

**Contralateral Neck Metastasis in Oral Squamous Cell Carcinoma-Report  
of Two Cases with Review of Literature**

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**ABSTRACT**

Lymph node metastasis in the neck is an important prognostic and survival factor in patients with Oral Squamous Cell Carcinoma (OSCC). Patients with pathologically negative cervical lymph nodes are believed to have a good prognosis. However, outcome of patients with lymph node metastasis, occurring after surgical excision and/or adjuvant therapy of the primary tumor is poor.

A review of literature shows that the frequency of contralateral neck node metastasis (CLNM) in oral carcinomas varies from 4% to 16.1%. The CLNM includes the presence of initial CLNM, occult CLNM confirmed by pathological study and contralateral neck relapse. The risk factors for CLNM are still controversial and debatable. Primary site and location of the tumor, its extension, clinical stage, pathologic grade, tumor thickness and perineural invasion are the most common risk factors involved in CLNM. In this paper, we discuss two cases of OSCC with CLNM following surgery with adjuvant chemotherapy and radiotherapy (CTRT).

The main objective of these case reports is to review the literature and look at the possible predictive clinicopathologic factors for CLNM in surgically treated primary OSCC.

**Key words:** Oral squamous cell Carcinoma; Contralateral neck metastasis; Lymphnode metastasis; Recurrence.

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**INTRODUCTION**

Oral squamous cell carcinoma is one of the most common head and neck malignancies found in the body and it accounts for approximately 3% of all malignancies.<sup>1</sup> OSCC has a high incidence of cervical metastasis and sometimes present with contralateral neck involvement because of rich submucosal lymphatic plexus of oral cavity that freely communicates across the midline.<sup>1</sup> CLNM is not common in patients with OSCC at the time of diagnosis and

various clinico-pathologic factors are related with the development of contralateral neck recurrence (CLNR) after surgical resection of primary OSCC.<sup>2</sup> Patients with loco regional recurrence have a higher incidence of CLNR than those without. There have been no comprehensive studies on the rate of CLNM or on the risk factors and principles of combined treatment for unilateral OSCC in young patients and with idiopathic aetiology.<sup>2</sup>

Herewith, we presenting two cases of unilateral OSCC treated by surgical resection of the primary tumour with adjuvant neck dissection followed by Radiotherapy and Chemotherapy, who developed CLNM post-operatively.

### **CASE REPORT**

#### **Case 1:**

A 43 year-old male reported to our department with the chief complaint of pain and swelling in the lower left back teeth region which had persisted for the past two months. Patient had the habit of drinking alcohol occasionally. On clinical examination an ulceroproliferative growth measuring approximately 3cm x 1cm was present in the lower left alveolus involving the gingivobuccal sulcus (Figure 1) and the lingual gingiva (Figure 2) in relation to 35, 36, and 37. He also had an enlargement of a single ipsilateral submandibular lymphnode which was tender, firm and measuring approximately 2x2cm in size. Computed tomography showed bony involvement (Figure 3) (cT4aN1M0). There were no palpable lymphnodes on the contralateral side at initial presentation. No abnormality was detected on the chest X-ray.

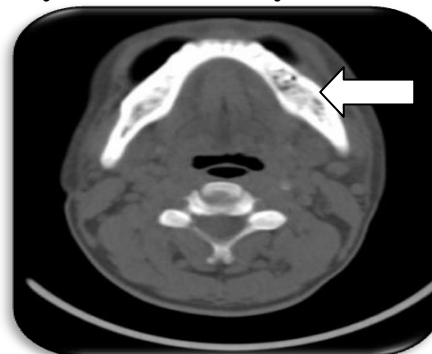
An incisional biopsy was done which was reported as moderately differentiated squamous cell carcinoma. The patient was operated for the same and underwent wide local excision with hemimandibulectomy, ipsilateral modified radical neck dissection (MRND III) and composite free fibular reconstruction. Sections from the bone underlying the tumor showed tumor invasion (pT4aN1Mx). Lymphnodes IA, IIB, III and IV showed only reactive lymphadenitis except IB which showed tumor metastasis with perinodal spread.

