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# Oral Squamous Cell Carcinoma Metastasising to Unusual Sites: A Case Series of Four Cases

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## **ABSTRACT**

Oral cancer ranks as the sixth most common malignancy worldwide, with Squamous Cell Carcinoma (SCC) being the predominant type observed in the head and neck region. Incidence and mortality rates of SCC have significantly increased over the past few decades. Smoking and tobacco chewing are the most common aetiological factors, predominantly affecting elderly males. Distant metastasis at the time of diagnosis is a rare occurrence, typically disseminating through blood vessels or lymphatics. The lungs are the most frequent site for distant metastasis, followed by bone, mediastinal nodes, and occasionally the liver. However, in our cases, we observed metastasis to uncommon sites, excluding the liver. Accurate diagnosis necessitates the correlation with clinical history, radiological, histopathological, and immunohistochemical findings. Despite employing various surgical and radiotherapeutic modalities, distant metastasis diminishes the chances of survival, successful treatment, and worsens the prognosis. This article presents four cases of oral SCC that exhibited metastasis to unusual sites. Two cases had a primary tumour in the left lateral border of the tongue, with distant metastasis to the breast and skin (chest wall), while the other two cases had a primary tumour in the left buccal mucosa and left mandibular region, with distant metastasis to the kidney and liver.

Keywords: Head and neck tumours, Metastasis, Oral squamous cell carcinoma, Rare sites

## INTRODUCTION

Oral cancer is the sixth most common malignancy worldwide [1]. It is the most common cancer among Indian males and the fourth most common among Indian women. According to Global Cancer Observatory (GLOBOCAN) data from 2020, there were 377,713 new cancer cases of the oral cavity and lip registered, with 177,757 new deaths worldwide, accounting for 1.8% of all cancer deaths [2]. In the head and neck region, Squamous Cell Carcinoma (SCC) is the most prevalent malignancy, accounting for over 90% of cases [3]. The majority of cases are moderately or well-differentiated types [4]. Loco-regional disease is common among such patients, with distant metastasis being a rare occurrence at the time of diagnosis [5]. Approximately 40% of the cases show metastasis to lymph nodes [6], with cervical lymph nodes being commonly involved and reducing the survival rates by 50% [7]. The most common site for distant metastasis is the lung, accounting for about 66% of cases, followed by the liver, mediastinal nodes, and bone [3,8]. This article presents four cases of oral SCC that exhibited metastasis to unusual sites.

## **CASE SERIES**

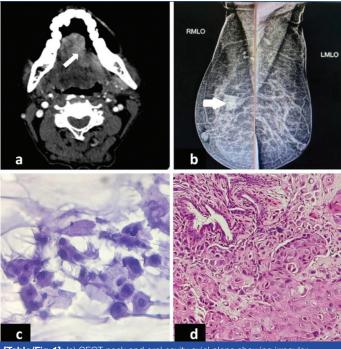
#### Case 1

A 50-year-old female patient presented to the Outpatient Department (OPD) with a complaint of an ulcerated lesion present over the left lateral border of the tongue for the past three months. Contrastenhanced Computed Tomography of the neck revealed an ill-defined malignant mass lesion measuring  $60\times40.3\times50.4$  mm, involving the left lateral border of the tongue, crossing the midline, and infiltrating up to the right lateral border of the tongue, left hyoid bone, left myelohyoid, digastric, and suprathyroid strap muscles, with bilateral cervical lymphadenopathy [Table/Fig-1a]. Biopsy results showed invasive nests and sheets of atypical polygonal cells, exhibiting round to oval pleomorphic nuclei with vesicular chromatin, prominent nucleoli, eosinophilic cytoplasm, and individual cell keratinisation. Due to the advanced stage at diagnosis, surgery was not performed. The patient received six cycles of chemotherapy and 35 cycles of

