

A COMPARATIVE STUDY BETWEEN NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY AND UPFRONT SURGERY IN LOCALLY ADVANCED OPERABLE SQUAMOUS CELL CARCINOMA OF ORAL CAVITYMohit Sharma*¹, Ketul Puj², Hemkant Verma² and Shashank J. Pandya³¹Associate Professor, Department of Surgical Oncology Gujarat Cancer and Research Institute (G.C.R.I.), Ahmedabad.²Resident Doctor, Department of Surgical Oncology Gujarat Cancer and Research Institute (G.C.R.I.), Ahmedabad.³Professor Department of Surgical Oncology Gujarat Cancer and Research Institute (G.C.R.I.), Ahmedabad.***Corresponding Author: Mohit Sharma**

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ABSTRACT

Introduction: Head and Neck carcinoma constitutes 46% of all adult malignancies in India.. Most patients with squamous cell carcinoma of the head and neck present with locally advanced stage of III or IV. In patients treated with surgical resection and postoperative radiation, long term survival rates are generally low ranging from 30% to 40% To improve local resectability, to increase locoregional control, to decrease distant micro-metastasis and to maintain critical functions, the induction chemotherapy has been investigated. The use of chemotherapy provides the potential for better regional & distant tumor control. **Aims and Objectives:** The aim of this study is to compare the prognosis of patients who underwent neoadjuvant chemotherapy followed by surgery to that of those who underwent primary surgery. Although the number of patients studied here was small & the results were from only a single institution, this is controlled clinical study on the efficacy of neoadjuvant chemotherapy for locally advanced (T4a) squamous cell carcinoma of oral cavity. **Material and Methods:** It is a prospective comparative study performed at Gujarat Cancer and Research Institute Ahmedabad. Total 101 patients of locally advanced head and neck cancer were enrolled for study from November 2013 to April 2016. 53 Patients were involved in upfront surgery arm and 48 patients were involved in neo adjuvant chemotherapy arm **Conclusion:** Neoadjuvant chemotherapy induces a high response rate that may facilitate definitive surgery in a borderline cases or where margin identification is difficult due to wet edematous borders of disease. Neoadjuvant chemotherapy is a feasible option in T4a squamous cell carcinoma of oral cavity with 70.83% cases without recurrence, with minimal addition and comparable morbidity and without mortality.

KEYWORDS: Advanced head neck cancer, Neoadjuvant chemotherapy.**INTRODUCTION**

Head and Neck carcinoma constitutes 46% of all adult malignancies in India. The gingivobuccal complex is the most common sub site of oral cancer. It is closely linked with the habit of chewing betel quid & gutkha containing tobacco. . Most patients with squamous cell carcinoma of the head and neck present with locally advanced stage of III or IV. In patients treated with surgical resection and postoperative radiation, long term survival rates are generally low ranging from 30% to 40%. Despite the diversity of these patients, loco-regional recurrence patterns are more often than distant metastasis.

To improve local resectability, to increase locoregional control, to decrease distant micro-metastasis and to maintain critical functions, the induction chemotherapy has been investigated. Frequently Cisplatin and 5 Fluorouracil, along with taxanes have been used

in neoadjuvant chemotherapy (NACT). Induction chemotherapy is highly active in this setting, inducing partial remission in 60% to 90% of previously untreated patients. However randomized trials have failed to demonstrate a clear impact on local tumor control or overall survival. The use of chemotherapy provides the potential for better regional & distant tumor control.

The aim of this study is to compare the prognosis of patients who underwent neoadjuvant chemotherapy followed by surgery to that of those who underwent primary surgery. Although the number of patients studied here was small & the results were from only a single institution, this is controlled clinical study on the efficacy of neoadjuvant chemotherapy for locally advanced (T4a) squamous cell carcinoma of oral cavity.

AIMS AND OBJECTIVES

1. To study clinical profile of T4a squamous cell carcinoma oral cavity.
2. To study response to neo-adjuvant chemotherapy in T4a squamous cell carcinoma oral cavity.
3. To study the patterns of recurrence following multimodality therapy.

Neo-Adjuvant Chemotherapy

To improve loco regional control, survival and maintain critical functions, combined modality therapy has been investigated. After introduction of Cisplatin to cancer therapy in the 1980's, Cisplatin based neo-adjuvant chemotherapy (NACT) has been widely used in the treatment of advanced head & neck SCC to achieve improvement of survival and organ preservation. Several randomized clinical trials showed that NACT increased survival of patients with nasopharyngeal SCC of advanced stage by decreasing distant metastasis (2, 40). NACT combined with radiotherapy was also reported to be benefit to organ preservation in patients with T2, T3 laryngeal SCC in several randomized clinical trials. (12)

The efficacy of NACT for head & neck SCC except nasopharyngeal & laryngeal SCC in still controversial. Induction chemotherapy is used to down stage the size of the tumor and maximize its response to loco regional intervention (21). NACT may facilitate surgery. Adequate loco-regional control, good predictor of response to RT and responders has acceptable survival and few sequelae with local therapies (30). It may help in mandible preservation and sterilization of margin in edematous wet lesions. The most widely used combination is Cisplatin and 5-FU regimen that had proven successful in the palliative treatment of patients with recurrent disease.

