

## **Original Research Article**

### **Neoadjuvant chemotherapy: Role in locoregionally advanced oral cancers**

**Running Title:** Neoadjuvant chemotherapy for oral cancer

#### **Abstract**

**Background and Aim:** Oral-carcinoma is one of the most common cancers world-wide. Its treatment in advanced conditions to increase the survival rate is a major concern. This study was aimed at assessing the use of neoadjuvant cancer therapy (NACT) for improving the operability in non-operable patients with advanced oral carcinoma (T4b and N3 stage) and to allow easier resection.

**Methodology:** This prospective study included total of 40 patients with advanced oral carcinoma (T4a, T4b, and N3 stages), who were administered with NACT - Cisplatin ( $80\text{mg}/\text{m}^2$ ) over 2 days and 5-fluorouracil ( $750\text{ mg}/\text{m}^2$ ) for 4 days for a period of 18 months. Followup of patients (6 months) was advised to assess adverse effects. Chi-square test was performed to analyze the association of NACT with resectability and operability in patients.

**Results:** Patients displayed T4a (70%), T4b (30%), and N3 (15%) stages of oral cancer. Stable disease was observed in 57.5% of patients, indicating its importance in cancer treatment. Easier resection was observed in operable (67.85%) and non-operable (50%) patients. Significant association of cancer staging with resectability ( $P=0.012$ ) and operability ( $P=0.001$ ) after NACT was observed. The major adverse events observed post NACT were nausea/vomiting (28.3%), neutropenia (11.66%), diarrhea (8.33%), and anemia (3.33%). Vomiting and neutropenia were significantly associated with cancer staging ( $P=0.014$ ) and gender ( $P=0.029$ ), respectively.

**Conclusion:** Resectability and operability were noted in majority of the patients with NACT in the non-operable group. Further studies on its profound use in oral squamous cell carcinoma can help reduce morbidity and increase the survival rate.

**Keywords:** Cisplatin, Neoadjuvant therapy, Neoplasm staging, Neutropenia

## **Introduction**

Oral cavity cancer is a universal problem with an incidence in 300,000 patients, 50% of who are at high risk as they are diagnosed at advanced stages.<sup>1</sup> Oral squamous cell carcinoma (OSCC) constitutes a major percentage (30%) of cancers in India.<sup>2</sup> Most cases are locally advanced and have a poor prognosis.<sup>1,3</sup> Oral cancer is a malignant neoplasm that occurs on the lip or in the oral cavity, as 90% of the cancers histologically originate in squamous cells.<sup>4,5</sup>

Treatment strategies are designed according to the disease stage, site of primary tumor site, operability, patient's age, and performance status. The treatment of locally advanced diseases/tumors is based on a multimodality approach (surgery, chemotherapy, radiation therapy [RT], targeted drug therapy, immune therapy, and/or in combinations). Resection is one of the modalities followed for a better outcome.<sup>2</sup> Neoadjuvant chemotherapy (NACT) is one of the approaches which shrinks the tumor and improves the locoregional control and survival of the patient, enhancing the organ preservation in resectable oral cavity cancer.<sup>2</sup> NACT is also used in unresectable tumors. Surgery is the preferred treatment for resectable tumors although radical radiotherapy may be used in some cases; however, primary RT with or without systemic therapy is the standard approach for patients whose tumors are unresectable or who are unwilling to undergo surgery.<sup>6,7</sup> In spite of the advances made in the diagnosis, surgery, radiotherapy, chemotherapy, and reconstruction over the past 50 years, oral cancers continue to pose a challenge to the surgeon. In India, the buccal mucosa and retromolar trigone are the most frequently encountered primary sites.<sup>7</sup>

Surgery and post-operative radiotherapy were substituted with NACT due to its reduced adverse effects. This involves 2-3 sessions of chemotherapy administration. The

most commonly used regimens are cisplatin plus 5-fluorouracil and cisplatin plus bleomycin. An overall response level of 80% is often achieved with these regimens although the complete response rate is only 30% with these drugs.<sup>8-10</sup>