radiotherapy. During the course of treatment, the patient noticed a lump in the left breast. Mammography revealed an irregular-shaped high-density mass lesion in the upper outer quadrant of the left breast with spiculated margins, distortion of breast parenchyma, and no microcalcification, consistent with Breast Imaging Reporting And Data System 5 (BI-RADS 5) [Table/Fig-1b]. Fine needle aspiration cytology study of the mass showed clusters and a few singly dispersed atypical polygonal cells with pleomorphic hyperchromatic nuclei and moderate amount of cytoplasm, suggesting a malignant lesion with the possibility of metastatic SCC [Table/Fig-1c]. The patient underwent a trucut biopsy, which revealed an invasive tumour surrounding the mammary ducts, composed of nests and sheets of atypical polygonal cells with moderately pleomorphic nuclei, vesicular chromatin, prominent nucleoli, eosinophilic glassy cytoplasm, along with single-cell keratinisation. A histopathological diagnosis of metastatic SCC was made [Table/Fig-1d]. The patient was planned for adjuvant chemoradiotherapy, but her condition rapidly worsened, and she passed away.

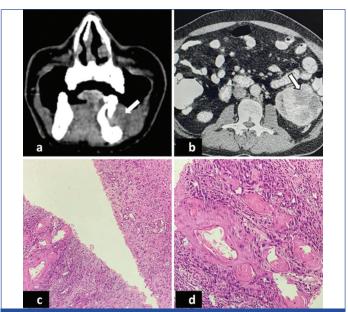
#### Case 2

A 56-year-old male patient presented with a complaint of a mass in the oral cavity for the past month. The patient had a history of beedi smoking and tobacco chewing for 15 years. Contrast-enhanced Computed Tomography revealed an ill-defined heterogeneously enhancing mass measuring 70x40.5x50 mm, involving the left buccal mucosa, left inferior and superior gingivobuccal sulcus, likely neoplastic mass with left cervical lymphadenopathy [Table/Fig-2a]. Biopsy results showed invasive nests and sheets of moderately pleomorphic atypical polygonal cells, exhibiting individual cell keratinisation and focal keratin pearl formation, consistent with the diagnosis of moderately differentiated Squamous Cell Carcinoma (SCC). The patient underwent left composite hemimandibulectomy with modified neck dissection, and a diagnosis of moderately differentiated SCC was confirmed. The patient was staged as pT4aN3b, with skin involvement and extracapsular extension. Frozen section margins were negative, and the patient was discharged with stable vitals. Four months after surgery, the patient complained of



[Table/Fig-1]: (a) CECT neck and oral cavity axial plane showing irregular marginated enhancing soft tissue density mass lesion in the left lateral border of the tongue (arrow) suggestive of carcinoma of the tongue; (b) Mediolateral oblique view of mammogram showing an irregular-shaped high-density mass lesion (arrow) in the upper outer quadrant of the left breast - BI-RADS 5; (c) Fine needle aspiration cytology showing clusters of atypical squamous epithelial cells (PAP, 400x); (d) High-power view of trucut biopsy of breast lump showing invasive nests of atypical squamous epithelial cells surrounding the normal mammary ducts (H&E, 100x, 400x).

abdominal pain and underwent imaging studies, including a Positron Emission Tomography and Computed Tomography scan, which revealed a hypermetabolic ill-defined heterogeneous enhancing soft tissue density lesion involving the lower pole of the left kidney, suggestive of metastasis [Table/Fig-2b]. A core needle biopsy from the same lesion was performed, showing the presence of invasive nests and sheets of atypical squamous epithelial cells, demonstrating moderate nuclear pleomorphism, moderate to abundant eosinophilic cytoplasm, individual cell keratinisation, and keratin pearl formation, suggesting a diagnosis of metastatic SCC [Table/Fig-2c,d]. The