Many small single institution phase II trials resulted in several major observations & conclusions. Tumor regression was found in 60% to 90% of previously untreated patients and a complete response was possible in 20% to 50% (16). Head & neck cancer doesn't yet appear to be "Chemo curable" disease such as lymphomas or testicular cancer and single modality treatment with CT cannot be recommended. The use of induction CT did not appear to adversely affect patient's tolerance for subsequent definitive management (4). Trials using NACT followed by surgery & definitive RT have failed to reproduce the survival advantage with the NACT treatment schedule. Licitra study from Italy showed NACT has reduced the number of mandiblectomies and need of adjuvant RT (35). Kohno *et al* (34), Basu *et al* (6) and Grau *et al* (23) reported that NACT was useful for increasing survival rate of patients with oral SCC. Kirita *et al* (33) and Earle *et al* (19) stated that NACT could be of benefit to preservation of organ function in those with locally advanced oral SCC. However, their results were based on uncontrolled clinical trial with small sample size, so there was no evidence to support the result. Schuller *et al* (73) and

Mazeron *et al* (38) showed no advantage of NACT for head & neck SCC in randomized clinical trials. Hill *et al* (25) reported no benefit of NACT for oral SCC by a histologically controlled study

Despite this failure of induction CT, many oncologists showed interest in wide spread adoption of NACT approaches. At present, one can only justify induction CT within the context of a clinical trial. The recent incorporation of several newer chemotherapeutic agents, such as the taxanes, into more aggressive drug combination might improve on the results of neoadjuvant therapy.

The combination of cisplatin and 5-fluorouracil is one of the most active regimens showing high overall response (73-93%) and complete response rates (23-54%).^[54]

A subset analysis of the MACH-NC limited to the 15 trials that used cisplatin, infusional 5-Fluorouracil suggested survival benefit of 5% (hazard ratio 0.88; 95% confidence interval, 0.79 to 0.97)^[55]

In the study reported by Paccagnella *et al*,^[43] 237 patients with stage III or IV head and neck cancer were randomized to four cycles of induction cisplatin and infusional 5-Fluorouracil followed by standard locoregional treatment (i.e. surgery plus radiation if resectable, radiation alone if unresectable) or upfront surgery or radiotherapy. Patients with unresectable disease benefited from the incorporation of induction chemotherapy for all outcomes including locoregional control (ORR 68%) distant control, and overall survival (3-year survival 24% vs. 10%; P: .04).

In a randomized trial-limited to patients with loco regionally advanced oropharyngeal cancer reported by Dometge *et al*.^[56] induction chemotherapy with cisplatin and 5-Fluorouracil significantly improved survival in terms of 5.1 years as compared to 3.3 year (P=0.03) loco regional treatment alone (i.e. surgery plus radiation or radiation alone). There was no change in loco regional control or distant metastases.

A randomized phase III organ preservation trial conducted by the European Organization for research and Treatment of Cancer (EORTC) evaluated PF induction chemotherapy with definitive radiation vs. standard surgery and radiation in patients who had operable pyriform sinus cancer. Preservation of the larynx was possible in 42% of cases, and there was a lower rate of distant failures without a significant difference in survival.^[57]

Meta-analysis of Neoadjuvant Chemotherapy

Meta-analysis was done to evaluate the role of the neoadjuvant chemotherapy with the cisplatin and fluorouracil (PF) regimen in enhancing the overall survival and decreasing locoregional relapse and distant metastasis in SCCHN patients.^[58]

In this meta-analysis SU Yu-xiong *et al.*^[58] concluded that Neoadjuvant chemotherapy with the TPF regimen in HNSCC patients has no effect on locoregional relapse. However, it showed a small but significant benefit in reducing distant metastasis and improved the overall survival.

Recent progress in the field of induction chemotherapy has been obtained by the use of taxanes in combination with 5-fluorouracil-Cisplatin. In particular, the TPF regimen compared favourably to 5-fluorouracil-Cisplatin in a matched analysis performed by Pignon *et al.*^[64] showing a significant benefit in survival in favour of the TPF regimen. This study was further confirmed by Vermorken *et al.*^[65] and Haddad *et al.*^[67] In three large randomized trials showing a significant benefit in favour of TPF, which proved to be more efficient than the 5-fluorouracil-Cisplatin regimen.

