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Neoadjuvant Chemotherapy InUnresectable Locally Advanced Oral Cavity Cancers: A Retrospective Analysis

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Abstract: *Background:Oral cavity cancer is a significant health problem in India. Majority of patients present with locally advanced disease requiring multimodality treatment. Despite recent advances overall prognosis remains guarded. Role of neoadjuvant chemotherapy is being explored with premise of reducing extent of surgical resection, improving loco-regional control and decreasing distant metastasis, thereby improving treatment outcomes by decreasing mortality and morbidity.Aim: To evaluate the impact of neoadjuvant chemotherapy in locally advanced,unresectable oral cavity cancers. Materials And Methods: Mono institutional retrospective analysis of patients with locally advanced oral cavity cancers, who were treated with neoadjuvant chemotherapy (NACT) during the period between october 2014 to October 2015. Data regarding patient characteristics, chemotherapy received, toxicity, response rates, local treatment offered, patterns of failure, and overall survival analyzed from a prospectively filled database. Result: A total of 70 patients analyzed, : A total of 70 patients received chemotherapy. Median age been 45 years (range 20-70 years). 14 of our patient received 3 drug regimen while the rest of our patients received 2 drug regimen. Partial response achieved in 17 patients, stable disease in 41 patients and progression was noted in 12 patients. Resectability was achieved in 21 of 70 patients and showed marginally better results the estimated median PFS , OS in patients underwent surgery was 7.04 months and 11 months respectively. For those treated with non-surgical treatment PFS , OS was 4.5 months and 6.05 months respectively. Conclusion: Induction chemotherapy was effective in converting unresectable oral cavity cancers to operable disease in approximately 30% of patients and was associated with marginally improved progression free survival and overall survival in comparison to nonsurgical treatment. More multi institutional trials are required to arrive at a definite conclusion or protocol with neoadjuvant chemotherapy that may make a difference in locally advanced unresectable OCC.*

Keywords: *oral cavity cancer, unresectable ,neoadjuvant chemotherapy, Adjuvant radiotherapy, surgery, locoregional treatment.*

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I. Introduction

Oral squamous cell carcinoma (OSCC) is the most common type of tumor in the oral cavity [1]. Early stage tumors account for about 30% of the tumors. The majority of the tumors are locally advanced and have relatively poor prognosis with 5 years survivals <50-60% [2,3,4]. Surgical excision is the mainstay of treatment for OCC followed by postoperative radiotherapy or chemoradiotherapy, depending on the presence of intermediate- or high-risk features[5]. The patients who are considered locally advanced and unresectable are usually treated with nonsurgical modalities like concurrent chemoradiation, radical radiation, palliative radiation and best supportive care. There is considerable heterogeneity in the intent and type of treatment offered to these patients. The current standard of management of T4b cancers is radical chemo-radiation alone. The results of chemo radiation or radical radiation alone in T4b cancers are not satisfying with 1-year disease-free survival in various studies ranging from 10% to 40% respectively [6,7,8,9,10,11,12,13]. Surgery is an option in exceptional cases. In a recent article Liao *et al*. reported results from their center on upfront surgery in T4b oral cavity cancers below the infrahyoid notch. The 5 year loco-regional control rate was 47% [14,15]. However, these are individual institutional reports and are not generally reproducible in conventional practice.With such disappointing outcomes, alternative treatment paradigms are required. Neoadjuvant chemotherapy (NACT) in head and neck cancers has been investigated for long with an aim of reducing surgical margins, distant metastasis rates, and improving outcomes. Results from the TAX 323 and TAX 324 trials have shown the role of induction chemotherapy in unresectable and locally advanced head and neck Cancer with response rates of around 68% [16,17]. Patil *et al*. published a retrospective study of 123 patients with

unresectable locally advanced oral cavity cancers. The response rate 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 (68.00%) and 36 patients with 2 drug regimen (37.89%). The estimated median OS was 12.7 months. This was statistically significant compared to patients treated with nonsurgical modalities postchemotherapy. The estimated median OS in these patients was 8 months ($P = 0.0001$). Use of neoadjuvant chemotherapy in this setting has been effective in down staging the tumor and make it operable[18]. In this study,we retrospectively assessed the impact of NACT in borderline unresectable OCC.