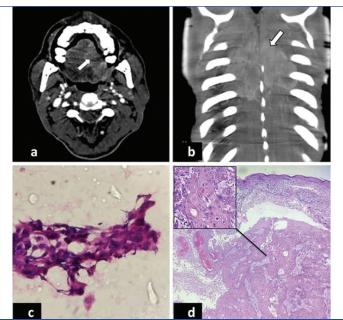


[Table/Fig-2]: (a) CECT neck coronal plane showing irregular marginated heterogeneous enhancing soft tissue mass in the left lower gingivobuccal sulcus (arrow) suggestive of carcinoma of the buccal mucosa; (b) CECT abdomen showing a hypermetabolic ill-defined heterogeneous enhancing soft tissue density lesion in the lower pole of the left kidney (arrow); (c) Low-power view of core biopsy from the kidney showing invasive nests of atypical squamous epithelial cells (left core) and the presence of normal glomeruli and tubules (right core) (H&E, 100X); (d) High-power view of the left core showing keratin pearls and invasive nests of atypical squamous cells (H&E, 400X).

patient was then started on radiotherapy. However, during the course of treatment, the patient's condition deteriorated markedly, and he passed away after receiving two cycles of radiotherapy.

#### Case 3

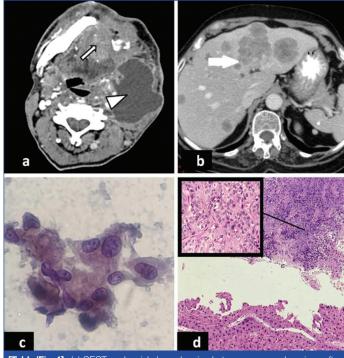
A 47-year-old male patient presented to the Outpatient Department (OPD) with complaints of an ulcer over the left lateral border of the tongue and difficulty in chewing for the past 1.5 months. The patient had a history of tobacco chewing. Contrast-enhanced Computed Tomography of the neck revealed an ulcerative heterogeneously enhancing irregular soft tissue density mass lesion measuring 40.2×20.2×10.3 mm involving the left lateral border of the tongue [Table/Fig-3a]. The patient underwent wide excision glossectomy with modified neck dissection, and the specimen was sent for histopathology. Microscopic examination revealed a tumour composed of invasive nests and sheets of moderately pleomorphic atypical squamous epithelial cells showing individual cell keratinisation and focal keratin pearl formation. A diagnosis of invasive moderately differentiated Squamous Cell Carcinoma (SCC) was made, and the tumour was staged as pT3N0. The patient received adjuvant chemotherapy and radiotherapy and was discharged with stable vitals. He was kept on regular followup. In the 7<sup>th</sup> month postoperatively, the patient reported a tender erythematous swelling over the posterior chest wall. Contrastenhanced Computed Tomography of the thorax showed a heterogeneously enhancing soft tissue density mass lesion in the posterior chest wall [Table/Fig-3b]. Fine needle aspiration cytology revealed clusters of atypical cells comprising round to oval pleomorphic nuclei with fine granular chromatin, prominent nucleoli, and a moderate amount of cytoplasm, favoring poorly differentiated carcinoma [Table/Fig-3c]. An incisional biopsy was performed, which showed nests and sheets of atypical polygonal cells showing moderate nuclear pleomorphism, vesicular chromatin, prominent nucleoli, and eosinophilic cytoplasm with individual cell keratinisation [Table/Fig-3d]. A histopathological diagnosis suggestive of metastatic SCC was made. The patient was advised concurrent chemotherapy and radiotherapy, but due to financial constraints, he denied treatment and was lost to follow-up.



[Table/Fig-3]: (a) CECT neck and oral cavity axial plane shows an irregular marginated heterogeneous enhancing soft tissue density mass in the left lateral border of the tongue (arrow) suggesting carcinoma; (b) Contrast-enhanced computed tomography thorax showed a heterogeneously enhancing soft tissue density mass lesion in the posterior chest wall (arrow); (c) FNAC showing a cluster of atypical cells suggestive of poorly differentiated carcinoma (PAP, 400x); (d) Low-power view of biopsy from the chest wall lesion showing ulcerated lining epithelium and involvement of the underlying dermis by an infiltrating tumour composed of atypical squamous epithelial cells present in nests and sheets (H&E, 100x). High-power view of nests of atypical squamous epithelial cells is shown in the box in the upper left corner (H&E, 400x).