The phase 3 TAX 323 trial, a direct comparison of PF and TPF induction chemotherapy conducted by the Vermorken *et al.*^[65] included patients with locally advanced and unresectable squamous cell head and neck cancer who were randomized to receive induction therapy with either PF and TPF every 3 weeks for 4 cycles, followed by radiotherapy or surgery. The overall rate of response among patients who received TPF induction chemotherapy was 68% compared with a 54% response rate in the group that received PF induction chemotherapy (P=0.07). With a median follow-up of 32 months, TPF-treated patients demonstrated significantly superior progression free survival (hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.56, 0.91; P=0.006), overall survival (HR 0.73; 95% CI 0.57, 0.94; P=0.016), and response rate (67.8% vs 53.6%; P=0.007).

A study of Sequential therapy (triple-drug-based induction chemotherapy followed by concurrent chemoradiotherapy) in 44 locally advanced inoperable head and neck cancer patients, done by Somani *et al.*^[69] concluded that 36% patients had CR and 35% patients had PR with the ORR of 71%.

The international TAX 324 trial^[70] conducted by Posner *et al.*, evaluated 501 patients with loco regionally advanced SCCHN (both, non resectable and organ preservation candidates) in a sequential therapy plan of induction chemotherapy with Cisplatin and 5FU or without Docetaxel followed by chemo radiation with Carboplatin and surgical resection in patients with locally advanced head and neck cancer. The overall response rate following induction chemotherapy showed a trend toward improvement with the addition of Docetaxel (72% vs 64%, P=0.07). Survival data at 3 year post treatment showed a highly significant (62% vs 48%) survival advantage for patients who received the TPF regimen. The HR was 0.70 (P=0.0058), indicating a 30% reduction in mortality in the TPF arm. Toxic deaths during TPF and PF were 7.84% and 1.63% respectively. The median overall survival was 71 months and 30

months, respectively. There was better loco regional control in TPF arm than in the PF arm, but the incidence of distant metastases in the two arms did not differ significantly.

In a phase III study conducted by Hitt *et al.*^[68] 383 patients were randomized to receive three cycles paclitaxel, cisplatin and 5-FU (TPF) in one arm, or cisplatin and 5-FU (PF) in the other arm, followed by cisplatin based CRT. Resectable and unresectable patients were included (66% resectable vs 33% unresectable). CR was observed in 33% in the TPF arm compared with 14% in the PF arm (p<0.001). The PR rate was similar between the two treatment arms (47% and 54% in TPF and PF arms respectively), but the difference in OR (overall recurrence rate) (80% and 68% with p<0.001) reached statistical significance. An increase in TTP (time to progression) was observed for unresectable tumors in the TPF group (17.7 vs. 21.7). TPF showed significantly improved progression free (12mo vs.20mo, P=0.003) and overall survival rates (37 months vs 42 months, p=0.031).

Another randomized phase III trial conducted by Calais *et al.*^[67], showed significant improvement in the response rate with the addition of a taxane. Patients with locally advanced cancer of the larynx or hypo pharynx were treated with cisplatin and 5-FU with or without docetaxel, followed by radiotherapy alone for responders or total laryngectomy with neck dissection and postoperative radiotherapy for non responders. The overall response rate was significantly higher with TPF (82% vs. 60%) and more patients with TPF were able to avoid undergoing laryngectomy compared with patients receiving PF (73% vs.63%).

The GORTC 2000-2001 trial compared three cycle of TPF versus PF, followed by radiotherapy in patients with resectable larynx and hypopharynx cancer. The three year actuarial larynx preservation rate was better in TPF versus the PF arm, (73% vs 63% respectively; p=0.036). Severe mucositis was significantly less frequent in the TPF arm compared with the PF arm.

MATERIALS AND METHODS

Study Design: Prospective, Comparative study
Place: Surgical Oncology Department
Gujarat Cancer and Research Institute attached to
B. J. Medical College, Ahmedabad, Gujarat, India
(A UICC approved Regional Cancer Centre)
Period: November 2013 to April 2016
Patients Population: 101
Up-front surgery group
(ARM I):- 53 cases
Neoadjuvant chemotherapy
Followed by surgery:- 48 cases

All patients underwent thorough clinical examination by joint committee of surgical, medical & radiation oncologist & examination under general anesthesia

for tumor staging and measurements whenever required, complete blood & serum profile, chest x-ray ECG & CT/MRI/PET Scan of the head & neck (whenever necessary). Clinical staging is determined according to the International Union against Cancer (UICC) classification.

Inclusion criteria

- All previously untreated, biopsy proven, resectable but locally advanced, non-metastatic SCC of oral cavity (cT4a).

Exclusion criteria

- Previously treated patients with recurrence or second primary.
- N3 or inoperable nodal disease.
- Patients with inadequate nutritional, cardiac, pulmonary status.

Surgery

All patients in the both the arms were operated with composite resection of buccal tumors, wide excision of tongue, segmental, distal or hemi mandibulectomy with or without lower partial maxillectomy. Selective and comprehensive neck dissections with SOHND, MND type I, II, III or RND performed. (bilateral neck dissection perform where required). Reconstruction was performed with various flaps, including the pectoralis major myo- Cutaneous Flap, Bilobed PMMC flap, Nasolabial flap or primary closure.

