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REVIEW ARTICLE

Frequency of Skip Metastases in Oral Cancer: An Overview

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ABSTRACT

Globally, over 3,00,000 people are diagnosed with oral cancer every year and it is considered as 8th most common malignancy worldwide. However, there is geographical variation; oral cancer being the 3rd most common in South East Asia which is 25 per 1,00,000 per annum. In the Indian subcontinent head and neck cancer accounts for 45% of all malignancy with oral cancer being the most common, accounting for 1/3rd of all cancers. Increasing number of head and neck cancer cases is a cause of major concern as it is associated with high morbidity and mortality. If oral cancer is detected early when confined to the mucosa only, the 5 years survival exceeds 80%. However, it drops to 40% in presence of regional metastases and to 20% in the presence of distant metastases. The prognosis worsens as the growth involves proximal to distal. Current knowledge of neck node metastases with special emphasis on skip metastases in oral cancers is discussed.

Keywords: Lymph nodes, Neck dissection, Oral cancer, Skip metastases.

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INTRODUCTION

Lymphatic spread is the usual pattern of metastases in case of oral cavity cancer. Cervical lymph node metastases is the single most important prognostic factor in head and neck cancer patients. A typical metastatic pattern is defined as the orderly involvement of successive anatomical nodal levels, i.e. submental nodes (IA), submandibular nodes (IB), upper jugular nodes (II), middle jugular nodes (III), lower jugular nodes (IV) and posterior cervical nodes (V) in the order described.

When the above-described order is lost and metastases is found in a higher level without involvement of the first echelon node or an intermediary node group then it is called skip metastases. The proper knowledge of skip metastases will enable a surgeon to avoid under treatment.[1]

The development of an erratic distribution of cervical metastases (skip metastases) bypassing the upper neck levels (levels I and II) and going directly to level III and/or IV challenges the role of supraomohyoid neck dissection in the treatment of oral cancer. In this setting, knowledge of the pattern of lymphatic spread for intraoral site is a crucial element to plan a proper management strategy of the neck. The ignorance of skip metastases will lead to incomplete clearance of the malignancy.[2]

According to the Memorial Sloan-Kettering Hospital, within the neck, which six groups of lymph nodes are recognized (levels Ia, Ib, IIa, IIb, III, IV, Va, Vb, VI). Oral cavity has a wide area of drainage and this is important because there is often free communication between two sides of the tongue; the posterior part of oral cavity either drains directly into upper deep cervical node level II/III, or indirectly *via* submandibular node level lb, more anterior part of oral cavity and tongue also drain to these nodes, but, in addition, may drain to submental nodes level Ia, or directly into jugular nodal chain, level II to IV. The tongue especially is known to cause 'skip metastases' to level IV.[3]

Mechanism of lymphatic invasion of tumor cells includes three molecular events are as follows:

1. Cellular adhesion molecule, E-cadherin downregulated, making cancer cells free to migrate.
2. Integrin provides adhesion receptor linkage between cell cytoskeleton and extracellular matrix.
3. Active migration of cancer cells in lymphatics is driven by production of autocrine and paracrine cytokines. Tumor cell homing to lymph node is probably mediated by L-selectine, a migratory cell-cell interaction molecule.[3]

The presence of regional lymph node metastases acts as an indicator of the ability of primary tumor to metastasize locally and to distant sites, rather than acting as an instigator of distant metastases on their own. This is because lymph node involvement indicates a host response. Therefore, the degree of lymph nodes involvement should be regarded as an indirect index of systemic tumor burden.[3]

Pattern of metastatic involvement of various lymph node regions usually progresses from superior to inferior

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in an orderly pattern, but it has been shown that in some situations lymph node group can be bypassed, leading to skip metastases.[3]

ETIOLOGY

Various factors have been blamed as the cause of oral cavity cancer namely:

