



# Distant Metastasis in Carcinoma Oral Cavity: Incidence and Prognostic Factors

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## Abstract

**Aim** The predominant pattern of failure for oral carcinoma is locoregional failure. With improvement in locoregional control, incidence of distant metastasis has increased. Reported incidence of distant metastasis is 8 to 10%. With an aim to define incidence and predictive factors for distant metastasis posttreatment of oral cavity cancer, the present analysis was done.

**Materials and Methods** This is a retrospective chart review of 531 patients who underwent surgery for oral cavity carcinoma from August 2013 to December 2017. All patients had undergone surgery followed by adjuvant treatment as per histopathology report.

**Results** The median age of the cohort was 49 years. The median follow-up of alive patients was 21 months (range: 1–56 months). Locoregional recurrence seen in 61, distant metastasis in 23, and 72 patients had locoregional recurrence with distant metastasis. Total incidence of distant metastasis was 18% (95 patients) with median detection 7 months' posttreatment. The sites of distant metastasis were: lung in 49 patients, bone in 9 patients, and multiple sites in 37 patients. Nodal stage (N2 and N3), differentiation, young age, and perineural invasion were associated with higher incidence of distant metastasis on multivariate analysis.

**Conclusion** The incidence of distant metastasis was found to be higher as compared with published literature. Possibility of adjuvant systemic therapy may be explored in future studies.

## Keywords

- ▶ carcinoma oral cavity
- ▶ differentiation
- ▶ distant metastasis
- ▶ nodal stage
- ▶ PNI

## Introduction

Head and neck squamous cell carcinoma is one of the most common cancers worldwide.<sup>1</sup> In the Indian population, it is the most common cancer in males and one of the three common cancers overall.<sup>2</sup> Carcinoma oral cavity forms the majority of head neck squamous cell carcinoma in our group of patients. Large proportion of patients in our country present with locoregionally advanced disease. Optimal management of oral cavity cancer includes primary surgery followed

by adjuvant treatment as per the histopathological report (radiotherapy with or without concurrent chemotherapy). The predominant failure pattern posttreatment is locoregional recurrence.

In the literature, incidence of distant metastasis of head and neck cancer has been reported at around 10%.<sup>3-5</sup> There has been a gradual improvement in locoregional control posttreatment. At the same time, more patients are being diagnosed with distant metastasis from head and neck cancers. This increase in distant metastasis incidence off sets

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any overall survival (OS) benefit for head and neck cancers from definitive locoregional treatment. This may be due to improved availability and use of positron emission tomography-computed tomography (PET-CT) and improvement in locoregional control.

With an aim to analyze incidence of distant metastasis and factors predicting distant metastasis for locally advanced squamous cell carcinoma (LAHNSCC), the present analysis was performed by our group.

## Materials and Methods

The present study is chart review of maintained database of oral cavity cancer patients undergoing surgical treatment in our group. All oral cavity patients undergoing curative intent treatment were included in the analysis. The patients who had unresectable disease (post neoadjuvant chemotherapy [NACT]) or had distant metastasis at presentation were excluded from the analysis. Whole-body PET-CT scan or contrast-enhanced CT scan of thorax, abdomen, and pelvis was done for the diagnosis of distant metastasis for this group of patients.

The time frame of the study was from August 2013 to December 2017. All patients had histologically proven squamous cell carcinoma of the oral cavity. Distant metastatic workup was done for the patients who had a clinical suspicion of distant metastasis or multiple bulky nodes or nodes present in lower neck at baseline. Histopathological factors were documented for all patients. They received adjuvant radiotherapy/chemoradiotherapy based on their histopathology report after appropriate surgical resection.

Clinical follow-up was done every 3 months after completion of adjuvant radiation/chemoradiation. Clinical examination of oral cavity, larynx, and neck was done on follow-up. Radiological investigations were done when deemed necessary based on suspicion of recurrent disease. Recurrent disease was suspected if the patient presented with recurrent lesion in oral cavity, swelling in the neck nodal stations. Distant metastasis was suspected in patients with bone pain, chronic cough with or without hemoptysis, unexplained weight loss, and anorexia. Metastatic workup was done for patients with symptoms of distant metastasis and/or with surgically salvageable locoregional disease. PET-CT scan was done whenever feasible. No metastatic workup was done for patients who had nonsalvageable locoregional disease. Patients were followed up every 3 months till 2 years, every 6 months until 5 years and annually thereafter.