Radiotherapy

All patients in both the arms were treated with megavoltage adjuvant radiation using linear accelerator. Treatment is delivered in fraction of 1.8 to 2 Gy/day, five fractions per week to a total dose of 60Gy to 66Gy. Toxicity to radiotherapy was assessed every month for three months after the end of radiotherapy, then every two months thereafter.

Adjuvant concurrent CT and RT is given in extracapsular spread and close or positive margin.

Follow up

All patients examined clinically and radiologically (if required) every 2 to 3 monthly for first 2 years and 6 monthly thereafter.

RESULTS AND ANALYSIS

In this study, from November 2013 to April 2016, 101 patients were enrolled with 53 patients in ARM I (Up-front surgery) and 48 patients in ARM II (NACT followed by surgery), after fulfilling the inclusion criteria.

Age Group: Most common age group was 40-49 years, with median age of 44 years in both the arms.

Sex: More common in males with a male to female ratio of 12.2:1 in Arm I (Up-front surgery) and 7:1 in ARM II (NACT followed by surgery).

Clinical presentation: Ulcer and trismus were the most common symptoms in both the arms, ulcer was noted in all patient and trismus in 66.37% of the patient, with median duration of 3 months.

Most common lesions in the oral cavity were ulcero-proliferative (75.2%), ulcero-infiltrative (18.2%) and ulcerative (6.6%).

Habits: 83.2% of patients had habit of tobacco consumption in both the arms. Other habits found were smoking and use of alcohol. Eight patients of the study (7.9%) were found to have no addiction.

Histological Grading

According to Borden classification moderate (Grade II) was most common grade in both the arms.

Grade	ARM I (Up-front surgery)	ARM II (NACT followed by surgery)
Well differentiated	12 (22.6%)	10(20.8%)
Moderate differentiated	37(69.8%)	35(72.9%)
Poorly differentiated	4(7.54%)	3(6.2%)
Total	53	48

Clinicopathological Involved Subsites of Oral Cavity

Most common involved subsite of oral cavity in our study is buccal-mucosal-alveolar complex (70.30%).

	ARM I (Up-front surgery)	ARM II (NACT followed by surgery)	Total
Tongue	18(33.96)	12(25%)	30
Buccal-mucosal-alveolar complex	35(66.03)	36(75%)	71
Total	53	48	101

Clinicopathological Skin/Bone/Tongue Involvement

Most of the cases in Up-front surgery group (ARM I) were having bone involvement (47.17%) where as NACT followed by Surgery group (ARM II) were having skin involvement, alone (27.08%) or along with involvement of skin & bone (20.83%) making a total of 47.91%.

	ARM I (upfront surgery)	ARM II(NACT followed by surgery)	Total
Skin involvement	6(11.32%)	13(27.08%)	19
Bone involvement	25(47.17%)	13(27.08%)	38
Both skin +bone involvement	4(7.55%)	10(20.83%)	14
Tongue with T4a lesion	18(33.96%)	12(25%)	30
Total	53	48	101

Clinical Nodal Staging

Most of the cases in both groups were having clinical N0 disease with 79.2% of ARM I and 60.41% in ARM II with a total of 70.30% cases in this study is having N0 disease.

N. Stage	Clinical	
	ARM I (up-front surgery)	ARM II (NACT followed by surgery)
N0	42(79.2%)	29 (60.41%)
N1	11 (20.8%)	18 (37.5%)
N2a	-	-
N2b	-	1(2.1%)
N2c	-	-
N3	-	-
Total	53	48

Chemotherapy Regimens

Patients received either two drug combination (Platinum + Taxane) or three drug combination (Platinum+5FU+docetaxel) chemotherapy. The major deciding factor was performance status and the socioeconomic status of the patients. Cisplatin was the first choice for all patients with normal renal parameters.

Docetaxel was administered at a dose of 75mg/m² over 2 hours on day 1, cisplatin was administered at a dose of 75mg/m² over 1 hour on day 1 and 5FU was administered at a dose of 750mg/m²/day as continuous infusion for 3 days. Patients were administered standard premedication prior to chemotherapy. Patients received G-CSF prophylaxis and oral antibiotics prophylaxis also. In 2 drug combination, either Docetaxel at a dose of 75mg/m² over 2 hours or Paclitaxel at a dose of 175mg/m² over 3 hours was administered on day 1 with either Cisplatin at a dose of 75mg/m² or Carboplatin at a dose of AUC(area under curve) of 6 on the same day. Standard premedication was used. However, this regimen was given on outpatient basis in the daycare. The chemotherapy was once given every 21 days in both regimens for total of 2 or 3 cycles on the basis of operating surgical team evaluation basis.

Regimen	No. of Pts
TPF	11(22.92%)
Pacli+Carbo	25(52.08%)
Pacli+Cisplatin	8(16.67%)
P+MTX	1(2.08%)
MTX	2(4.17%)
PMF	1(2.08%)
Total	48

Response to Chemotherapy

Taxel+Platin+5FU

3 cycle of TPF as NACT showed good response in tumor regression in 100% of the cases and 83.33% good response in 2 cycle of TPF.