- *Cigarette smoking*: Compared with persons who do not smoke, the risk of oral cancer in persons who smoke low/medium-tar cigarettes and high-tar cigarettes is 8.5- and 16.4-fold greater, respectively.
- *Alcoholic beverages*: May contain carcinogens or procarcinogens, including nitrosamine and urethane contaminants and ethanol. Ethanol is metabolized by alcohol dehydrogenase and, to some extent, by cytochrome P450 to acetaldehyde, which may be carcinogenic.
- *Betel nut and similar habits*: The betel quid contains a variety of ingredients, including betel vine leaf, betel (areca) nut, catechu and often, slaked lime together with tobacco. Some persons chew the nut only and others prefer paan, which includes tobacco and sometimes lime and catechu. In 1986, the International Agency for Research on Cancer has deemed betel-quid chewing an important risk factor, and the areca (betel) nut habit with or without tobacco use can cause cytogenetic changes in oral epithelium. Various other chewing habits, usually combinations that contain tobacco, are used in different cultures, (e.g. Qat, Shammah and Toombak). Tobacco chewing by people from parts of Asia appears to predispose to oral squamous cell carcinoma (OSCC), particularly if it is started early in life and is used frequently and for prolonged periods. Studies from India have confirmed the association between paan tobacco chewing and OSCC, particularly cancer of the buccal and labial mucosa.
- *Diet*: A significant protective effect of diet against oral cancer has generally been shown in persons who consume beta-carotene-rich vegetables and citrous fruits.
- *Mouthwash use*: The effect of the alcohol in mouthwash appears to be similar to that of alcohol used for drinking although the contribution of mouthwash use to oral cancer must be small in terms of attributable risk. This controversy continues.
- *Socioeconomic status*: Behaviors that lead to social instability itself have been linked to an increased risk of oral cancer.
- *Infective agents*: *Candida albicans* and viruses, such as herpes viruses and *Papilloma* viruses, may be implicated in some cases.
- *Others*: There is association between oral cancer and various oral conditions (oral submucous fibrosis, oral lichen planus, lupus erythematosus, dyskeratosis congenita and Fanconi anemia).[4]

INCIDENCE

Oral cancer is one of the most common cancers in the world, with approximately 2,74,300 new cases and 1,27,500 deaths occurring each year. Two-third of those cases occur in developing countries and the majority are over the age of 40 years at the time of diagnosis. The highest incidence has been observed in the Indian subcontinent. Indian studies have reported male:female ratio to be 4.7:1.[5-7]

Madani et al observed that oral cancer was three times more common in urban as compared to rural poulation.[8]

Mishra et al reported site distribution 42, 23.5, 13.5, 12.3, 5 and 3.7% of tongue, buccal mucosa, floor of mouth, lower alveolus, retromolar trigone and lip cancer respectively.[7]

Dias et al showed incidence of occult neck disease, 17.4% in stage I and 27.6% in stage II of OSCC patients.[2] Kim et al observed occult metastases in 15% cases out of which 26.3% in T2 patients and 12.5% in T4 cases.[9] Deo et al reported, 20.5% cases in N0 group had occult neck secondary.[10] The rate of occult neck secondary was 17.6 and 23% in early and advanced T stages respectively.

Jamsed et al analyzed a total of 1056 cervical lymph nodes. The number of nodes in levels I, II, III, IV and V was 261, 295, 230, 250 and 20 respectively. The result was 53% (16/30) of the patients had positive cervical nodal disease. The distribution of positive nodes in neck was 40, 40, 20, 10 and 0% in level I, II, III, IV and V respectively.[4] Deo et al has reported, Level I was the most common level involved in pN+ group (67.8%). Level II was involved in 17.5% of pN+ patients. The overall involvement of level IV and V was 9.4 and 4.7% respectively.[10]

Magremanne et al showed metastases of 30% in their study.[11] Balasubramanian et al observed an incidence of 32.6% metastases in oral tongue cancer.[5] Pandey et al reported a incidence of 36%.[12] Nithya et al has reported a incidence of 44% of metastases to neck nodes in tongue cancer.[13] Woolgar et al diagnosed metastatic disease histologically in 47 (45%) out of the 104 patients.[14] Berg et al reported that incidence of lymph node metastases in patients with squamous cell carcinoma (SCC) of the oral cavity was 20 to 30%.[15] Deo et al reported that 37.2% had positive lymph nodes on pathologic analysis of the neck dissection specimen (pN+).[10]

Stage, Histopathology and Grade of Primary Tumor

Important prognostic indicators that are known to affect regional metastases and therefore outcome include size of

primary tumor, site, grade, depth of invasion, perineural invasion, biological tumor marker and patient compliance.

