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ROLE OF SURGERY AFTER NACT IN ORAL CAVITY CANCERS

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INTRODUCTION

Primary tumors of the oral cavity may be derived from the mucosa, salivary glands, neurovascular tissues, bone and dental tissues. Over 90% of the tumors of the oral cavity are Squamous cell carcinoma arising from the mucosa. Oral cavity cancer is the 8th most common malignancy.[1] Every year about 3,00,000 people are diagnosed with oral cancer globally. Geographic variation is seen commonly with oral cavity malignancy, presenting as third most common malignancy in South East Asia region.[2] In India age-adjusted rates of oral cancer are high, that is 20 per 1,00,000 population and accounts for over 30% of all cancers in the country. Annually almost 80,000 cases are being diagnosed. In adult population mean age of occurrence is around 55 years. It ranks among top three cancers in the country.[3]Oral cancer is of significant health importance in India. Firstly, it is diagnosed at later stages which result in low treatment out comes and considerable costs to the patients whom typically cannot afford this type of treatment. Secondly, rural areas also have inadequate access to trained providers and limited health services. As a result, delay has also been largely associated with advanced stages of oral cancer.[4] High incidence of oral cancer in India can be attributed to a number of an etiological factors. Tobacco uses and alcohol are known risk factors for cancers of the oral cavity.[5]Estimates indicate 57% of all men and 11% of women between 15-49 years of age use some form of tobacco. Besides smoking, use of smokeless tobacco is also widely prevalent. Betel quid, also referred to as pan, consists of pieces of area nut, processed or unprocessed tobacco, aqueous calcium hydroxide (slaked lime), and some spices wrapped in the leaf of piper betel vine leaf. This is very common and is accepted socially and culturally in many parts of India.[6] Additionally, and powdered tobacco custom mixed by vendors. Commercially available sachets of areca nut, lime with or without powdered tobacco have become very popular, particularly among younger Indians. pan or gutka is kept in the cheek and chewed or sucked for 15-20 minutes. The majority of cases present to a healthcare facility at later stages of cancer subtypes, thereby chances of survival due to delays in diagnosis.[7]The treatment of advanced-stage oral cavity carcinoma currently involves a multi- disciplinary team approach led by the head and neck surgeon, radiation oncologist, and medical oncologist. The mainstay of curative treatment for these patients is surgical resection, neck dissection, and postoperative radiation treatment directed at the primary site of disease and the draining nodal basins in the neck. However, the advanced oral cancers are associated with dismal prognosis and high recurrence rates.[8] The rationale of proposing neo-adjuvant chemotherapy (NACT) in locally advanced oral cancers is to improve the overall outcome by reducing the tumor burden before radiation, facilitate possible resection following tumor shrinkage, and to prevent distant metastasis.

AIMS AND OBJECTIVES

This study was conducted with the following aims and objectives.

1. To understand the role of surgery after neo adjuvant chemotherapy in the locally

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advanced squamous cell carcinoma of buccal mucosa (T4a) who are resectable.

2. To compare the outcome of the patients who respond to neo-adjuvant chemotherapy with those who do not respond to neo-adjuvant chemotherapy in locally advanced carcinoma of buccal mucosa (T4a) who are resectable.

MATERIALS AND METHOD

Prospective single-center study conducted in 54 patients were found to be having locally advanced resectable (T4a) Squamous cell carcinoma of the buccal mucosa from December2019 to December 2021 in Department of Surgical Oncology at Tertiary Care cancer Hospital.

Inclusion criteria: Patients age 18 to 75 years with histologically confirmed Squamous cell carcinoma originating in buccal mucosa were eligible. Patients were required to have a locally advanced (T4a) lesion according to AJCC staging manual (8^{th}edition).[9] Other inclusion criteria included: Karnofsky performance status >60%, WBC count >3,000/L, hemoglobin > 8 g/L, platelet count > 80,000/L, ALT and AST > 2.5 times the upper limit of normal, bilirubin and serum creatinine <1.5 times the upper limit of normal.