	2 cycles	3 cycles	4cycles	Total
Good response	5(83.33%)	5(100%)	0	10 (90.91%)
Partial response	1(16.67%)	0	0	1(9.09%)
Stable disease	0	0	0	0
Total	6	5	0	11

Paclitaxel+Carboplatin

Most of the cases with paclitaxel+carboplatin as NACT showed partial response in tumor regression(56%).Most cases received 2 cycle of NACT(84%).

	2 cycle	3 cycle	4 cycle	Total
Good response	6(28.57%)	2(50%)	0	8(32%)
Partial response	12(57.14%)	2(50%)	0	14(56%)
Stable disease	3(14.28)	0	0	3(12%)
Total	21	4	0	25

Paclitaxel+Cisplatin

Most cases receiving paclitaxel+cisplatin as NACT showed partial response(75%). Upto 4 cycles of this regime was used as NACT.

	2 cycle	3 cycle	4 cycle	Total
Good response	1(20%)	0	0	1(12.5%)
Partial response	3(60%)	1(100%)	2(100%)	6(75%)
Stable disease	1(20%)	0	0	1(12.5%)
Total	5	1	2	8

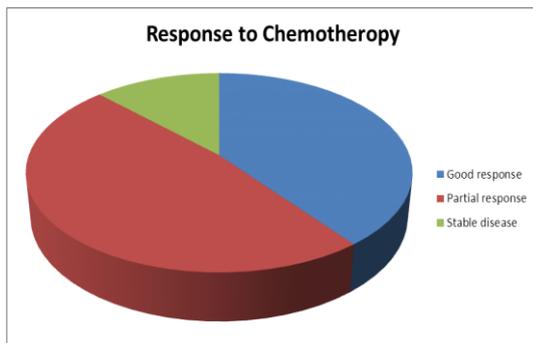
Paclitaxel+Methotrexate/Paclitaxel+Methotrexate+5FU/
Methotrexate

These regimes were used mainly in older case of 2013 showing partial response and stable disease mainly with no case with good response to these regimes.

	2cycle	3cycle	4cycle	Total
Good response	0	0	0	0
Partial response	2(1PMF, 1P+Mtx) (100%)	0	0	2 (50%)
Stable disease	0	0	2(Mtx) (100%)	2 (50%)
Total	2	0	2	4

In this study good response was in 39.58% and partial response (PR) was in 47.9% of cases.

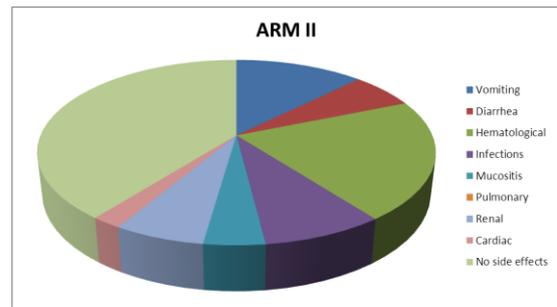
Response	Present study	Aldo lop et al	Amal Khalifa et al	Adriano et al
%	%	%	%	%
Good response (GR)	19 (39.58%)	9	23	7
Partial Response (PR)	23 (47.9%)	59	45	73
Stable disease (SD)	6 (12.5%)	18	22	14



Chemotherapy Induced Toxicity

In this study the chemotherapy induced hematological side effects in the form of low total leukocyte count and neutropenia was the most common toxicity (21%) followed by vomiting, infection and diarrhea.

Toxicity	Present study	Adriano et al	Aldo lop et al
Vomiting	6(12.5%)	41(%)	21(%)
Diarrhea	3(6.3%)	25(%)	6(%)
Hematological	10 (21%)	18 (%)	15(%)
Infections	4(8.4%)	-	-
Mucositis	2(4.2%)	19(%)	12(%)
Pulmonary	-	-	-
Renal	3(6.25%)	8(%)	4(%)
Cardiac	1(2.1%)	-	-
No side effects	19 (39.58%)		
Total	48		



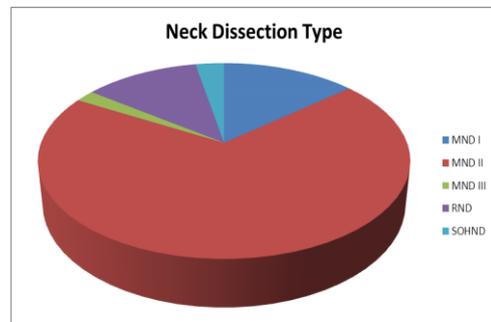
Surgical Details

Neck dissections done in the form of MND II most frequently (69.30%) followed by MND I (13.86%). Resection of primary most commonly performed with segmental, distal or hemi-mandibulectomy.