All statistical analysis was done using Statistical Package for the Social Sciences (SPSS 20, SPSS Inc., 233, Chicago, Illinois, United States) software. Survival analysis was done using Kaplan–Meier methods. Prognostic factors affecting the various disease end points were analyzed by log-rank test for univariate and cox proportional hazard method for multivariate analysis.

## Results

Five hundred and thirty-one patients were enrolled in this analysis from August 2013 to December 2017. The median age of the cohort was 49 years (range: 17–71 years) with male predominance (M:F ratio of 5:1). Ninety-five percent of patients had a history of tobacco/smokeless tobacco consumption. Eighty-five percent of patients had locally advanced disease at the time of presentation. Two hundred and ninety patients (54%) had pathological neck-node positive for metastasis, of which 184 patients (63%) had multiple neck nodes. All demographic and histopathological parameters are shown in ► **Table 1**.

Majority of the patients had microvascular reconstruction for the defect postsurgery. The microvascular reconstruction was done in 317 (66%) patients while pedicle flaps in 121 (23%) patients. Remaining patients had either primary closure or local flap.

NACT was given for 28 patients (5%). Four hundred and sixty-two patients (87%) received adjuvant radiotherapy. Concurrent chemotherapy was given in 220 patients. The median dose of radiation was 60 Gy. Cisplatin was given weekly at 30 mg/m<sup>2</sup> and the median number of concurrent chemotherapy cycles was 5 (range: 3–6).

At the time of analysis, 406 patients were alive with 374 patients without any evidence of disease. The median follow-up of alive patients was 21 months

**Table 1** Baseline characteristics

	Number of patients (%)
Age, median (range)	49 (17–71)
Gender	
Male:female	452:79
Smoking habit	
Nonsmoker (%)	35 (6)
Smoker (%)	496 (94)
Site	
Buccal mucosa/alveolus	317 (60)
Tongue/FOM	172 (32)
Lip	7 (2)
Maxilla	29 (6)
Stage	
I, II	78 (15)
III, IV	453 (85)
Reconstruction	
Primary closure	83 (15)
Local flap	10 (2)
PMMC	121 (23)
Microvascular free flap	317 (60)

Abbreviations: FOM, floor of mouth; PMMC, pectoralis major myocutaneous flap.

(range: 1–56 months). Overall, 133 patients had locoregional recurrences.

Distant metastasis was seen in 95 patients (18%). Of these 95 patients, 72 patients had locoregional failure along with distant metastasis. There were 10 patients with nonsalvageable local or regional recurrence for which metastatic workup was not done to document synchronous distant metastasis. These patients were not recorded as distant metastasis event for the present analysis. The most common site of distant metastasis was lung, followed by bone. Thirty-seven patients had a combination of lung/bone and skin nodules involvement (► **Table 2**).

The overall distant metastasis-free survival for the cohort was 79% at 2 years and 75% at 3 years. The median time to develop distant metastasis was 7 months' (range: 1–34 months) postsurgery. Twenty-four patients had developed distant metastasis within 4 months' postsurgery. Median survival postdevelopment of distant metastasis was 2 months (range: 1–21 months).

On univariate analysis, multiple factors were significant for the development of distant metastasis.

However, on multivariate analysis, patients with high nodal burden ( $p = 0.02$ ) and perineural invasion (PNI) ( $p = 0.04$ ),

Differentiation ( $p = 0.04$ ), patients receiving NACT ( $p = 0.002$ ), and age <40 years ( $p = 0.05$ ) were significant factors for distant metastasis (► **Table 3**).

## Discussion

The incidence of distant metastasis in our group of patients is 18% with a 2-year distant metastasis-free survival of 79%.

Conventionally, head and neck cancers are being considered as locoregional disease. The predominant pattern of failure is locoregional recurrences.<sup>6,7</sup> All treatment intensification has been traditionally targeted toward improvement in locoregional control. In spite of improved locoregional control, OS has been stagnant. One of the results of stagnant OS is higher incidence of distant metastasis. This rise is specially seen in the last couple of decades.<sup>8</sup>

Conventionally, the incidence of distant metastasis has been reported at around 8 to 13%.<sup>3-5,9,10</sup> The reported incidence is higher for our group of patients. One of factors could

**Table 2** Follow-up status

Follow-up status	No of patients (%)
NED	374 (70)
Primary recurrence	4 (1)
Nodal recurrence	1 (0)
Primary + nodal recurrence	56 (10)
Distant metastasis	23 (4)
Locoregional recurrence + distant metastasis	72 (14)
Second primary	1 (0)

Abbreviation: NED, no evidence of disease.