Two weeks postoperatively, the patient developed gaping of intraoral wound with gradual detachment of soft tissue pedicle of the fibula graft and underlying bone exposure. It was immediately addressed by excision of detached soft tissue pedicle and primary closure of the wound. The patient was advised for adjuvant chemotherapy (CT) and radiotherapy (RT) for which the patient requested to get it done at his native place. The CT and RT treatment got delayed for one month because of patient related factors. Two months post operatively the patient reported with swelling over the left side of the face and right level IB CLNM (Figure4). CT neck-contrast was done and it showed necrotic cervical lymphadenopathy (Metastatic?). The patient was referred for CT and RT treatment and he was advised five cycles of chemotherapy but could tolerate only three cycles (Cisplatin 70mg). He completed six weeks of radiotherapy (Boost-2160 cGry/12fr on Cobalt-60, ATC-conventional technique) treatment during which he developed orocutaneous fistula, mucositis and local recurrence at the intra oral operated site. After the completion of radiotherapy treatment the patient was discharged and advised periodic follow-up. One month later he succumbed to the disease.

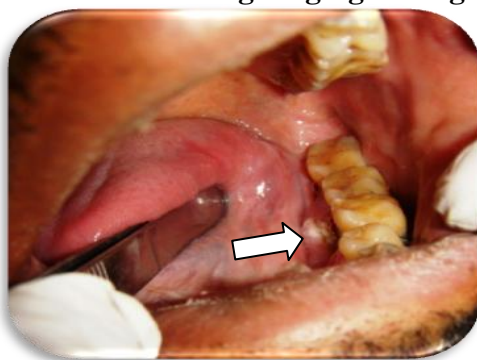
**Figure 1: Pre operative primary lesion in relation to left GBS region**



**Figure 3: Pre operative CT showing primary lesion with bony involvement**



**Figure 2: Pre operative primary lesion in relation to left lingual gingival region**



**Figure 4: Two month Post operative swelling over left side of the face and right submandibular region**



### Case 2:

A 60 year-old male reported to our department with the chief complaint of burning sensation and growth in the lower left cheek region since two months. Patient had the habit of chewing betel nut and keeping the quid in the left vestibular region since 30 years. On clinical examination an ulcerative growth was seen in the left vestibular region in relation to 36 and 37 (Figure 5). A single Left sub mandibular lymph node measuring approximately 2x1cm was palpable and tender at initial presentation (cT2N1M0). Pre operative panoramic radiograph showed no signs of bone involvement (Figure 6). An incisional biopsy was done and it was reported as well differentiated squamous cell carcinoma. FNAC of left submandibular lymphnode was positive for malignancy (Metastatic Squamous Cell Carcinoma). Chest X-ray showed no distant metastasis.

He was operated for the same by wide local excision (WLE) with Marginal mandibulectomy, ipsilateral MRND III and Reconstruction with local tongue flap and buccal pad of fat on left side. Histological examination revealed well differentiated squamous cell carcinoma (pT<sub>2</sub>N<sub>2b</sub>M<sub>0</sub>). The left cervical lymph nodes (four in number) showed metastasis with focal perinodal extension. The Patient was referred for adjuvant CT and RT and Radiation Oncology department was requested to include the left supra clavicular region during the

treatment. The patient was given complete six weeks of RT (External Beam Radiation-4500cGy, 25fr) and concurrent Chemotherapy (Cisplatin 5cycles-50mg).