In our series in both the arms the pedicled pectoralis major myo-cutaneous flap (PMMC) was most commonly used for reconstruction either unilobed or bilobed (total 72.27%). For skin replacement bilobed PMMC was done. For smaller defects either nasolabial flap or primary closure of the defect was done.

Neck Dissection Type (Both Arms)

Type	Number of cases
MND I	14(13.86%)
MND II	70(69.30%)
MND III	2(1.98%)
RND	12(11.88%)
Ext. SOHND	3(2.97%)
TOTAL	101



Neck Dissection Type

Most common neck dissection performed in both the ARMs is MND II(69.30%). MND III or extended SOHND were not performed in any case of ARM II.

Type	ARM I (up-front surgery)	ARM II (NACT followed by surgery)	Total
MND I	8(15.09%)	6(12.50%)	14
MND II	38(71.70%)	32(66.67%)	70
MND III	2(3.77%)	0	2
RND	2((3.77%)	10(20.83%)	12
Extended SOHND	3(5.66%)	0	3
Total	53	48	101

Reconstruction Flaps Used

Reconstruction Flap	ARM I (up-front surgery)	ARM II (NACT followed by surgery)	Total
PMMC	24(45.28%)	16(33.34%)	40
Bilobed PMMC	8(15.09%)	25(52.08%)	33
Nasolabial	4(7.55%)	1(2.08%)	5
Primary closure	17(32.07%)	6(12.5%)	23
Total	53	48	101

Complications of Surgery

In this study the most frequent surgical complication was wound infection in both the ARMs. 2 cases (4.2%) of ARM II were having total flap necrosis.

	ARM I (up-front surgery)	ARM II (NACT followed by surgery)
Partial Mucosal dehiscence	1(1.9%)	5(10.5%)
Wound Infection	9(17%)	7(14.7%)
Leak	1(1.9%)	4(8.4%)
Seroma	2(3.8)	2(4.2)
Partial flap necrosis	4(7.6)	-
Total flap necrosis	0%	2(4.2%)
Bleeding	1(1.9%)	2(4.2%)
No complication	35(66.03%)	26(54.17%)
Total	53	48

Recurrence Patterns

In ARM I most common patter of first recurrence was at local site(3.8%) where as in ARM II most common site of recurrence is regional(23%). 3 recurrences in NACT ARM were treated with surgery rest with palliative CT except one patient who did not take any treatment.

ARM I (up-front surgery)

	Present Study	K H Lee et al	Diaz et al
Local	3.8%(2)	12%	23%
Regional	1.9%(1)	-	11%
Both	-	25%	9%
Distant	4%(1)	-	-
No recurrence	49(92.45%)		
Total	53		

ARM II (NACT followed by surgery)

	Present Study % (n)	K H Lee et al %	Adriano et al %
Local	2.1%(1)	25%	60%
Regional	23%(11)	5%	12%
Both	4.2%(2)	0%	5%
Distant	0%	0%	0%
No recurrence	34(70.83%)		
Total	48		

In Recurrent Cases, Type of Neck Dissection Previously Done

In ARM I, three cases (75%) recurrences occurred in the cases previously operated with MND II. In ARM II recurrences, 12 cases (85.72%) were previously operated with MND II.

Type	ARM I (up-front surgery)	ARM II (NACT followed by surgery)	Total
MND I	1(25%)	0	1
MND II	3(75%)	12(85.72%)	15
RND	0	2(14.28%)	2
Total	4	14	18

Pathological Nodal Disease in Recurrent Cases of ARM I (up-front surgery)

Out of 4 recurrences in ARM I, two were at local site with one case having N+ disease and perineural invasion positive on pathology while other local recurrent case was with N0 disease but lymphovascular invasion was positive in its pathology. One each case with N0 disease had regional and distant recurrence.

Recurrence site	N + disease	N0 Disease	Total
Local	1 (PNI+) (100%)	1(LVI+) (33.34%)	2
Regional	0	1(33.34%)	1
Distant	0	1(33.34%)	1
	1	3	4

Pathological Nodal Disease In Recurrent Cases Of ARM II (NACT followed by surgery)

Out of 14 recurrences in ARM II, two were at local site with one case having N+ disease and perineural invasion positive on pathology while other local recurrent case was with N0 disease and close margin of 0.3cm. In regional recurrent cases, 8 were with N+ disease and 2 with N0 disease. Both these were with no other adverse pathological factors. Both (local + regional) recurrence occurred in 2 cases with N+ disease having 0.2cm closest margin of resection in each one. No distant recurrence occurred in ARM II.

Recurrence site	N + disease	No Disease	Total
Local(L)	1 (PNI +) (9.09%)	1(close margin 0.3cm) (33.34%)	2
Regional(R)	8(72.73%)	2(66.67%)	10
Both (L+R)	2(close margin 0.2cm in both) (18.18%)	0	2
Distant	0	0	0
Total	11	3	14

Progression free survival

There were total 4 recurrences in the Up-front surgery arm and 14 recurrences in NACT Arm with a median PFS 87 and 99 days respectively.