In studies done thus far, the commonest histological variants of OSCC have been moderately differentiated squamus cell carcinoma (MDSCC) followed by Well differentiated squamous cell carcinoma (WDSCC) followed by poorly differentiated squamous cell carcinoma (PDSCC).[16] Previous study reported 48% of MDSCC, 32.8% of WDSCC and 19.2% of PDSCC.[17] Beenken et al reported 60.9, 32 and 7.1% of WDSCC, MDSCC and PDSCC respectively in his study.[18]

Deo et al reported 74% of patients in their study presented in an advanced stage (stage III and IVA) of the disease.[10] The largest contributing factor to delay in treatment of head and neck cancers continues to be patient driven, with the average delay of 3.5 to 5.4 months. The average professional delay is approximately 14 to 21 weeks.[19]

Nithya et al reported 13, 33, 15 and 14% of cases for T1, T2, T3 and T4 stage and 41, 26, 6 and 2% for N0, N1, N2b and N2c nodal stages.[13]

Balasubramanian et al reported 46, 36.5, 15.3 and 2% of their cases for T1, T2, T3 and T4 stage and 67.2, 25 and 3.8% in N0, N1 and N3 stages.[7] Lodder has reported 12.5, 49, 23.5, 28% of stage T1, T2, T3 and T4 cancer and 63.5, 24, 23 and 2.5% of N0, N1, N2 and N3 stages.[1]

The 'T' stage of a tumor is an accepted prognostic and therapeutic indicator. Mishra et al reported the rate of metastases in relation to T stage was 20.8% with T1 stage, 41.4% with T2 stage and 75% with T3 stage.[9] Deo et al reported metastases of 33.3 and 44.7% in early (T1 and T2) and late T stages (T3 and T4) respectively.[12]

Study of patients with cancer of anterior tongue showed that a tumor thickness greater than 5 mm was the only predictor of recurrence in the regional nodes.[20] It has been shown that threshold was breached for tumors with thickness of 2 to 4 mm depth of invasion and then LN are at risk of metestasis.[21] Ajith et al reported, treatment of neck nodes in early (T1, T2) cancer of the oral tongue can be expectant in cases where tumor thickness is less than 04 mm, but where it is more than 04 mm elective treatment of the neck is recommended.[22] Even T1, and tumor thickness >2 mm are risk factors for occult neck metastases.

DIAGNOSIS OF METASTATIC LYMPH NODES

Lodder et al showed sensitivity of clinical staging of 81% and specificity of 91%.[1] Deo et al reported the sensitivity of clinical examination for detection of neck nodes as 86.7%, but the specificity was 30.5%.[10] However, clinical examination is unreliable for detection of nodes and incidence of occult nodal metastases even in early oral cancer varies from 16 to 40% in tongue cancer.[23] Computed tomography (CT) has a sensitivity varying from 55 to 95% and a specificity of 39 to 96% for assessing neck node metastases.[23] Woolgar et al reported CT scan with sensitivity and specificity of 49 an 87% respectively and clinical examination 49 and 87% respectively.[14]

Rassekh et al in 79 patients found sensitivity of 41% and specificity of 57% in N0 patients assessed intraoperatively.[24] Finn et al analyzed 34 patients in whom surgeons had divided lymph nodes, intraoperatively, into clearly benign, clearly malignant and suspect and correlated the clinical impression and pathological results. Sensitivity of macroscopical evaluation was 56% and specificity was 70%.[25] Wein et al in study of 36 patients, with biopsy of suspicious lymph nodes, found a sensitivity of 41% and specificity of 100%.[26]

SKIP METASTASES

One of the most important prognostic factors in head and neck cancer is the presence or absence, level and size of metastatic neck disease. There are about 150 lymph nodes on either side of the neck with the normal size varying from 3 mm to 3 cm, but most nodes are less than 1 cm in size. The oral cavity has a wide area of drainage and this is important because there is often free communication between the two sides of tongue. This means that normal acts of mastication and swallowing facilitate tongue massage and can promote both early and rapid lymphatic spread directly to low in the neck. The posterior parts of oral cavity drain directly to upper deep cervical nodes or indirectly via submandibular lymph nodes. More anterior parts of oral cavity and tongue also drain to these nodes but in addition, may drain to the submental nodes or directly to the jugular nodes. The tongue is especially known to cause 'skip metastases' to level IV. The region specific drainage translates well into clinical practice and it is possible to predict the site of a primary tumor based on the distribution of cervical metastases and *vice versa*.[27]