On post operative six months follow-up at radiation oncology department he presented with a small vesicle in the left post auricular region (Figure 7) with serous collection. It was aspirated and sent for histopathological examination which was negative for malignancy. The patient was kept on follow-up, periodic aspiration and PET scan was done to rule out metastasis. At one year follow-up he presented with a swelling with an ulcer at the centre at the same site. He also had enlarged right contralateral Supraclavicular group of lymphnode for which FNAC was done. It was suggestive of metastatic squamous cell carcinoma. An incisional biopsy of the lesion at the post auricular region revealed SCC. Chest X-ray showed no abnormality. He was operated for the same by WLE in the left post auricular region and Right MRND III was done including level II, III and V and lower jugular nodes. The histopathology report of the post auricular lesion was suggestive of moderately differentiated squamous cell carcinoma involving skeletal muscle fibres, not involving the overlying skin but had chronic inflammation. Level II to V regional lymphnodes were examined out of which two lymphnodes showed metastasis. The left suboccipital lymphnode also showed metastasis but there was no venous or perineural invasion. One month Post operatively, once again recurrent growth was noticed at the post auricular region for which he was referred to medical oncology for opinion. There he was advised for palliative chemotherapy (Cetuximab 800mg, Paclitaxel 200mg and Carboplatin 300Mg). A total of 6 cycles of palliative chemotherapy was given. After about six months the patient succumbed to the disease.

**Figure 5: Primary lesion in relation to left GBS region**



**Figure 6: Pre operative OPG showing no bony erosion**



**Figure 7: Recurrence of the lesion at the left posterior auricular region**





## **DISCUSSION**

Contralateral Neck Metastasis is not common in patients with OSCC, but when it is present it could suggest a poor prognosis.<sup>1,4</sup> There are few reports in the literature which have involved the factors responsible for CLNM. Many authors have reported that the T stage, number of ipsilateral lymphnode metastasis, histopathology grade, lymphocytic infiltration, degree of differentiation, number of mitotic figures, tumor thickness of more than 5mm are the significant predictors of CLNM.<sup>3</sup>

The factors responsible for oral cancer vary geographically and culturally.<sup>5</sup> SCC of Buccal mucosa commonly occurs in people aged between 50-80 years. The tumors are usually diagnosed at the ages between 50 and 79 years, 96.6% being over 40 years old.<sup>6</sup> The incidence of SCC is highest in people above 45 years of age and it is because of aggregating harmful effects of carcinogens.<sup>7</sup> Oral cancer is more common in males than in female and it can be attributed to exposure to various habits by men.<sup>8</sup>

OSCC is less common in younger age less than 50years and is usually seen in males.<sup>9</sup> 6% of Oral cancer occurs in young group who are less than 45 years of age and many cases are reported before 40 years of age.<sup>8</sup> SCC in young patients is considered to be particularly aggressive with a poor prognosis when compared to that of older patients. Some studies have shown that young patients tend to present a greater loco-regional recurrence rate and a smaller survival rate.<sup>10</sup> Younger patients with OSCC often follow a different clinical course than older people and they may have different disease characteristics which include stage and site which may lead to different outcomes.<sup>10</sup> In case (1), the patient was 43 year old and had SCC of the left alveolus and lower gingiva and even after undergoing aggressive management he had local recurrence, CLNM and short survival rate. In case (2), the patient was 60 year old male and had SCC of left buccal mucosa not involving bone. He also underwent aggressive management but developed CLNM later.

Etiological factors which play an important role in OSCC are (i) Cigarette smoking (ii) Alcoholic beverages (iii) Betel and similar habits (iv) Diet.<sup>6</sup> The other causative factors for OSCC includes genetic predisposition, viral infection (CMV,HPV, EBV),feeding habits, immunodeficiency status, occupational exposure to carcinogens, socio-economic condition and oral hygiene.<sup>10</sup> In our reported cases, case (1) was a non smoker and occasionally used to take alcohol. Case (2) had the habit of chewing betel nut and keeping the quid in the buccal vestibule for 20 years.

In India and other Asian countries carcinoma of buccal mucosa is more common and accounts for 40% of oral cancer. In western countries cancer of the tongue is common amounting up to40-50% of oral cancer. The other sites which are commonly involved in oral cancer are floor of the mouth, gingivae and palate.<sup>5</sup> The incidence of delayed metastasis is largely influenced by the location and extension of the primary tumor. It is believed that involvement of anterior site is usually associated with better prognosis than the posterior site.

