alcohol for 10 min. Sections were washed in running tap water for 3–5 min and were stained with Harris's hematoxylin for 5 min, washed in running tap water; differentiation was achieved by dipping the slides in acid alcohol for one dip, then dipped in ammonia for one dip, and washed in running tap water for bluing. Slides were transferred to eosin for a single dip after which the slides were dehydrated through descending grades of alcohol; the slides were cleared in xylene and mounted with dibutyl phthalate in xylene.

Data Collection

The slides were viewed under the microscope by two independent blinded observers and the DOI was noted and tabulated. The DOI was measured using the magna software, and the patient's information was recorded using the patient records. Measurement was done by experienced pathologists in millimeters.

RESULTS

The majority of the patients were male (57%) and the mean age was around 53.61 years. In addition,

more than half of the patients had SCC of the buccal mucosa followed by lateral border of tongue. About 79% of the patients had well differentiated SCC. Furthermore, DOI above 6 mm was established in 80% and developed nodal metastasis and 13.33% had recurrence.

DISCUSSION

Since late 1800s, radical neck dissection was performed to avoid cancer recurrences even though it caused significant post-operative complications such as shoulder dysfunction. In 1980s, more selective neck dissections were performed where the lymph nodes which drained the primary site of the tumor were removed. However, sometimes it results in shoulder dysfunction despite of how conservative the management is.^[19] Multiple factors can affect the rate of cervical metastasis and survival from oral cavity cancer including size of the primary tumor, site, T stage, grade, DOI, biological tumor markers, perineural invasion, and patient compliance.^[9,20] Therefore, many prognostic models were devised to determine the extent of spread of the metastasis, earlier the tumor width and the site were considered to be the main prognostic factors. Recently, the DOI of a tumor is been given importance.

“DOI” means the extent of cancer growth into the tissue beneath an epithelial surface. In cases, in which the epithelium is destroyed, some investigators reconstruct a surface line and measure from this line. However, the DOI is sometimes expressed by referring to the microscopic, anatomic deep structures that are reached, rather than by referring to objective micrometer measurements in millimeters.^[21-24]

In our study, we have found the DOI of the excisional specimens and have correlated with the nodal metastasis to prove a POI and concurrent nodal metastasis. The mean age in present study was 53.61 years. Similar findings found in another studies, where mean age of patients was 52.6 years and 59.5 years, respectively.^[25] The most common site of tumor being the buccal mucosa followed by the lateral border of tongue. Many studies have reported predominance of carcinoma tongue in males as seen in our study. This is due to the fact that Indian males are exposed to smokeless and smoked tobacco. But recently, there are a number of cases that have been reported without any previous history of habits which may lead to the development of oral cancers including tongue.

In our study, we have found that in 53% of the cases the most commonly affected node is Level I-B and in 21% of the cases Level III node is affected. Previous studies have proven that there is infiltration of Level III nodes in cases of OSCC of the lateral border of tongue; our findings have been consistent to the other studies.

It was observed that the cutoff point is most strongly associated with neck metastasis when, DOI exceeding 5 mm and was noted in 100% of the cases, thus, DOI may be useful for predicting the occult cervical lymph node metastasis. There are similar studies which shows the most common site of involvement Level II followed by level III node in case of carcinomas of the lateral border of tongue.

Table 1 shows the DOI and the levels of nodal metastasis, it was noted that beyond 10 mm the tumor cells cross the Level I cervical nodes and beyond 15 mm the tumor cells traverse through all the levels of the cervical lymph nodes.

The DOI is considered as an important marker in the metastatic status and the prognosis. This is due to the fact that the deeper the tumor islands are found into the connective tissue the closer it is near the blood vessels and lymphatics. The proximity to blood vessels and lymphatics is what determines an increased risk of nodal metastases as it facilitates the tumor's ability to expand.^[21] The DOI is a marker to show the proximity of the tumor cells to the lymphatics and thus reach other sites, leading to the metastasis of the tumor and worse prognosis for the individual.

O-charoenrat *et al.* have used 5 mm as cutoff and demonstrated that 5-year survival was 95% with tumor thickness of 5 mm and 30% when tumor thickness was >5 mm recommended by AJCC, cancer staging manual, 2017. With increasing DOI particularly >10 mm, there is significantly increased risk of occult nodal metastasis (53%) and decrease in 5-year survival to 45%.^[26]

Therefore, it would be better to take into consideration the actual mass that is present beneath the theoretical reconstruction of a basement membrane (DOI) rather than the thickness of the entire tumor.^[21]

In India due to various factors including the use of tobacco, genetic reasons and epigenetic changes, the prevalence of OSCC has been on the rise. Recently, many cases of OSCC have been reported with no habits in relation to the individuals affected. And thus, newer methods of diagnosis, treatment, and prognostic markers are being studied on.

Our study is based on the fact that the DOI of a tumor can be used as a prognostic marker. Our study is first

Table 1: Correlation between the depth of invasion and the nodal metastasis

Depth of invasion	Nodal metastasis
<1 mm	Nil
1 mm–5 mm	Nil
6–10 mm	Single node involvement-Level I
11–15 mm	Level I involvement
>16 mm	Level I, II, and III involvement

of its kind, where the DOI of the tumor is compared to the nodal metastasis in a South Indian population.

DOI also has its own limitations; in some cases, it is difficult to determine the DOI, especially in cases with perineural invasion. Many authors also pointed out some of the problems related to measuring tumor thickness, the main one being the difference in complexity when measuring thickness in mucosal tumors, where there is often no mucosal surface on the slide to use as a reference point.^[21] Another limitation is that it was noted that lack of standardized method of measuring tumor thickness/DOI has resulted in different cutoff values to decide elective neck dissection for clinically negative neck.^[19] In spite of these limitations, it is clear in our study that there is a correlation between the DOI and the nodal metastasis, which would give us newer insights into planning the treatment of the patients.

CONCLUSION

DOI was found to be a predictor for cervical nodal metastasis. Our study is first of its kind in south Indian population and we have postulated that DOI >5 mm to be significantly associated with and increased risk of occult metastasis. At the same time, depth <5 mm is not often seen with nodal metastasis and elective neck dissections should be considered.

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