Exclusion criteria: Patients were excluded if they had distant metastasis or other cancers, had undergone surgery involving primary tumor or lymph nodes (except diagnostic biopsy), had received prior radiotherapy or chemotherapy, had other malignancies within 5 years, or had creatinine clearance < 30 ml/min. Patients who progressed on neo-adjuvant chemotherapy to become unresectable were also excluded from the study.

Interventions: In all patients selected for study, 2 cycles of neo-adjuvant chemotherapy were given. Chemotherapy consisted of Docetaxel 75 mg/m^2 intravenously on day l, Cisplatin 75 mg/m^2 intravenously on day l and 5-fluorouracil 750mg/m^2 on days 1-5. Neo-adjuvant chemotherapy was administered every 3 weeks for two cycles, unless there was disease progression or unacceptable toxicity. Supportive measures included Dexamethasone, Antiemetics, and hydration. Radical resection of the primary lesion and radical neck dissection with appropriate reconstruction was performed. Postoperative radiotherapy was initiated 6 to 8 weeks after surgery in all patients. Concurrent chemotherapy was also in patients with following high risk features: Positive surgical margins & Extracapsular extension in cervical lymphnode.

Assessments: A complete medical history was obtained, and tumor assessment was performed at baseline. Clinical tumor response was determined by clinical evaluation and imaging studies (performed at baseline and 3 weeks after cycle two of induction chemotherapy). Responses were characterized according to RECIST criteria. Each variable is analysed and divided into responders and non responders and compared. Chi-square value was calculated and p-value derived. p value <0.05 is considered significant . p value was calculated using SPSS software**.** After completion of radiotherapy, patients were monitored every 3 months till the end of the study.

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OBSERVATIONS AND RESULTS

AGE (YEARS)	Responders	Non-Responders
10-25	3	5
26-40	4	7
41-55	7	10
56-70	5	4
71-85	0	2
Total	19	28
P value not significant as it is >0.05.		
The mean age was 44.5 years.		

Table No 1: Age Distribution

Sex	Responders	Non-Responders
Male	17(89.4%)	24(85.71%)
Female	2 (10.5%)	4 (14.28%)
Total	19	28
P value is not significant as it is >0.05.		

Table No 2: Sex Distribution

Addiction	Responders	on-Responders
Tobacco	15(78.94%)	23(82.14%)
Alcohol	9 (47.36%)	12(42.85%)
P value is not significant as it is >0.05.		

Table No 3: ADDICTION

	MEAN(n)
Responders to NACT	4.1cm
Non-responders to NACT	4.4cm
P value is not significant as it is >0.05.	

Table No 4: Size of Primary Tumor

Clinical Nodal Stage	Responders	Non-Responders
N0	0	2
N1	4	6
N2a	3	5
N2b	12	15
N2c	0	0
Total	19	28
P value is not significant as it is >0.05.		

Table No 5: Nodal Stage

Pathological complete response	2 (4.16%)
Partial response	17(35.41%)
Stable disease	27(56.25%)
Progression	2 (4.16%)
Total	48

Table No 6: Response to Neo-Adjuvant Chemotherapy

Nodal staging	Responders (19)	Nonresponders (28)
Same stage	11(57.89%)	23(82.14%)
Upstaging	0	5 (17%)
Down staging	8 (42.1%)	0

Table No 7: Lymph nodal response to NACT

Complications	No Patients (N=48)
Anemia	4
Neutropenia	1
Nausea and vomiting	44
Diarrhea	6
Peripheral neuropathy	8
Alopecia	45
Mortality	0

Table No 8: Complications OF Chemotherapy

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Type of Surgery	No of patients
WLE of tumor along with skin + Partial mandibulectomy	22
WLE of tumor with marginal mandibulectomy	3
WLE of tumor with sparing mandible	3
WLE of tumor with segmental mandibulectomy	19
Total	47