According to study of Balasubramanian et al, objective nodal metastases from oral tongue SCC follows a predictable pattern. Isolated level IV involvement called skip metastases may be present. Their study included 52 consecutive patients with T1 to T4 N0 stage who underwent excision of the primary tumor with neck dissection (level I–IV). The incidence of isolated level III or IV involvement pathologically and isolated nodal recurrence in level III and IV were analyzed. Pathologically isolated level III involvement occurred in two (3.8%) patients. Isolated level IV occurred in 1 (1.9%) patient. Mean follow-up was 24 months. Two patients had recurrence in the primary site; one had recurrence in neck level II. None

had recurrence in level III or of level IV. They concluded, skip metastases is rare in T1 and T2 oral tongue cancer. Inclusion of level IV is not mandatory in selective neck dissection for clinically and radiologically negative neck disease in early tumors (T1 and T2).[5]

According to study of Pandey et al, retrospective analysis of 100 consecutive neck dissections for carcinoma of buccal mucosa was carried out to evaluate the pattern of lymphatic spread. Only 36 patients were found to harbor metastases in the lymph node on pathological examinations. Most of these were present in level I and II only. Skip metastases was not detected in any patients. None of the patients was found to have involvement of level V nodes, whereas one patient had involvement of level IV.[12]

According to the study of Lodder et al, out of 226 neck dissection performed for oral cavity cancer, skip metastases to level III or level IV occurred in 14 cases, which is about 6% of the total cases. Ten skip metastases occurred in level III only, which is about 4% of the total cases. Thus, four necks had metastases in level IV. In case of oropharyngeal cancer skip metastases to level III or level IV occurred in 6 of 92 cases, which is about 7%. Five skip metastases occurred in level III only, which is about 5%. This means that of the necks containing skip metastases only 1 neck, i.e. 1% had metastases in level IV.[1]

Woolgar found 10% skip metastases in level IV in 526 neck dissection. All patients were treated for oral cavity or oropharyngeal cancer.[28]

Kowalski and Sanabria defined skip metastases as metastases that exceed the theoretical lymphatic drainage pattern of specific tumor sites. In the case of oral cavity tumor, the expected order of metastases would be level I and II first and after surpassing this barrier levels III to V will occur. The number of this type of metastases at level IV rises from 3 to 8%.[29]

According to the study of Dias et al based on the series of 339 patients undergoing surgical treatment for stages I and II cancer of tongue and floor of mouth, they found levels I and II (46.9 and 75.3%) to be greater risk of developing nodal metastases. Level IV (6.5%) and level V (2%) were rarely involved, as well as skip metastases bypassing level I and II (2%). They studied a group of 339 patients previously untreated with T1 T2 N0 M0 SCC of the tongue and the floor of mouth. A total of 0.9% (3/339) had skip metastases in level IV, which would have been missed in a selective neck dissection. They concluded that the result of their study support the indication for supraomohyoid neck dissection for N0 and a more comprehensive neck dissection (level I–V) for N+ patients in early cancer of tongue and floor of mouth.[2]

Byers et al studied 277 untreated patients with SCC of the oral tongue. Of all patients 15.8% had skip metastases to either level III and/or level IV, without disease in level I to II.[16] Kafif et al calculated the incidence of skip metastases in Byers study when patients with clinically positive neck nodes were excluded. Five patients were found to have skip metastases to level IV in the initial neck dissection specimen and eight patients in whom level IV had not been dissected subsequently recurred in this level. Thus in the entire series of 270 patients 13, i.e. 4.8% had skip metastases or subsequent recurrence in level IV.[30]