#### Case 4

A 38-year-old male patient presented to the outpatient department (OPD) with complaints of a mass over the left mandibular region for the past 1.5 months. The patient had a history of tobacco chewing for 10 years. Magnetic resonance imaging of the neck revealed a heterogeneously enhancing necrotic mass in the angle of the left mandible. Contrast-enhanced Computed Tomography of the neck revealed a mass lesion involving the left mandible measuring 80.3×70.6×10.7 mm, with destruction of the underlying mandible and enlarged left cervical level 1b and II nodes [Table/Fig-4a]. Biopsy results showed a tumour composed of invasive nests and sheets of atypical polygonal cells showing mild to moderate nuclear pleomorphism, vesicular chromatin, prominent nucleoli, and a moderate amount of eosinophilic cytoplasm with single cell keratinisation and focal keratin pearl formation, consistent with the diagnosis of moderately differentiated Squamous Cell Carcinoma (SCC). Contrast-enhanced Computed Tomography of the abdomen revealed multiple variably sized hypodense lesions in both lobes of the liver, with decreased enhancement relative to the background liver parenchyma, most conspicuous in the portal venous phase, suggesting metastases [Table/Fig-4b]. Ultrasound-guided fine needle aspiration cytology from a liver nodule was performed, showing atypical polygonal cells present in clusters comprising pleomorphic round to oval nuclei with vesicular chromatin, prominent nucleoli, and a moderate amount of cytoplasm. The features were suggestive of metastatic poorly differentiated carcinoma favoring SCC [Table/Fig-4c]. A biopsy was performed, revealing nests and sheets of atypical polygonal cells showing mild nuclear pleomorphism, round to oval nuclei with vesicular chromatin, prominent nucleoli, and moderate to abundant eosinophilic cytoplasm with individual cell keratinisation and intercellular bridges, suggesting metastatic SCC [Table/Fig-4d]. The patient was then planned for chemotherapy, following which he was discharged with stable vitals and advised regular follow-up.



[Table/Fig-4]: (a) CECT neck axial plane showing heterogeneous enhancing soft tissue density mass lesion in the left angle of the mandible (arrow) with destruction of body and alveolar process on the left side with a necrotic lymph node in the left submandibular region (arrowhead) suggesting malignant mass of the left mandible; (b) CECT abdomen showing multiple variable-sized hypodense lesions in both lobes of the liver suggestive of metastases; (c) Fine needle aspiration cytology of the liver nodule showing malignant cells favoring poorly differentiated carcinoma, possibly squamous cell carcinoma (PAP, 400x); (d) Low-power view of core biopsy from the liver nodule showing invasive nests and sheets of atypical squamous epithelial cells (upper core) and normal hepatocytes (lower core). High-power view of atypical squamous cells is shown in the box in the upper left corner (H&E, 100x, 400x).

The findings of all four cases have been summarised below [Table/Fig-5].