Table No 9: Type of Surgery Done

Type of reconstruction	No of patients
Naso labial flap	2
Pectoralis major myocutaneous flap	23
Bilobed pectoralis major myocutaneous flap	16
PMMC with deltopectoral fasciocutaneous flap	3
Forehead flap	3

Table No 10: Type of Reconstruction Done

Complications	Responders	Non-responders
Would infection	3	5
Minor flap loss	1	1
Major flap loss	0	1
Neck hematoma	1	1
Chylous fistula	0	0
Mortality	0	0
Total	5	9

Table No 11: Postoperative Complications

	Responders	Non-responders
Absent	17(36.17%)	24(51.06%)
Present	2(4.2%)	4(12.76%)

Table No 12: Presence of Lymphovascular Invasion

	Responders	Non-responders
Absent	17(36.17%)	25 (53.19%)
Present	2(4.2%)	3(6.3%)

Table No 13: Presence of Perineural Invasion

Mucositis	37
Dermatitis	33
Trismus	31
Dysphagia and odynophagia	28
Xerostomia	44
Mortality	0

Table No 14: Complications of Radiotherapy

	No of Patients
Responders	3 (15.78%)
Non-responders	7 (25%)

Table No 15: Local Recurrence

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	No of Patients
Responders	3 (15.78%)
Non-Responders	5 (17.85%)

Table No 16: Nodal Recurrence

	Mean Time
Responders	14.1 months
Non-Responders	9.5 months

Table No 17: Time to development of Local Recurrence

	No of Patients
Responders	5 (26.31%)
Non-Responders	10(35.71%)

Table No 18: Locoregional Recurrence

	Mean Time
Responders	14
Non-responders	9.25

Table No 19: Time to develop Loco-Regional Recurrence

	Responders	Non responders	Total
Distant mets(%)	7(36.8%)	10 (35.14%)	17(36.17%)
Mean duration	11months	10.5months	

Table No 20: Distant Metastasis

	No of Patients
Responders	15(78.94%)
Non-responders	21 (75.0%)
Total	36(76.59%)

Table No 21: Overall Survival

DISCUSSION

Treatment of advanced oral Squamous cell carcinoma classically includes surgical resection with postoperative adjuvant radiotherapy. Despite this aggressive dual modality therapy, the disease outcome has remained constant at 30% local or regional disease recurrence, 25% distant metastasis, and 40% five survival.[8] Neo-adjuvant chemotherapy has been studied over the past two decades and used for patients with locally advanced Squamous cell carcinoma of the and neck. However, use of neo-adjuvant therapy in resectable or low stages of OSCC is controversial. The study volume (47 cases) was reasonable compared to the previous studies in which Maggiore et al examined 89 patients and Park et al studied 114 patients.[10,11] Tumor size, lymphnode involvement, age and follow-up time were the variables in this study. Zhong et al considered the demographic, pathologic, treatment, and survival data in their study.[12]Chinn et al. studied 19 patients with stages III and IV. They determined age, gender, pretreatment stage, T and N classifications, smoking status, alcohol consumption, or tumor subtype on the basis of American Joint Committee on Cancer.[13]Tabrizi et al also retrospectively analysed 94 cases dividing the patients into two groups, one receiving neo-adjuvant chemotherapy and other one directly taken for surgery.[14]

The mean age in our study was 44.5 years and with male to female ratio of 6.8. In

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the study by Zhong et al the mean age was 55 years with male to female ratio of 2.46.[12]In the study by Licitra et al mean age of oral Squamous cell carcinoma was 50 years with male to female ratio of 3.