According to Woolgar study, in 25 cases of lateral tongue cancer 21 cases had unilateral metastases out of which two cases were skipping directly to level IV and one case skipping from II to IV. Among four cases of bilateral metastases, one case with skipping direct to IV and another one case skipping from II to IV were found. In 33 cases of ventral tongue cancer 29 cases had unilateral metastases out of which one case skipping direct to IV and another one case skipping from II to IV. Among four cases of bilateral metastases none was skipping direct to IV and 1 case was skipping II to IV.[31]

Jamsed et al analyzed 30 patients with oral tongue SCC (pT1 and pT2) treated with curative surgery at Shaukat Khanum Memorial Cancer Hospital and Research Centre which were analyzed retrospectively. There were 18 males and 12 female patients. The median age for the group was 48 years (15–74 years). All the patients underwent partial glossectomy with neck dissection. Neck dissection was ipsilateral in 28 patients (93%) and bilateral in two patients (7%). Sixteen patients (47%) had pT1 and 14 patients (53%) had pT2 tumors. A total of 1056 cervical lymph nodes were analyzed. The number of nodes in level I, II, III, IV and V was 261, 295, 230, 250 and 20 respectively. The result was, 53% (16/30) of the patients had positive cervical nodal disease, and 61% (11/18) of males and 41% (5/12) of females had pN+ disease. A total of 55% of patients 40 (5/9) years of age had pN+ in comparison with 52% (11/21) of patients > 40 years of age. The distribution of positive nodes in neck was 40, 40, 20, 10 and 0% in level I, II, III, IV and V respectively. Skip metastases in level III and IV were seen in 10% (3/30) of the patients. No patient had isolated level IV involvement. In pT1 disease 44% (7/16) and in pT2 64% had neck node metastases; patterns of neck nodal involvement in level I, II, III, IV and V for pT1 was 25, 31, 19, 12 and 0% and for pT2 was 57, 50, 21, 7 and 0% respectively.[4]

De Zinis et al found metastases in level IV in 15% of patients with SCC of the oral cavity who had positive lymph nodes. A total of 28% of the level IV nodes were skip metastases. A total of 28% level IV nodes were skip metastases.[32] In a study by Crean et al occult metastases in level IV occurred in five of 49 patients. They noted

the occurrence of skip metastases to level IV, and recommended including this level in the dissection for tongue cancer.[33]

Anatomical variants of lymph nodes and pattern of lymphatic drainage of head and neck region have been previously described in detail by Rouvière.[34] The most frequent pattern of lymphatic drainage from tumors is toward levels II or I, which are the most frequent first levels also shown in other studies. Levels III, IV, or V involvement is generally associated with positive nodes in levels I or II. But micrometastases could be detected by immunohistochemistry. However, it is important to take into account the variability of the lymphatic drainage of the head and neck. In this study, eight (6.7%) patients were found to have a different pattern of lymph node invasion. The first explanation is that the first direct draining lymph node level was not level II as expected, defining an 'atypical lymphatic drainage'. The second explanation is that carcinomatous cells (transit cells) can pass through the expected first draining level, corresponding to the so-called 'skip metastases' process, a phenomenon which has also been observed in 5% of all upper aerodigestive carcinomas. In this study, two continuous sections on four different levels of each node were examined by both hematoxylin eosin stain (HES) and immuno histochemistry, but incubation with the pan-cytokeratin antibody AE1/AE3 did not reveal any additional micrometastases. Therefore, in the eight patients with atypical patterns of node metastases, this result suggests that the variability of lymphatic drainage could be explained by an 'atypical lymphatic drainage' instead of 'skip metastases.' However, they could not really exclude 'skip metastases' if a more sensitive technique was used, i.e. real-time polymerase chain reaction (RT-PCR).[35]

CONCLUSION

The lower nodal station may be involved (levels III or IV) without involvement of preceding nodal levels. The concept of skip metastases was first reported by Byers et al for oral tongue cancer.[18] The presence of cervical lymph node metastases is associated with a 50% decrease in the 5 years survival of patients with oral SCC. Therefore, it is important to detect or predict the presence of lymph node metastases in order to treat oral SCC effectively. However, even examinations using imaging techniques, such as CT, magnetic resonance imaging (MRI) and ultrasonography (USG), are still not reliable for detection of micrometastases because of the high incidence of occult neck disease.[36]

The relevance of skip metastases to level IV specifically lies in the choice of neck dissection for treatment.

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