DISCUSSION

The gingivo-buccal complex and anterior tongue is the most common sub site of oral cancer in Indian Sub-continent. The gingivo-buccal complex consists of buccal mucosa, alveolus, and both upper & lower gingivo-buccal sulcus and retro molar trigone (4). Chaudary et al (10) reviewed 399 cases of buccal mucosa cancer treated with radiotherapy or surgery at Tata memorial Hospital. In their series, 150 patients with stage III and IV diseases received palliative radiation (57 cases), radical surgery (54 cases), or combination of both (39 cases). The 2 year disease free survival rates were 5% for radiotherapy and 33% for surgery in the advanced stages. Of the 39 patients treated by surgery and radiation, only 9 patients were under loco regional control, 12 patients had loco regional failure, and 18 patients were lost to follow up.

Cervical lymph node metastasis in squamous cell carcinoma of the buccal mucosa has been presented to occur less frequently than in other oral cavity sites. Dhawan et al (14) reported histologically proven lymphnode metastasis in only 16% of patients who underwent selective neck dissection. A limitation of their study was the limited neck dissection. In this study, however 13 patients of 22 (58.09%) had pathological evidence of the disease (PN+). The presence of regional metastasis strongly affects the survival. Pop et al (71) reported a 5 yr survival rate of 23% when metastatic cervical lymph nodes were present. E.M. Diaz et al (15) reported a 5 yr survival rate of 24% and 69% in patients with cervical lymph node metastasis with or without extracapsular spread. Urist et al (75) in their study found that the tumor thickness (6mm) was a significant independent variable for poor prognosis.

Despite the use of aggressive multimodality managements, patients with locally advanced buccal mucosa and tongue cancer still suffer poor local control,

poor quality of life & survival. The rationale underlying the use of neo adjuvant chemotherapy in locally advanced oral cavity (T4a) cancer is the possibility of better drug delivery in well vascularised tumours, tumors shrinkage and sterilization of initial oedematous wet margins would allow better results when surgery & or RT are added, and it will also help to eradicate micro metastasis. Though the NACT seems to be promising, but loco-regional control, survival benefits and appropriate NACT regimen are still to be defined. Patients diagnosed early with any oral squamous cell carcinoma have a greater chance of survival compared with those with more advanced disease.

Currently available evidence does not support the use of chemotherapy in addition to surgery in head and neck cancer, although chemotherapy has an established role in organ-preserving integrated approaches based on radiation therapy. In particular, as far as oral cavity cancer is concerned, standard treatment is surgery, followed by radiation therapy in advanced cases. Preoperative chemotherapy has been investigated in head and neck cancer, but the results are still inconclusive, if not negative.

In oral cavity cancer patients, demolitive surgery entails mandibulectomy, which translates into significant functional impairment. Although not formally assessed, some effect on quality of life is plausible. This could justify the incorporation of chemotherapy in the treatment strategy, at least in selected patients. Patients treated NACT with significant pre-operative down staging can be benefitted with less demolitive surgery. This would be in line with the organ- and function-preserving approaches currently used in other head and neck cancers. In oral cavity cancer, the benefit would essentially be functional, in terms of better mastication and cosmetic.

In this study, total 101 patients were compared into two arms, 53 patients to receive primary surgery followed by adjuvant radiotherapy and 48 patients into neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy.

In our study, most common age group was 40-49 years, with median age of 44 years in both the arms. More common in males with a male to female ratio of 12.2:1 in Arm I and 7:1 in ARM II Ulcer and trismus were the most common symptoms in both the arms, ulcer was noted in all patient and trismus in 66.37% of the pateint, with median duration of 3 months.

Most common lesions in the oral cavity were ulcero-proliferative (75.2%), ulcero- infiltrative (18.2%) and ulcerative (6.6%).Most of the cases i.e. 83.2% of patients had habit of tobacco consumption in both the arms. Other habits found were smoking and use of alcohol. Eight patients of the study (7.9%) were found to have no addiction.

Juan Grau et al (31) reported a 50% partial response & 16% complete response following NACT. Amal Khalife et al (3) reported a 45% complete response, 23% partial response, 22% stable disease & 10% progressive disease following NACT in their study. In our study, there was good response in 19(39.58%), partial response in 23(47.9%) and stable disease in 6 (12.5%) patients following NACT. Progressive diseases during NACT were excluded from our study.

Adequacy of excision and achieving oncological resection margins is an important fundamental in the head & neck squamous cell carcinoma. Fang et al (21) reported on 57 patients, all treated with surgery and adjuvant radiotherapy. In this study patients with a negative surgical margin achieved a significantly improved three year loco regional control rate compared to those with a close or positive margin (71%) v/s 39%, P=0.02).