II. Materials And Methods

This was a retrospective observational study conducted at Department Of Radiotherapy NSCB Medical college Jabalpur on patients treated from October 2014 to October 2015. These patients were considered unresectable in a multidisciplinary joint clinic. AJCC staging 2010 defines very advanced, local disease, or unresectable T4b OCC as tumor invading the masticator space, pterygoid plates, and skull base, or encasing the internal carotid artery [19]. However, the resectability remains controversial term with limited consensus among the surgical teams. The term unresectable has been also used to include tumors which are not staged as T4b but are known to carry poor prognosis and high morbidity after surgical resection. A rationale of proposing NACT in these cases is to improve the overall outcome by reducing tumor burden prior to radiation or facilitate possible resection following tumor shrinkage. Patients were randomly selected to receive either three drug combination (Platinum + 5FU+taxene) or two drug combination chemotherapy (Platinum + Taxane). Docetaxel was administered at a dose of 75 mg/m2 over 2 hours on day 1, cisplatin was administered at a dose of 75 mg/m2 over 1 hour on day 1 and 5 FU was administered at a dose of 750 mg/m2/day as continuous infusion for 5 days with standard prior premedications , G-CSF support and oral antibiotic prophylaxis. In the 2 drug combination, either docetaxel at a dose of 75 mg/m2 over 2 hours or paclitaxel at a dose of 175 mg/m2 over 3 hours was administered on day 1 with either cisplatin at a dose of 75 mg/m2 or carboplatin at a dose of AUC (area under curve) of 6 on the same day.Standard premedication was used. The chemotherapy was given once every 21 days in both the regimens. All patients were assessed before each successive cycle for toxicity and clinical response. Inclusion criteria included histologically proven oral squamous cell cancer, male and female {non pregnant} ,previously untreated cases, age between 20 and 70 years, no distant metastasis, normal renal and hepatic functions. All patients after the completion of the 2nd cycle were reassessed by radiology and clinical examination. The response and potential for resectability was decided in the multidisciplinary joint clinic. Patients who were considered to have resectable disease underwent surgical resection. Patients whose surgery was delayed by more than 5 weeks due to any reason (operative waiting list, anesthetic fitness, logistic issues) were given one more cycle of chemotherapy. Patients who did not achieve resectability after chemotherapy were treated based on the final extent of disease and the response to neoadjuvant chemotherapy. These patients underwent radical chemoradiation, radical radiation, palliative radiation, palliative chemotherapy or best supportive care as decided in the clinic. The treatment decision was made based on the performance status, extent of disease and patients choice. All the patients, irrespective of treatment were followed-up until progression, recurrence, relapse or death, whichever occurred earliest. Data regarding patient characteristics, chemotherapy received, toxicity, resonse rates, local treatment offered, pattern of failure, progression free survival and overall all survival were analysedusing SPSS software version.16.The response rates and percentage of patients achieving resectability at the end of the second cycle were calculated. Progression free survival (PFS) was calculated from the date of first chemotherapy till date of recurrence or progression or until date of death if it occurred prior to failure.

Overall survival was defined from the date of the first day of chemotherapy till the date of death or last day of follow-up. The overall survival of the patients who underwent surgery was compared to the patients who remained unresectable.

III. Results

Over the mentioned time period in our database, 70 patients with T4b were offered NACT. The baseline characteristics have shown in TABLE[1].

The majority of our patients had buccal- alveolar complex as the primary site followed by tongue/fom and hard palate. Most of them were N2 staging. Reason for giving NACT includes involvement of masticator space, infratemporal fossa, extensive skin infiltration and extension to hyoid cartilage. Three drug regimen given to 14 patienta while rest received two drug regimen. 63 (90 %) patients received at least 2 cycles of chemotherapy.The median number of cycles delivered were 2 (range 1-3). 7 patients took only one cycle. 3 had disease progression, 1 had severe toxicity and 3 withdrew consent for chemotherapy. Only 4 patients received dose reduction25%.

The response assessment was done after receiving NACT as shown in TABLE [2]. The overall response rate was 24.28%, 17 achieved partial response while 41 patients had stable disease and 12 underwent

progression. Resectability achieved is shown in TABLE [3]. 21 patients achieved resectability, use of three drug regimen had better association with resectability. The details of grade 3-4 toxicity can be seen in TABLE[4]. The rate of neutropenia was 12.85 % while 38.5 % had vomiting. Some developed grade 3 diarrhoea and anemia. All toxicities were managed well giving the GCSF , antibiotic and other supportive measures. One patient left the treatment due to sever toxicity.