Patients with tumors of the tongue and floor of the mouth, those involving the retromolar region or the lower gingiva also have a higher risk for CLNM.<sup>2</sup> It is a very well established

fact that primary tumors crossing the midline and those involving the base of the tongue are the most important predictors of CLNM due to the involvement of contralateral lymphatic drainage.<sup>1</sup> Martin et al reported that primary tumor of the oral cavity involving the midline had showed higher incidence of CLNM. It was reported that 16% of the tumors crossing the midline less than 1cm developed CLNM and it increased to 46% in cases where the midline invasion was greater than 1cm.<sup>1</sup> The exact mechanism for CLNM is not very clear and it occurs in different ways such as crossing the afferent lymph vessels, tumor crossing the midline to reach the efferent collateral lymphatic vessels.<sup>1</sup> In Case (1), the primary tumor was present in the Left alveolus and also involved the buccal and lingual gingiva in relation to left second premolar, first and second molar. In Case (2), the primary tumor was present in the Left buccal mucosa in relation to the Left first and second molar region abutting the alveolus. In Case (1), as the primary tumor involved the lower lingual gingiva and this might have lead to the CLNM? In Case (2), the primary tumor was not crossing the midline but developed CLNM post operatively which may be attributed to an alternative lymphatic pathway.

Tumor size plays a very important role in CLNM and a study by Koo et al reported that patients with T4 stage had higher incidence of CLNM.<sup>1</sup> The overall 5-year survival has been reported which varies according to tumor size (T1/T2 commonly referred to as “low-risk tumors” and T3/T4 commonly referred to as “high-risk”). The disease outcome is greatly influenced by the stage (especially TNM). The study conducted by Soo in 1988 on 283 patients of squamous cell carcinoma reported that the disease was 30% diagnosed at T1, 48% at T2, 17% at T3, and 11% at T4. Also 95% of the cases required resection, 32% required marginal resection, and 63% required segmental resection. Increase in the tumor size can be attributed to cervical involvement, high recurrence rate and poor prognosis.<sup>6</sup> The study conducted by Koo et al reported that the rate of CLNM was 8% for T2, 25% for T3 and 18% for T4.<sup>1</sup>

In our reported cases, case (1) had a T4 size primary lesion and it may be the reason for CLNM but case (2) had a T2 primary lesion, even then he developed CLNM?

Tumor thickness is considered as a more accurate histological prognostic factor for cervical node metastasis and a study conducted by Bier-Laning et al found that no CLNM was seen when the primary lesion had thickness of <3.75mm. There is approximately 5% of increased risk of getting CLNM, if there is an increase in tumor thickness by 1-mm.<sup>1</sup> In our reported cases, case (1) had a tumor thickness of 20mm and case (2) had 5mm. As it was found that the tumor thickness was more than 4mm in both the cases and this could be one of the contributing factors for CLNM.

In oral squamous cell carcinoma (OSCC) the presence and extent of cervical lymphnode metastases at the initial diagnosis is considered as one of the important prognostic factor for tumor behaviour.<sup>1</sup> Poor prognosis is expected in patients with ipsilateral, contralateral or bilateral nodal involvement and worst prognosis is seen in bilateral than contralateral nodal involvement.<sup>6</sup> Various studies have confirmed that patients with ipsilateral metastatic lymphnodes have high risk for CLNM (4.8 times higher) in comparison with those with no metastasis on the same side of the neck. It also been demonstrated that the involvement of

multiple ipsilateral nodes involvement has higher risk for CLNM or bilateral metastases than those with single or negative nodal involvement. Kurita et al reported that the incidence of CLNM is higher in patients with multiple ipsilateral nodal involvement (50%) than those with single node involvement (26.1%).<sup>1</sup> Contralateral neck lymphnodes are occasionally involved in OSCC. It varies from 4% to 16.1% and differs from one institution to another in the range of 0.9% to 36%.<sup>1, 3</sup> In our reported cases; Solitary ipsilateral nodal enlargement was seen in both patients with no lymphnode enlargement in the contralateral neck. Later histopathology report confirmed ipsilateral IB metastasis in case (1) and multiple ipsilateral (four) nodes in case (2). In Case (1), patient developed CLNM in spite of solitary ipsilateral node involvement at initial presentation. In case (2), since the patient had multiple ipsilateral lymph node involvement, could it be attributed for CLNM post-operatively? Both the patients later succumbed to death which shows the poor prognosis associated with CLNM.

