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Role of Neoadjuvant Chemotherapy in Locoregionally Advanced Oral Cancers

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aim: Oral-carcinoma is one of the most common cancer 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 disease) and to observe easier resection in T4a disease.
Methodology: This prospective study included total 40 patients with advanced oral carcinoma (T4a, T4b, and N3 stages), who were administered with NACT- Cisplatin (80 mg/m^2) over 2 days and 5-fluorouracil (750 mg/m^2) for 4 days along with hydration and antiemetics (3 cycles for every 4 weeks) and later, if resectable, will be taken for the surgery . Follow up of patients (6 months) was advised to assess recurrence if any. Chi-square test was performed to analyze the association of NACT with resectability and operability in patients. Histopathological examination was done to see for extent and margns status post surgery. Non operable cases were given palliative radiotherapy and symptomatic treatment.
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 67.85% i.e. 19 patients. Significant association of locoregionally

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advanced oral cancer (T4a, T4b and N3 disease) with respectability (*P*=0.012) and operability (*P*=0.001) after NACT was observed. The most common adverse events observed during NACT were nausea/vomiting (28.3%), neutropenia (11.66%), diarrhea (8.33%), and anemia (3.33%).
Conclusion: Easier resection in 67.85% cases among operable group seen and 50% of cases among non operable group became operable. 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.

1. 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 stage [1]. Oral squamous cell carcinoma (OSCC) constitutesa major percentage (30%) of cancers in India [2]. Most cases arelocally advanced and have a poor prognosis [1,3]. 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 [4,5].

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 [2]. 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 [2]. 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 [6,7]. 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 [7].

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 [8-10].

According to the literature, the advantages of NACT include cancer reduction, regional control, decline 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 [10]. 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 easier resectability (T4a) in advanced carcinoma.

2. MATERIALS AND METHODS

A total of 40 patients attending the Oncology Department with locally advanced oral 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 (EC NO: KIMSDU/IEC/03/2017).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. 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 ($80mg/m^2$) for 2 days and 5-fluorouracil

(750mg/m^2) for 4 days along with hydration and antiemetics. If the patients had resectable tumors, they were taken for surgery, and follow up was done for 6 months to assess for recurrence after chemotherapy and adverse effects. CT (head, neck and face) was the guiding tool before, after NACT and during follow up period. Histopathological examination was done too see the extent and margins status post surgery. Non operable cases were given palliative radiotherapy and symptomatic treatment.

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 $P<0.05$.

3. 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 NACT (Table 2). Recurrence was observed during the 6-month follow up .

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, with majority of them showing symptoms of nausea/vomiting (28.33%), neutropenia (11.66%), diarrhea (8.33%), and anemia(3.33%).

4. DISCUSSION

Enhanced oral squamous cell carcinoma procedure classically requires surgical resection and postoperative adjuvant radiotherapy. Given this intensive dual-modality treatment, the disease result remained constant at 30% local or regional recurrence, 25% DM, and 40% five-year survival. Neoadjuvant chemotherapy has been researched over the last two decades and has been used in patients with locally enhanced squamous cell carcinoma of the head and neck. Concurrent radiochemotherapy is the standard treatment in clinicians with unresectable, nonmetastatic locoregionally progressive head and neck squamous cell carcinoma [11].

The main end-point in the management for regional recurrent oral squamous cell carcinoma is the conservation of tissues. It minimizes the acute and chronic effects of diagnosis, contributing to a better quality of life and prolonging total and progression-free longevity.

Current results suggest the possibility of more aggressive operation with induction chemotherapy in oral cavity squamous cell carcinoma without loss of life or decreased relapse. The literature review reveals that the use of the induction chemotherapy procedure for the diagnosis of non-metastatic oral cavity squamous cell carcinoma was restricted in specific situations. The role of induction chemotherapy in the survival of organs in larynx, oropharynx and hypopharynx tumors is well established.

Similarly, induction chemotherapy is prescribed for the treatment of oral cavity squamous cell carcinoma in which demolition surgery, such as full resection of the tongue or pharyngectomy, is needed. Theoretically, chemotherapy before surgery or radiotherapy may be advised owing to the preserved tumor vasculature which enables medications to be administered to the tumor more effectively [7].

4.1 Demographic Characteristics

In the present study, we assessed the demographic features of the study subjects. We observed that the majority of the study subjects were males (87.5%) and 12.5 % cases were

females. The male:female ratio observed in the current study was 1:0.142.