According to the literature, the advantages of NACT include cancer reduction, regional control, decline in recurrence, decreased remote metastases, organ preservation in resectable tumors, reduced need for postoperative radiotherapy and mandibulectomy, and an improvement of 4-6% in the survival rates.<sup>10</sup> Therefore, it is necessary to use these neoadjuvants in the treatment of resectable oral carcinoma which can increase the survival rate in patients. NACT has very less adverse effects compared to surgery and radiotherapy. Hence, this study was performed to determine the effect of NACT on operability (T4b and N3 stages) and resectability (T4a) in advanced carcinoma.

## **Materials and Methods**

A total of 40 patients attending the Oncology Department with locally advanced cancer (T4a, T4b, and N3 stages) in the oral cavity or palpable neck nodes were selected for this prospective study conducted between December 2017 and June 2019. The study was initiated in a tertiary care hospital in Maharashtra, India, after the Institutional Ethical Committee's clearance. Patients with history of previous treatment, distant metastases, abnormal renal and hepatic function, and aged <20 years and >80 years were excluded from the study. A written consent was obtained from all the patients before initiation of the study. Convenient sampling methods were used to recruit study participants.

The demographic characteristics, clinical and past medical history, and family and social history were recorded in a standard, semi-structured case record proforma. All patients with advanced oral carcinoma (T4a, T4b, and N3 stages) were given 3 cycles of NACT every 4 weeks. The medications used were Cisplatin (80 mg/m<sup>2</sup>) for 2 days and 5-fluorouracil (750 mg/m<sup>2</sup>) for 4 days along with hydration and antiemetics. If the patients had resectable tumors, they were taken for surgery, and followup was done for 6 months to assess for recurrence after chemotherapy and adverse effects.

Statistical analysis was performed by using the IBM SPSS version 22.0 software. Results were expressed as frequency and percentage. Association of resectability and operability with the set variables (age, site, and stage of cancer) was assessed by Chi-square test and considered significant at  $P < 0.05$ .

## Results

Demographic data indicated that majority of the patients were males (87.5%), with a male to female ratio of 7:1. Most of the patients were in the age group of 41.5 years (32.5%). The most common sites of oral cancer were the buccal-alveolar complex (BAC) (87.5%), tongue (7.5%), and hard palate (5%) (Table 1).

Based on the set criteria, 70% of the cases had T4a, 30% had T4b, and 15% had N3 stage cancer. After NACT treatment, majority of the patients' disease stabilized (57.5%), 27.5% of the cases showed partial response, and 15% reported progressive disease (Table 1). Easier resection of tumors was achieved in 67.85% of the patients (among the operable cases), and 50% (among non-operable cases) were operable after chemotherapy (Table 2). Recurrence was observed following chemotherapy during the 6-month followup examinations.

An association between the socio-demographic variables and the outcome (resection/operability) of NACT was observed (Table 3). Age, gender, and site of cancer had no impact on the chances of resectability and operability of the oral cancer after NACT. However, Chi-square test revealed that staging of oral cancer had a significant association with resectability ( $P=0.012$ ) and operability ( $P=0.001$ ) indicating that the stage of cancer is important for treatment irrespective of age, gender, and site of cancer. Age and gender do not play a role in cancer initiation and progression; however, the site of cancer may impact the treatment in certain situations.

Adverse effects of chemotherapy (Table 4) were noted during 6 months of followup studies with majority of them showing symptoms of nausea/vomiting (28.33%), neutropenia (11.66%), diarrhea (8.33%), and anemia (3.33%). Table 5 indicates a significant association between gender and neutropenia ( $P=0.029$ ) and also between staging and vomiting ( $P=0.014$ ). However, there was no significant association between response to treatment and complications with regard to the other variables (Table 5).