We noted that 80.85% of the study population was addicted to tobacco consumption and 44.68% of the study population was addicted to alcohol. Zhong et al found that 49% and 59.4% of their study population was addicted to tobacco and alcohol consumption respectively.[12] In retrospective study of Indian population by Walvekar et al around 86.4% people were addicted to tobacco abuse.[16] India ranks to be the second largest country for tobacco consumption globally and accounts for one-sixth of world's deaths due to tobacco.[17]

The T stage in both the arms was T4a, however it should be noted that most of the patients had advanced nodal stage when presented. 74.46% of the patients had advanced nodal stage at presentation. In the study by Walvekar et al, it was found that palpable lymphadenopathy was there in 65% of the patients at presentation.[16]Tabrizi et al calculated that advanced nodal staging was present in about 70% of the study population.[14] Study by KlugC et al concluded presentation of palpable lymphadenopathy in around 70% of population studied.[8] It is known that presence of Lymphadenopathy in head and neck Squamous cell carcinomas is itself a poor prognostic factor, decreasing the overall survival by 50%.[18]

In our study, we calculated response to neo-adjuvant chemotherapy according to RECIST criteria in four variables.[19]Pathological complete response was noted in 2 patients, partial response in 17 patients, stable disease in 27 patients and progression in 2 patients. The overall response rate to neo-adjuvant chemotherapy was 39.58%. It is important to note that both the patients who had complete pathological response developed local recurrence. Zhong et al established 80.6% response to neo-adjuvant chemotherapy however they did not find any correlation between response to neo-adjuvant chemotherapy and overall and disease free survival.[12]

In the study by Licitra et al which is a randomized trial involving 195 patients objective response rate to neo- adjuvant chemotherapy was seen in 82% of the patients.[15] However, they observed that in stage 4 tumors the response rate was only 18% which is consistent with our study where response rate was 39.58%. Licitra et al noted that survival was better in patients had complete pathological response with neo-adjuvant chemotherapy.

In our study responders to NACT have significant decrease in local and loco regional recurrence.[15] Patil et al also found response rate of 27% with two drug regimen.[20] Three drug regimen has been shown to have better response rate than two drug regimen. But, the three drug regimen has been associated with more toxicity and is used with caution. In our study, the toxicity of the neo-adjuvant chemotherapy was low. None of the patients developed grade 4 toxicity, grade 3 febrile neutropenia was seen in

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1 patient and grade 2 peripheral neuropathy was seen in 8 patients. In the study by Patil et al, 3 patients (3%) developed febrile neutropenia after receiving two drug regimen and 9 patients (34.6%) developed febrile neutropenia after receiving three drug regimen. The most common toxicities in both the studies were alopecia, nausea and vomiting.[20] However in the study by Zhong et al, none of the patients developed grade 4 toxicity with three drug regimen.[12]In their study also, the most common toxicities were alopecia and vomiting. Most of the patients receiving neo-adjuvant therapy are able to complete the planned treatment.

All patients who were resectable after neo-adjuvant chemotherapy were operated. Appropriate surgical resection with neck dissection was done in all patients. Pectoralis major myocutaneous flap (PMMC) was the most common flap used for reconstruction. The postoperative complications were similar in both responders and nonresponders.

In the study by Patil et al, the disease free survival and overall survival in the patients who were operated was significantly better than the patients who could not be operated.[20]Hence, surgery should be done in all patients who are resectable after neo-adjuvant chemotherapy. In the study by Zhong et al, the post operative complications were not affected by the administration of neo-adjuvant chemotherapy.[12]

In the study by Patil et al, surgery was done in patients who became resectable after neo-adjuvant chemotherapy. They did not report increase in the post operative complications in these patients.[20]

The above data shows that surgery can be safely done after administration of neo-adjuvant chemotherapy. Administration of neo-adjuvant chemotherapy does not affect the immediate surgical outcome in terms of morbidity or mortality. Presence of lymphovascular and perineural invasion was comparable in both the arms. Overall 12.76% of the population had lymphovascular invasion and 10.63% had perineural invasion. The incidence of lymphovascular and perineural invasion was similar in both the arms. Our study was comparable with the study of Walvekar et al in which 10.4%ofthe population had perineural invasion.[16] In the study by Jardim et al, lymphovascular and perineural invasion was present in 10% and 13% of the study population respectively and found it to be a poor prognostic factor. Regarding the lymph nodal response to NACT total of 34 patients had same stage with 11 (57.8%) from responders and 23 (82.14%) from non responders group and none were upstaged in responders group. This shows lymph nodal response to NACT is better in responders group.