In the present study, we assessed the age distribution of the study subjects. We observed that the majority of the study subjects belonged to the age group of 41-50 years (32.5%), followed by 51-60 years among 20% cases and 17.5% cases belonged to 31-40 years age group

Ramchandra stated that the most common age group of patients with oral cancer is 31–40 years (38.5%) and is followed by the younger age group of 21–30 years (35.2%). Das AK et al. in their case report of an oral cancer case, found the age 30 years of their study subject. Rajesh Jain et al. [11], in their study observed that, the median age of study subjects was 45 years. They found that 89.47% of study subjects were males while 10.52% of cases were females. The M:F ratio was 1:0.11. L Olasz et al. [12] in their study reported that the mean age of the study subjects was (+/− SD) was 52.4 (+/− 9.7) and 85 were male. S. Sadighi et al. [13] In their study reported that The mean age was 59 ± 14.4 years old with a median of 62. Among the participants, there were 14 men.

4.2 Site of Oral Cancer

In the present study, we assessed the site of oral cancer among the study subjects. We observed that in the majority of the study subjects, the oral cancer was located at the buccal-alveolar complex (87.5%), followed by tongue among 7.5% cases and hard palate among only 5% cases.

Rajesh Jain et al. [11], in their study observed that, the most common site involved was buccal-alveolar complex among 81.57%, which was similar to the current study. Patil et al. [12] in their study observed that the most common site of oral cancer was Buccal mucosa:69.3%, Anterior 2/3 of the tongue:21.8%, Floor of mouth:4%, Alveolus:3.9%. L Olasz et al. [12] in their study reported that The percent in the localization of tumours were as follows: the floor of mouth 39, tongue 29, gingiva 20, retromolar trigone 6, palate 4, buccal 2.

S. Sadighi, et al. [13], In their study reported that the tongue, gingiva and mouth floor were the most commonly affected areas.

4.3 Distribution according to Staging

In the present study, we classified the study subjects according to various parameters such as tumour size, nodal status.

According to the set inclusion criteria, in this study we included T4a or T4b cases. 60% of cases belonged to T4a, while 40% of cases have belonged to T4b. 15% of cases have belonged to the N3 group. Rajesh Jain et al. [11], in their study observed that, 57.89% of cases of N2 stage and 2.63% cases of N3 stage.

S. Sadighi, et al. [13]. In their study reported that approximately 37% of tumours were well-differentiated, 37% intermediately differentiated and 25% were poorly differentiated; 12% of tumours were 3-4cm in size (T2), 63% more than 4cm in size (T3) and 25% had invaded into surrounding tissues (T4). Only 7(29%) patients had no lymph node involvement. However, 12 patients had unilateral lymph node involvement, and 5 patients had bilateral cervical lymph node involvement.

4.4 Response Achieved after NACT

In the current study, we evaluated the cases according to the response achieved after NACT. We observed that among the majority of the cases it remained a stable disease (57.5%), 27.5% of cases showed partial response and 10% cases reported progressive disease among them.

Rajesh Jain et al. [11], in their study observed that The overall response rate was 24.28%, 53.94% patients had stable disease and 15.78% cases underwent disease progression and 22.36% cases reported partial response. Findings reported in the current study were similar to their study.

S. Sadighi, et al. [13] In their study reported that Three (16%) patients showed complete pathological response to the treatment and only one patient showed progress with the extension of the tumour (more than 20% increase in size) during the chemotherapy courses. A total of 15 patients experienced relapse and 18 died until October 2014. Most relapses were because of loco-regional tumour progress. However, 3(10%) patients experienced distant metastases.

4.5 Efficacy

4.5.1 Resectability and operability

In the current study, we assessed the resectability and operability among the cases after chemotherapy. We observed that post-chemotherapy, the easier resection which was

achieved in 67.85% cases (among operable cases).

In the current study, we assessed the operability among non operable cases following chemotherapy. We observed that operability was achieved among 6 cases of 12 (50%), after chemotherapy.

Patil et al. [14] In their retrospective series reported the resectability close to 40%. S Arya et al. in their study, observed that the resectability was achieved among 68% patients with 3 drug regimen and 37.89% patients with 2 drug regimen.

Patil VM et al. [15], also found similar findings as S Arya et al. The response rate in their study with the three-drug and two drug regimens was 32.00% and 27.37%, respectively. Resectability was achieved in 17 patients with 3 drug regimen (68%) and 36 patients with 2 drug regimen (38%).

Jain Rajesh et al. [11], in their study obtained resectability of 65% in 3 drug regimen and 21.4% in the two-drug regimen.