In this present study, recurrence rate of 7.54% (4/53) in the arm-I (Up-front surgery followed by RT) and 29.17% (14/48), in the arms-II(NACT followed by surgery and RT) has been noted not consistent with other series recurrence rates in the range of 20-80%. Higher occurrence of loco regional recurrences in Arm II may be indicative of more aggressive clinical disease, presence of patchy response to NACT or may be result of bias. However, there were no distant recurrences in Arm II as compared to Arm I. This observation needs further evaluation on larger studies. Chun –Shu-Lin et al reported a recurrence rate of 57%, & K. H. Lee et al (27) reported a recurrence rate of 25% following NACT followed by surgery and RT in their study. Italian study by Licitra et al, 195 patients with T2-T4 oral cancer has shown same overall survival in both the arms but fewer mandibular resections (31% v/s52%) and less post-operative irradiation was necessary (33% V/s 46%) with LRR of 28% and 38% in both the arms respectively (35). Majority of recurrence occurred at the primary site, not consistent with our study in which regional recurrence in more common mode of first recurrence. Diaz et al (15) reported a recurrence rate of 45% (54/119), & K.H. lee (32) reported a recurrence rate 38% (3/8) following surgery and RT. Urist et al (75) also reported a 28% recurrence rate with median time to recurrence of eight months. K.H. Lee et al recorded a median time to recurrence of five months. In our study, recurrence rate of 7.54% (4/53) in the arm-I (Up-front surgery followed by RT) and 29.17% (14/48), in the arms-II(NACT followed by surgery and RT) and has been noted with a median PFS 87 and 99 days respectively.

In our study, 7% of recurrences occurred in the patients who were operated with MND I while 17% of recurrences in patients operated with MND II neck dissection, favoring MND I as more effective in prevention of recurrences.

A large number of phase III NACT studies using both single and combination agents have been conducted. The results of these phase III trials have been consistent and failed to demonstrate a survival advantage for the NACT schedule.

Many explanations have been suggested for the failure in NACT in phase III studies. Many of the trials have been criticized for valid methodical reasons, including small patient numbers patients and tumor heterogeneity, use of relatively ineffective drugs in suboptimal doses or drug scheduling. However five of these studies with 800 patients have shown response rate from 57% to 80%. Indeed, as already known in head and neck cancer a clinical and pathologic complete response proved a strong prognostic factor predicting a better long term survival rate. However in our study, there were no complete clinical/pathological response.

The largest of these meta-analysis from meta-analysis of chemotherapy in Head & Neck cancer (MACH-NC) Collaborative group based in France, reviewed 63 randomized trials, including more than 10,000 patients with updated data. Loco –regional treatment was compared with some chemotherapy for locally advanced head and neck SCC. The median follow up period was 6 years. An absolute survival benefit of 4% was seen in patients given chemotherapy with concomitant regimens. Data from more than 5000 patients treated with NACT regimens were analyzed and no statically significantly survival advantage was found when compared with loco-regional treatment alone.

It has been suggested that in the advent of newer chemotherapy molecules & regimens and more aggressive drug combinations might result in survival benefit after NACT schedule. This study demonstrated the feasibility of induction chemotherapy in more aggressive T4a lesion oral cavity with acceptable results. However elaborate studies are necessary from surgical, medical and radiation oncologist community before this NACT approach could legitimately be incorporated into standard care.

Due to short available follow up survival analysis is not possible.

Large scale multicentre randomized, controlled trials and meta-analysis are necessary to evaluate the efficacy of NACT in locally advanced (T4a) oral cavity squamous cell cancer as this approach may be worth for further exploration.

CONCLUSION

1. Gingivo-buccal complex and oral tongue cancer are the most common cancer of oral cavity found in men with median age is 44 yrs with ulcer and trismus as the most common presenting symptoms and almost all patients have history of tobacco consumption.

2. Advanced oral cancers have poor prognosis. Tumor invasion of skin & soft tissue have worst prognosis than bone.
3. Surgical excision is the mainstay of treatment of oral cancers. The aim of the surgery is to completely excise tumor with wide margins.
4. Neoadjuvant chemotherapy induces a high response rate that may facilitate definitive surgery in a borderline cases or where margin identification is difficult due to wet edematous borders of disease.
5. Neoadjuvant chemotherapy is a feasible option in T4a squamous cell carcinoma of oral cavity with 70.83% cases without recurrence, with minimal addition and comparable morbidity and without mortality.
6. The likelihood of a chemotherapy induced response increases with taxane based regimen.
7. Three cycles of chemotherapy having better response rate as compare to 2 cycles.
8. Neoadjuvant chemotherapy is advisable in borderline resectable cases.
9. In surgical management of neck dissection, MND I appears to be more effective than MND II in prevention of the recurrence.
10. There is no difference in complications of surgery in upfront surgery and NACT followed by surgery.
11. Large scale multicentre randomized, controlled trials and meta-analysis are necessary to evaluate the efficacy of NACT in locally advanced (T4a) oral cavity squamous cell cancer as this approach may be worth for further exploration.
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