Parameter	Case 1	Case 2	Case 3	Case 4
Age/Sex	50 year/Female	56 year/Male	47 year/Male	38 year/Male
Site of primary lesion	Left lateral border of tongue	Left buccal mucosa and gingivobuccal sulcus	Left lateral border of tongue	Left mandibular region
Duration	3 months	1 month	1.5 months	1.5 months
Radiological findings of primary lesion	CECT neck- mass measuring 60×40.3×50.4 mm in left lateral border of tongue, crossing midline with bilateral cervical lymphadenopathy	CECT neck-heterogeneously enhancing mass measuring 70×40.5×50 mm involving the left buccal mucosa with left cervical lymphadenopathy	CECT neck-heterogeneously enhancing soft tissue density mass lesion measuring 40.2×20.2×10.3 mm involving the left lateral border of tongue	CECT neck-mass lesion involving left mandible measuring 80.3×70.6×10.7 mm with enlarged left cervical level 1b and II nodes
Surgical procedure	Not performed	Left composite hemimandibulectomy with modified neck dissection	Wide excision glossectomy with modified neck dissection was done	Not performed
Histopathological diagnosis	Squamous Cell Carcinoma (SCC); moderately differentiated	SCC; moderately differentiated	SCC; moderately differentiated	SCC; moderately differentiated
Staging	-	pT4aN3b	pT3N0	-
Site of distant metastasis	Breast	Kidney	Skin (chest wall)	Liver
Time since primary lesion	During course of treatment of primary lesion	4 months postoperatively	7 months postoperatively	During course of treatment of primary lesion
Radiological findings of metastatic lesion	Mammography-irregular shaped high density mass lesion with spiculated BI-RADS 5	PET and MSCT-heterogenous enhancing soft tissue density lesion involving the lower pole of left kidney likely Metastasis	Not done	CECT abdomen- multiple variable sized hypodense lesions in both lobes of liver? Metastases
Fine needle aspiration cytology findings	Malignant lesion with possibility of Metastatic SCC	Not performed	Favour poorly differentiated carcinoma	Metastatic poorly differentiated carcinoma favouring SCC
Histopathological findings of metastatic lesion	Metastatic SCC	Metastatic SCC	Metastatic SCC	Metastatic SCC
Follow-up	Death	Death	Lost to follow-up	Patient discharged with stable vitals and advised regular follow-up

[Table/Fig-5]: Summary of the four cases.

DECT: Contrast enhanced computed tomography; MSCT: Multislice spiral computed tomography; PET: Positron emission tomography

## **DISCUSSION**

In the head and neck region, Squamous Cell Carcinoma (SCC) is the most common type of malignancy worldwide. Patients who exhibit metastasis to regional lymph nodes during the initial diagnosis have a 30% risk of developing distant metastasis within 9 to 12 months [9]. The tongue is the most common primary site for distant metastasis [10]. In our study, two out of the four cases showed carcinoma in the left lateral border of the tongue. A review by Irani S indicated that the gingiva is the most frequent primary site of involvement for distant metastasis [10].

Metastases to the breast from extramammary tumours are very rare, comprising 0.5% to 6.6% of cases. The most common primary tumours metastasizing to the breast are contralateral breast carcinoma, followed by lung, gastrointestinal, gynaecological, haematological carcinomas, and melanoma [11]. Breast metastases from SCCs of the head and neck region are extremely uncommon, and only a few cases have been reported in the literature [3]. The mean age at diagnosis is usually 50 years, which is consistent with our case. The age range typically varies from 32-87 years [11]. Metastases usually appear after 30 months of the primary extramammary malignancy diagnosis or during the course of treatment of the primary malignancy, as in our case [11]. It is challenging to differentiate primary breast carcinoma from metastases because the clinical presentation might be similar to primary cancer, and it may be the initial presentation of a metastatic disease of unknown origin [12].

Radiology plays a critical role in diagnosing metastatic breast disease. On mammography, metastases present as single or multiple well-circumscribed masses, commonly located in the upper outer quadrant. Spiculations, calcifications, and desmoplastic reaction are absent, which are mainly seen in primary breast carcinomas [13]. Histopathological and immunohistochemical examinations play an important role in accurately diagnosing the metastatic lesion and tailoring appropriate treatment [11]. Surgery may be indicated only for symptom palliation or when an isolated breast metastasis is identified with a long interval from the diagnosis of the primary tumour [14]. The prognosis is extremely poor, with an overall survival rate of less than a year from the time of diagnosis [14].