The prognostic importance of extra capsular spread (ECS) was studied by Liao et al and they reported that patients with ECS have higher incidence of CLNM (39%) than those without (12%).<sup>1</sup> In our cases, Case(1) had metastasis in the single ipsilateral IB node with perinodal spread which may have led to CLNM. Case (2) had multiple (four) ipsilateral positive nodes with perinodal spread which might have lead to CLNM even though it was a T2 primary lesion.

The surgical margin involvement by the tumor cells is also considered as one of the most important prognostic factor in OSCC. Earlier studies have shown that adequate margin with complete tumor excision is important during surgery. The surgical margin includes both the surface mucosa at the edge of the tumor and the submucosal and deeper connective tissues all around the defect. The study by Nason et al has shown that with each additional millimeter of clear surgical margin, it decreased the death risk to 5years by 8%. According to UK guidelines, if the margin is 5mm or more it is considered as clear, 1-5mm as close and <1mm as involved. The surgical margin with 1cm or more of non involved tissue around the tumor is considered as adequate and many authors have reported that if the surgical margin is less than 1cm then the chances of developing CLNM are around 11.6%. Several studies have also shown that patients with clear surgical margin always do not have good outcome and local recurrence has been seen, ranging from 4% to 18%.<sup>1</sup> In Case (1), histopathologically, the tumor was located 0.5 cm from anterior soft tissue resected margin, 0.8cm from anterior bony resected margin, 4cm from posterior soft tissue resected margin and 5.4cm from posterior bony resected margin. In the second case the primary tumor was encroaching on to the left GBS and was upto 1cm, 1.2cm, 1.3cm, 1.4cm respectively away from anterior, superior, posterior and inferior soft tissue margin. As in both the cases the surgical margin of the primary tumor was free from tumor even then they had recurrence and CLNM. However, in case (1) two surgical margins were less than 1cm and this might be attributed to CLNM? Clear surgical margins should not prevent one from indicating the patient for post-op RT to the primary site. All other factors such as tumor size, site and thickness should also be taken into consideration.

Depending upon the degree of keratinization, cellular and nuclear pleomorphism, and mitotic activity, the SCC is categorized into three categories: (i) well differentiated, (ii) moderately differentiated, and (iii) poorly differentiated. The study conducted by Kademani in 2006 on

215 patients, reported that the degree of differentiation is a significant predictor of loco regional failure and tumor recurrence.<sup>6</sup> It has been reported that higher the degree of histopathological grading then the chances of getting CLNM is more in OSCC. In a study conducted by Gonzalez-Garcia et al it was found that 13.5% of the patients had CLNM with poorly differentiated SCC when compared to 5.2% with well-differentiated tumor.<sup>1</sup> In case (1) the tumor was moderately differentiated type and in case (2) it was well differentiated, even then CLNM was seen which suggests more studies are required in this aspect or other tumor related factors could have been contributory.

Lymphovascular invasion with perineural infiltration are closely associated with CLNM in OSCC. According to Jacobson et al Lymphovascular invasion was classified according to the presence or absence of tumor cells located both in the wall and in the blood or lymphatic vessels and it implies the presence of metastatic growth.<sup>1</sup> In our reported cases both the patients did not have Lymphovascular invasion, yet developed CLNM.

The perineural spread affects the overall prognosis and survival as the tumor cells spread easily though the nerve and surrounding tissues. The study conducted by Gonzalez-Garcia et al reported that the presence of perineural invasion is one of the strong predictors of CLNM and they have illustrated perineural invasion in 17.02% of pathologic contralateral lymph neck nodes in comparison with 4.1% of those without perineural involvement.<sup>1</sup> In our reported cases both the patients did not have any perineural invasion and had CLNM?