## Discussion

This study was conducted to determine the use of NACT for improving the operability and resectability in non-operable patients with advanced OSCC (T4b and N3 stage) and further determine the recurrence in the patients. High-risk advanced stage carcinoma patients (T4a, T4b, and N3) were included by random sampling and observed for the response to 3 cycles of NACT for 4 weeks.

In this study, majority of the cases were males (35, 87.5%) and were in the age group of 41-50 years (32.5%). Smoking and tobacco chewing were the main reasons for the prevalence of oral cancer in middle-aged men. This could be the probable reason for the difference in gender- and age-related oral cancers in rural population.<sup>11</sup> Majority of the patients showed oral cancer in the buccal-alveolar complex (87.5%), tongue, and hard palate in the present study, which was similar to the findings in the studies by Jain et al with 81.7% in the buccal-alveolar complex.<sup>12</sup> Patil et al also observed similar results in the buccal mucosa (69.3%), anterior two-third of the tongue (21.8%), floor of the mouth (4%) and the alveolus (3.9%).<sup>13</sup> In Olasz et al's study, the presence of oral cancer on the floor of the mouth was 39% but was very low in the buccal mucosa (2%),<sup>14</sup> whereas Sadighi et al reported tongue, gingiva, and mouth floor as the most commonly affected areas.<sup>15</sup> Therefore, oral carcinoma is prevalent in all these sites and needs further attention and treatment.

The staging of oral cancer is important for the selection of postoperative adjuvant therapy and determining the course of treatment. According to the American Joint Committee on Cancer based on the criteria for TNM staging (2017), the disease is considered as advanced if it is at the 3<sup>rd</sup> and 4<sup>th</sup> stage; is called localized disease if it is detected at 1<sup>st</sup> and 2<sup>nd</sup> stages; and if the patient undergoes surgical resection, it is a pathological stage (pTNM). In this study, most of the patients belonged to T4a (70%), T4b (30%), and N3(15%) stages, indicating the advancement of cancer. T4a and T4b stages had a tumor size of >4 cm and a depth of >10 mm depth. At N3 stage, the tumor size was >6 cm in the lymph node (metastasis). These patients underwent NACT, and the operable patients further underwent resection of the tumors to reduce the morbidity. Response to treatment with Cisplatin and fluorouracil was achieved in 57.5% of the patients with stable disease while 27.5% patients showed a partial response. However, the response rate was comparatively high in the present study than that reported by Jain et al, wherein the overall response rate was 24.28%, 53.94% patients had stable disease, and 15.78% had disease progression.<sup>12</sup> The possible reason could be the number of cycles of NACT in this study being high (3 cycles for 4 weeks) than in the previous report (2 cycles).

The resectability was high in both operable (67.85%) and non-operable (50%) patients after chemotherapy whereas Patil et al reported 40% resectability.<sup>16</sup> In this study, resectability was noted in 68% of the patients on a 3-drug regimen and 37.89% on a 2-drug regimen which was almost similar to the findings of Jain et al and Patil et al with high resectability on 3-drug regimen.<sup>12,16</sup> Low resectability in previous studies could be probably due to the advanced

stages of oral carcinoma in the sample population. Meta-analysis revealed that most of the single- and triple-regimen therapy failed to show resectability and survival advantage after induction of chemotherapy;<sup>17</sup> however, in this study, all patients had resectable tumor and only 20% of the patients were with T4 stage oral carcinoma. Also, recurrence was not observed in any of the patients after 6 months of followup.

Chemotherapy and its adverse effects include diarrhea and neutropenia, with an incidence rate of 82% which is very high. However, mortality and morbidity due to these events are not established.<sup>18</sup> The present study reported the common adverse events after chemotherapy like nausea/vomiting (28.33%), neutropenia (11.66%), and diarrhea (8.33%). Anemia (3.33%) was noted in very few patients after chemotherapy, indicating decreased effects in relation to diarrhea and neutropenia. Other studies have also reported similar common adverse events after chemotherapy. Olasz et al reported alopecia (grade I-II), dermatitis (grade I), and leucopenia (20%).<sup>14</sup> Patil et al also reported thrombocytopenia (11.54%) along with febrile neutropenia (34.62%) and anemia (11.54%).<sup>13</sup>

The study was limited by the sample size and also lacked data on the patients' addictions which could be the reason for oral cancer.