**Table 3** Prognostic factors (univariate analysis)

	Number of patients	2 years DMFS (%)	p-Value (Log rank)
Sex			
Male	452	80	0.253
Female	79	75	
Age			
<50	280	83	0.189
>50	251	77	
NACT			
Given	28	54	0.001
Not given	503	81	
Free microvascular flap			
Yes	317	81	0.271
No	214	77	
T stage			
T1, T2	114	91	0.000
T3, T4	417	76	
Nodes			
No, N1	347	89	0.001
N2, N3	184	62	
Nodes			
Negative	241	90	0.001
Positive	290	70	
pT size (cm)			
<4	384	84	0.01
>4	147	75	
Thickness (cm)			
<1	216	87	0.01
>1	315	73	
Differentiation			
Well	53	94	0.002
Moderate	384	81	
Poor	93	65	
LV I			
Absent	425	81	0.05
Present	106	72	
PNI			
Absent	291	84	0.001
Present	240	73	
PNE			
Absent	330	86	0.001
Present	201	69	

(Continued)

**Table 3** (Continued)

	Number of patients	2 years DMFS (%)	p-Value (Log rank)
Conc chemotherapy			
Yes	220	79	0.09
No	311	82	

Abbreviations: DMFS, distant metastasis-free survival; LV I, lymphovascular invasion; NACT, neoadjuvant chemotherapy; PNE, perinodal extension; PNI, perineural invasion.

be higher proportion of gingivobuccal complex tumors in our series that has a better locoregional control as compared with tongue cancers. However, this was not significant on univariate analysis.<sup>11</sup>

The most common site of distant metastasis for head and neck cancers is reported to be lung and bone.<sup>12</sup> Similar trend was seen in our analysis where lung was the most common site for distant metastasis followed by bone and skin nodules. We saw a higher distant metastasis in patients with higher node positive disease (N2, N3), PNI, and young patients. This is similar to reported literature except for perinodal extension.<sup>8</sup>

Distant metastasis predicts poor survival for head and neck cancer patients. The median OS after detection of distant metastasis in our study was 2 months (range: 1–21 months), as compared with 7 months reported by Wiegand et al post-distant metastasis survival depends on the general condition and fitness of patients. About one-fourth of patients are not able to receive any palliative chemotherapy postdistant metastasis.

High incidence of distant metastasis highlights the need for intense and effective systemic therapy. A meta-analysis has shown no significant benefit with either neoadjuvant or adjuvant chemotherapy for LAHNSCC.<sup>13</sup> This option of adding systemic therapy needs to be explored further with alternate agents/schedules changing of agents and/or schedules. Over the last few years, the use of oral metronomic therapy has shown encouraging results for recurrent and/or unresectable head and neck cancers.<sup>14</sup> Oral metronomic therapy is beneficial due to its convenience to use, lower cost, higher compliance, and favorable toxicity profile as compared with intravenous chemotherapy. The addition of oral metronomic therapy may be explored in future studies especially in high-risk group.

The most common chemotherapy schedule in concurrent setting is 3 weekly high-dose cisplatin in Western population. However, in Indian subcontinent, weekly cisplatin and 30 mg/m<sup>2</sup> is practiced widely due to favorable toxicity profile. All patients in the present cohort had received weekly cisplatin. Recently, Noronha et al have shown that, weekly cisplatin is inferior in terms of oncological outcomes as compared with 3 weekly cisplatin.<sup>15</sup> The cumulative dose of more than 200 mg/m<sup>2</sup> may be needed for optimal outcomes. The incidence of systemic failures was similar in both arms.

As per the current guidelines, baseline metastatic workup is not routinely done for oral cavity carcinoma. The median time to development of distant metastasis in our study is

7 months with 24 patients developing metastasis within 4 months' posttreatment. This gives indirect evidence that these patients may be harboring distant metastasis at the time of locoregional treatment. We strongly recommend doing metastatic workup for LAHNSCC prior to any definitive locoregional treatment. This would prevent toxicity, morbidity, and cost related to locoregional treatments.

The strength of our analysis includes large series with good long-term follow-up. There are few limitations including retrospective analysis, use of weekly cisplatin and dose of 30 mg/m<sup>2</sup> as concurrent chemotherapy.

## Conclusion

The reported incidence of distant metastasis is higher in our series as compared with reported literature. A baseline metastatic workup may be routinely done for LAHNSCC patients. Future studies may be designed to explore effective systemic therapy that as of now remains as an unmet need.

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## Conflicts of Interest

There are no conflicts of interest.

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