Elective contralateral neck dissection is usually recommended only when the tumor crosses the midline.<sup>2</sup> Prophylactic contralateral neck dissection is suggested for OSCC with floor involvement or tumor crossing midline or advanced tumor (>T3) as it reduces the risk of CLNM.<sup>7</sup> In Case (1), the patient had bony involvement by the primary lesion which was confirmed by CT scan and a stage of T4N1M0 was made which may suggest that more advanced primary, then more chances of CLNM. However, since the tumor size was T4 and ipsilateral node was present and considering the age of the patient, 43years, prophylactic contralateral neck dissection could have been considered in this case. Whereas in Case (2), the patient had clinical stage T2N1M0 without bony involvement but he also had CLNM later postoperatively. This suggests that even the small primary tumor can show aggressive behaviour and has to be treated aggressively in terms of both surgical and adjuvant therapies especially when ipsilateral multiple nodal metastases are present.

The Relationship between the local-regional recurrence and CLNM is not clearly known and the Study conducted by Liao et al stated that local recurrence was one of the risk factor for CLNM. It was reported that CLNM is seen in 18% patients with local recurrence and in 5% without recurrence.<sup>1</sup> It suggests the incomplete removal of the disease during elective neck dissection and the recurrent disease will have histologically unfavorable features. Godden et al confirmed that patients with recurrent neck disease often get metastasis at multiple levels and invariably have extra capsular spread.<sup>11</sup> Case (1), had early local recurrence within two months and Case (2) had local recurrence after six months in the left post auricular region and this could also be one of the factors for CLNM.



The two reported cases had OSCC of left mandibular alveolus and buccal mucosa respectively without midline involvement by the primary tumor. Though modified radical neck dissection followed by CT and RT were given, they developed recurrence with CLNM. In case (1), in spite of surgical treatment and adjuvant CT and RT he had local recurrence and contralateral right submandibular node (IB) metastasis within a short period of time. Could delayed RT, because of wound infection and loss of soft tissue pedicle at the primary operated site have contributed to contralateral IB nodal involvement?

The low incidence of level IIB nodal metastasis in head and neck SCC makes it unnecessary to remove level IIB nodes when performing elective neck dissection (END). This prevents the complication of shoulder dysfunction syndrome after END.

In Case (2), the patient underwent neck dissection, RT and CT and had recurrence in the post auricular region with contralateral Supraclavicular nodal involvement. It may be suggestive of incomplete clearance of the ipsilateral level IIB lymphnode during primary surgical procedure and failure in early recognition of the recurrence during follow-up? This might have lead to escape of tumor cells metastasis in neck region (skip metastasis).<sup>12</sup>

In case (1), the factors which were in favour of CLNM includes the size of the primary (T4a), bony involvement, positive ipsilateral nodal involvement (N1), positive perinodal spread, close surgical margin (anterior-0.5cm), delay in radiotherapy and chemotherapy, young patient (< 45yrs), idiopathic etiology? and moderately differentiated type of OSCC.

In case (2), although the primary lesion was small (T2), surgical margins >1cm, no bony involvement, tumor was well differentiated, prompt radiotherapy and chemotherapy was given, was on regular follow-up, but still there was CLNM? In this case the factors which were in favour of CLNM include multiple ipsilateral nodal involvement (Four Nodes-N2b), positive perinodal spread, and delay in recognition of the recurrence in the post auricular region (incomplete clearance of the level IIB nodes?).

### **CONCLUSION**

Contralateral lymphnode metastasis is not common in OSCC patients, but when it is present it could suggest poor prognosis. The risk factors responsible for early recurrence and CLNM as seen in the two cases reported appears to be multifactorial or a combination of factors. Advanced clinical stage of the disease, either primary lesion or size and number of neck nodes, tumor thickness of more than 4mm, perinodal spread and surgical margin less than 1cm are indicators of poor prognosis. Therefore these patients should be screened properly and we should anticipate early recurrence and CLNM which mandates aggressive surgical approach, elective contralateral neck dissection and prompt adjuvant therapies for better outcomes. Delayed treatment and failure in recognition of the recurrence mandates the multidisciplinary team to work concurrently through which the progression of the disease can be restricted which in turn leads to better prognosis.

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