## **Conclusion**

From the current study, it was evident that use of NACT (Cisplatin) increased the chances of operability and delayed the disease progression in T4b stage, which can lead to reduced morbidity and increase the survival rate after surgery. Hence, multi-institutional trials in larger cohorts can provide a definite protocol for use of NACT and improve the prospects for non-operable oral malignancies.

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**Table 1:** Demographic and other set variables for oral cancer in patients

<b>Variables</b>	<b>Frequency; n (%)</b>
<b>Gender</b>	
Male	35 (87.5)
Female	5 (12.5)
<b>Age (years)</b>	
21-30	3 (7.5)
31-40	7 (17.5)
41-50	13 (32.5)
51-60	8 (20.0)
61-70	5 (12.5)
71-80	4 (10.0)
<b>Site of Cancer</b>	
Tongue	3 (7.5)
BAC	35 (87.5)
Hard palate	2 (5.0)
<b>Staging</b>	
T4a	28 (70.0)
T4b	12 (30.0)
N3	6 (15.0)
<b>Response</b>	
Satisfactory response	11 (27.5)
Stable disease	23 (57.5)

Unsatisfactory response 6 (15.0)

BAC, Buccal alveolar complex

**Table 2:** Operability and resection in the patients after neoadjuvant chemotherapy

	Operability	Easier resection		Total
		Achieved n (%)	Non-achieved n (%)	
<b>Before Chemotherapy</b>	Operable	25 (89.28)	3 (10.72)	28
	Non-operable	6 (50.00)	6 (50.00)	12
	Total	31 (77.50)	9 (22.50)	40
<b>After Chemotherapy</b>	Operable	6 (100.00)	-	6
	Non-operable	25 (73.53)	9 (26.47)	34
	Total	31 (77.50)	9 (22.50)	40

**Table 3:** Association of resectability and operability with demographic variables

Demographic variables	Resectability		P value	Operability		P value
	Achieved	Not Achieved		Achieved	Not Achieved	
<b>Gender</b>						
Male	26	9	0.433 <sup>C</sup>	0	5	0.564 <sup>C</sup>
Female	5	0		6	29	
<b>Age (years)</b>						
21-30	2	1		0	3	
31-40	5	2		1	6	
41-50	12	1	0.725 <sup>C</sup>	2	11	0.932 <sup>C</sup>
51-60	5	3		2	6	
61-70	4	1		0	4	
71-80	3	1		1	3	
<b>Site of cancer</b>						
BAC	27	8		5	30	
Hard palate	1	1	0.342 <sup>C</sup>	0	2	0.585 <sup>C</sup>
Tongue	3	0		1	2	
<b>Staging</b>						
4a	25	3	0.012 <sup>C*</sup>	0	28	0.001 <sup>C*</sup>
4b	6	6		6	6	

BAC, Buccal alveolar carcinoma; C, Chi-square test

\*Significant at  $P < 0.05$

**Table 4:** Adverse effects after neoadjuvant chemotherapy

Adverse Events	Frequency; n (%)
Anemia	2 (5.0)
Neutropenia	7 (17.5)
Vomiting	17 (42.5)
Diarrhea	5 (12.5)

**Table 5:** Association of adverse effects post NACT with demographic variables

Adverse effects	Gender	Age	Site of cancer	Staging
Anemia	0.269	0.558	0.091	0.563
Neutropenia	<b>0.029*</b>	0.177	0.720	0.418
Vomiting	0.364	0.535	0.371	<b>0.014*</b>
Diarrhea	0.111	0.113	0.491	0.308

NACT, Neoadjuvant chemotherapy

\*Significant at  $P < 0.05$