As far as local recurrence is concerned, the responders to NACT group up had slightly lesser local recurrence rate of 15.78% than non- responders to NACT group which had 25.0% local recurrence, the difference was significant (P<.05). Nodal recurrence in the responders group was 15.78% as compared to 17.85% in non-responders to NACT group (P>0.05). Overall loco- regional recurrence (local + nodal) in responder group was 26.31% and 35.71% in non-responders group. Thus, we concluded that neo-adjuvant chemotherapy may reduce loco-regional recurrence rates. In the study by Licitra et al there was no difference interms of recurrence rates in the

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two studied arms.[15] At a median follow up of 30 months in the study by Zhonget there was no difference in disease free survival rates in both arms.

Our results differ with the above studies and our study needs more follow up to compare recurrence rates. However it should be noted the time to develop local and loco regional recurrence was significantly lesser in the responders group than non responders group (14 months vs 9.25 months, p<05). This could be due to the shorter follow up time of our study. Long term follow up is required to assess the loco regional recurrence rate in both groups. In our study 17 patients developed distant metastasis (36.17%). Among them 7 were from responders (36.8%) and 10 from non responders (35.14%). This shows no significant difference between both the groups (p>0.05) Overall survival at the end of study was observed as 78.94% in responders to NACT group and 75% in non-responders to NACT group. No significant difference was found in the two groups after doing statistical analysis.

There was no decrease in overall and disease free survival when all 141 patients were compared.[15]In summary, the immediate surgical outcome was similar in both the groups. Use of neo-adjuvant chemotherapy does not increase post operative complications. The patients responding to neo-adjuvant chemotherapy had significant delay in time to develop recurrence. However, surgery is able to achieve good loco-regional control even in patients who do not respond to chemotherapy.

The impact of neo- adjuvant chemotherapy on the survival of patients is still a matter of debate and warrants further studies. One of the major limitations of our study was small sample size and shorter follow up time. We recommend multi-institutional randomized controlled trials on this issue as it is a major health problem in our country. Another limitation of our study was follow up period. Long term follow up of atleast 5years is needed in such patients to understand the outcome. Most of the institutions are using cisplatin based three drug regimen. However, majority of our patients are not fit to tolerate this regimen. Failure to assess the biological factors of the tumor like EGER mutations, activity of p53, RANK WRANK signaling system and human papilloma virus in tumor specimen are also the limitations of our study.

CONCLUSION

This study was conducted to understand the management of locally advanced Squamous cell carcinoma (T4a) of buccal mucosa. Based on our study following conclusions can be drawn:

The three drug regimen (docetaxel , cisplatin & 5-Fu)neo-adjuvant chemotherapy is well tolerated. The response to neo-adjuvant chemotherapy is not affected by the age or sex of the patient. Presence of lymphovascular or invasion in the tumor does not affect the response to neo-adjuvant chemotherapy. Surgery has an important role in the management of the patients with locally advanced (T4a) squamous cell carcinoma of buccal mucosa. However, surgery should be avoided in patients who have progression with neo-adjuvant chemotherapy. Pectoralis Major Myocutaneous flap (PMMC) is the most common flap used for reconstruction in these patients, especially at a high volume centre like ours. No wonder, it is known as the "work horse flap" for head and neck oncosurgery. Neo-adjuvant chemotherapy does not affect the immediate surgical

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outcome in terms of post operative morbidity or mortality. Patients who respond to neo-adjuvant chemotherapy have significantly delayed loco- regional recurrence than the patients who do not respond to chemotherapy. However, the effect of neo-adjuvant chemotherapy on overall survival is still controversial and warrants further studies Neo-adjuvant chemotherapy is an important tool in the armamentarium of an oncosurgeon to stabilize the disease and to prevent early loco-regional recurrence. These patients are best managed by multidisciplinary approach. Surgical resection is still the mainstay of treatment. Judicial use of adjunctive therapies (chemotherapy and radiotherapy) has been helpful to improve outcome.

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