Metastases to the kidneys are very rare and are often erroneously diagnosed as primary tumours. The incidence of extrarenal tumours metastasizing to the kidneys varies from 2 to 20% [15]. Distant metastasis of SCC of the tongue to the kidney is extremely uncommon, with only two reported cases in the literature [15]. The median patient age is around 56.7 years, similar to our case, where the patient was a 56-year-old male. Imaging studies are the mainstay for diagnosing metastases [9]. Radiologically, they are usually subcapsular in location, multicentric, small, and bilateral, with a known history of a primary tumour [15]. Zhou C et al. reported a radiology pathology concordance of 51%, while Wu AJ et al. reported a concordance of 54% [16,17].

In cases of secondary renal involvement, it is essential to rule out other possible differential diagnoses such as urothelial carcinoma with squamous differentiation and collecting duct carcinoma. Immunohistochemistry can be a useful tool, but it is not completely diagnostic due to overlapping features [9]. SCCs usually show negativity for Cytokeratin 20 (CK20), whereas some urothelial carcinomas showing squamous differentiation are positive. Urothelial tumours are frequently CK7 positive, while SCCs are negative. Primary urothelial carcinoma typically exhibits strong diffuse expression of GATA3 [9]. Paired-Box Gene 8 (PAX8) and CK7 can be helpful in distinguishing SCC from collecting duct carcinoma, with the latter being positive. A known history of a primary tumour can also be a helpful clue.

In a study by Wu AJ et al., the median time interval between primary diagnosis and metastases was reported to be three years, whereas Singh GK et al. and Elsarraj HS et al. reported a median interval of 18 months [17,18,9]. In our study, the interval was 4 months, which

was similar to the study by Thyavihally YB et al., who also reported a median time interval of four months [19]. The median overall survival is about a year, and surgical interventions can help improve overall survival to more than two years [9].

The frequency of cutaneous metastasis from primary malignancies varies from 0.7% to 9%. In patients with head and neck SCC, the incidence of cutaneous metastasis is around 0.8-1.3% [20]. The skin of the head and neck and chest region are the most common sites for metastasis [21]. In our case, the site of metastasis was the posterior chest wall. One of the first reported cases of skin metastases was by Schultz and Schwartz in 1985, where a patient developed skin metastases secondary to carcinoma of the hypopharynx [22]. Among all cancers of the head and neck region, laryngeal cancer is most often associated with skin metastasis [20].

FNAC and biopsy should be done to rule out the presence of malignancy even if the lesion appears clinically benign. Rastogi M et al. reported a case of SCC of the base of the tongue that showed multiple cutaneous metastases after 18 months of follow-up [20]. Rahman T et al. reported cutaneous metastasis in a patient with carcinoma of the base of the tongue, in which lesions appeared one month after completion of treatment. This could possibly be due to the presence of occult skin metastasis during the course of treatment or at the time of diagnosis, which might have been missed [23]. In our case, cutaneous metastasis occurred in the 7th month of follow-up. Treatment is usually palliative, and prognosis is very poor, with a survival of only a few months [20].

Metastases to the liver from head and neck cancers are rare, with an incidence of about 4.4% [24]. Clinical history, imaging findings, FNAC, and biopsy can be used to accurately diagnose the metastatic lesion.

Metastatic nodules on ultrasonography are usually multiple and may be cystic, hypoechogenic, or hyperechogenic without a peripheral halo [24]. Cases with isolated nodules in the liver and a history of head and neck cancer may show raised Lactate Dehydrogenase (LDH) levels, which could be the only alarming sign [23]. Marcy PY et al. reported distant metastases from head and neck carcinomas to the liver in 0.9% of the studied population, while Merino E et al. reported liver metastasis in 0.7% of cases [24,25]. Prognosis is usually very poor, with a median survival of only four months [24].

## CONCLUSION(S)

Distant metastasis from oral SCCs is a rare event and mostly occurs during advanced stages. Careful evaluation of patient during the treatment of primary malignancy can have a remarkable impact on the overall survival and prognosis. Clinicopathological correlation can be immensely helpful in making a correct diagnosis and tailoring an appropriate cost-effective treatment.

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