Table 1. Comparison of resectability obtained in various studies

Studies	Resectability
Current study	67.85%
Patil et al. [14]	40%
S Arya et al.	68%
Patil VM et al. [15]	68%
Jain Rajesh et al. [11]	65%

Table 2. Distribution of study subjects according to their gender

Gender		Frequency	Percent
Valid	Male	35	87.5
	Female	5	12.5
	Total	40	100

Table 3. Distribution of study subjects according to their age group

Age group	Number of cases	Percentage
21-30	3	7.5
31-40	7	17.5
41-50	13	32.5
51-60	8	20
61-70	5	12.5
71-80	4	10
Total	40	100

Table 4. Distribution of study subjects according to site of oral cancer

Site of cancer	Number of cases	Percentage
Tongue	3	7.5
Buccal-alveolar complex	35	87.5
Hard palate	2	5
Total	40	100

Table 5: Distribution according to staging

Staging	Number of cases	Percentage
T4a	28	70
T4b	12	30
N3	6	15

Table 6. Distribution of study subjects according to response achieved after NACT

Response Achieved after NACT	Number of patients	Percentage
Satisfactory Response	11	27.5
Stable Disease	23	57.5
Unsatisfactory respons	6	15
Total	40	100

TABLE 7. Status of easier resection among operable cases

Status of easier resection among operable cases	Post-chemotherapy	
	Number of patients	Percentage
Achieved	19	67.85
Not achieved	9	32.14
Total	28	100

Table 8. Operability among non operable cases

Operability among non operable cases	Post-chemotherapy	
	Number of patients	Percentage
Achieved	6	50
Not achieved	6	50
Total	12	100

Table 9. Distribution of study subjects according to recurrence

Recurrence	Number of patients	Percentage
Yes	0	0
No	40	100
Total	40	100

Table 10. Distribution of study subjects according to adverse events

Adverse events	Number of patients	Percentage
Anemia	2	3.33
Neutropenia	7	11.66
Vomiting	17	28.33
Diarrhoea	5	8.33

Biologically, oral cancers may be less sensitive to chemotherapy than pharyngeal malignancy. This was demonstrated in a single-institution study where induction chemotherapy was shown to be associated with detrimental effects. In another trial by Lictria et al. In resectable oral cavity cancers, the addition of induction chemotherapy failed to produce a survival advantage. However, in this trial all patients had resectable cancer and only 20% of patients with T4 stage.

4.6 Recurrence

In the present study, we assessed the study subjects according to recurrence the following chemotherapy during 6 months follow up. We did not found any recurrence among the study subjects.

Patil VM et al. [15], in their study observed that The median duration of follow up is 15 months. Seventy-seven events had taken place during this time. In the majority, i.e., 71 patients, these were loco-regional events. Fourteen patients had an only nodal failure while the rest had both local and regional failure. Distant metastases were seen in six patients. The sites of distant metastases were the lung in three patients and skin nodules in the rest.

4.7 Adverse EVENTS

In the present study, we assessed the adverse events following chemotherapy. We reported that

most common adverse event was nausea-vomiting among 28.33% cases, followed by neutropenia among 11.66% cases, diarrhoea among 8.33% cases and anaemia among 3.33% cases.

Rajesh Jain et al. [11], in their study observed that, the rate of neutropenia was 12.85 % while 38.5 % had vomiting. Some developed grade 3 diarrhoea and anaemia. L Olasz et al. [12] in their study the side effects of chemotherapy were slight and reversible. Alopecia (Grade I–II.) was observed in 33%. Grade I dermatitis was noted in 2% and 6% had Grade I–II gastritis. Grade I–II mucositis developed in 18% and 7% was Grade II nausea. 28% of the patients developed Grade I anaemia and 20% leucopenia.

Patil VM et al. [15], in their study, observed Anemia among 11.54% cases, Febrile neutropenia among 34.62% cases, Thrombocytopenia among 11.54% cases, Vomiting among 46.15 cases and Diarrhea among 30.77% cases [16-17].

5. CONCLUSION

From the current study, it was concluded that:

1. In the current study, we observed that post-chemotherapy, the operability achieved among non-operable cases was 50%.
2. The easier resection was achieved in 67.85% cases (among operable cases).
3. At the 6 months follow up, we did not find any recurrence of the disease.
4. We observed that in majority of the study subjects, the oral cancer was located at buccal-alveolar complex
5. The use of induction chemotherapy in T4b unresectable cancer delays the progression of disease, gives partial response macroscopically, is safe and feasible
6. This approach is likely to lead to a survival advantage in patients who undergo surgery.
7. More multi-institutional trials in larger cohorts with prospectively collected data are required to arrive at a definite conclusion or protocol with NACT that may make a difference in inoperable oral malignancies.

CONSENT

A written consent was obtained from all the patients before initiation of the study.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s). (EC NO: KIMSDU/IEC/03/2017).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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