The treatment offered post induction chemotherapy was radical treatment in 38 patients (54.2%) and palliative treatment in rest. 63 patients completed NACT. Post-NACT surgery was done in 18 patients, chemo radiation in 29 patients, radical radiation in 1 patient, palliative radiation in 10 patients, palliative chemotherapy in 5 patients and 7 patients did not undergo any further treatment. The median duration between completion of chemotherapy and date of surgery was 1.38 months. Though 21 patient had achieved resectability, 18 patients underwent surgery, 2 of these 3 patients defaulted and one patient opted for chemo radiation. No patient had achieved pathological complete response. Pathological downgrading in staging was achieved in 6 patients, with 1 tumor being pT1, 2 being pT2 and 3 being pT3 respectively. 17 patients received adjuvant post-operative chemo radiation. one patient had local recurrence while awaiting the start of chemo radiation. Postoperative radiation dose is 60-66Gy All patients were planned with conventional fraction schedule 200 cGy per fraction for 5 days a week with conventional, two, parallel, lateral opposing portals, source to axis distance technique with dose prescription been done along the central axis on the mid separation point.

The estimated median PFS, OS in patients who underwent surgery was 7.04 months and 11 months respectively. For those treated with non-surgical treatment PFS, OS was 4.5 months and 6.05 months respectively. 41 patients have had failure defined as locoregional recurrence or progression in 37 patients and 4 distant in failed. The predominant pattern of failure was local 37 out of 41 failures (90.2 %).

TABLE 1

CHARACTERISTICS	**PATIENT NO.**
Median age	45 Year
Male/female	68/8
Site of cancer	
Tongue/fom	6
Buccal-alveolar complex	62
Hard palate	2
N stage	
No	14
N1	10
N2	44
N3	2
Reason for NACT	
Masticator space	61
Others	9
REGIMEN	
2 drugs	56
3 drug	14

TABLE 2

RESPONSE ACHIEVED AFTER NACT	**NUMBER OF PATIENTS**
CR	0
PR	17
SD	41
PD	12

TABLE 3

REGIMEN	**RESECTABILITY**	
	ACHIEVED	**NOT ACHIEVED**
3 DRUG	9{65%}	5
2 DRUG	12{21.4%}	44

TABLE 4

GRADE 3-4 TOXICITY	NUMBER OF PATIENTS
Anemia	2
Neutropenia	9
Vomiting	27
Diarrhea	6

IV. Discussion

As per 7 th edition of AJCC staging classification T4b oral cavity cancers are considered unresectable [20]. Indian council of Medical research recommend that the intent of treatment in these patients be palliative from the outset. Radical radiation, with or without chemotherapy is the standard therapy for such patients. However, several studies from India have documented poor results with this approach [8,11,12,21]. Investigators have reported different approaches to improve the poor outcomes in T4b tumors. Liao *et al*. studied the role of meticulous surgery in those patients where the tumor involvement of the MS was restricted to a plane below the jugular notch. The results were impressive with 5 year OS rate of 47%[14,15]. However, these results have not been replicated elsewhere.

Neoadjuvant chemotherapy {NACT} in head and neck cancers has been investigated for long with an aim of reducing surgical margins,distant metastasis rates and improving outcomesLicitra L et al. reported their experience of primary chemotherapy in resectable oral cavity squamous cell carcinoma. Patients were randomized to receive either initial surgery or neoadjuvant (induction) chemotherapy with three cycles of cisplatin and 5-FU followed by surgery. The study noted a pathologic complete response rate of 27% at the primary site after the neoadjuvant chemotherapy. Thirty-three percent of patients had a pathologic complete response or near complete response at both the primary site and regional lymph nodes. Although the addition of neoadjuvant treatment did not impact overall survival, it did have some intriguing effects. "Less demolitive surgery (31% vs 52%)" was required in the surgery arm without an increased rate of positive margins and less postoperative radiotherapy (33% vs 46%) was used[22]. Okura *et al*. published a retrospective review of induction chemotherapy in patients with operable oral cavity cancers. The induction chemotherapy comprised of two cycles of cisplatin, vincristine and peplomycin, with or without mitomycin C. The overall response rate was 51.5% and there was a documented decrease in the rates of distant metastases. Surprisingly, the loco regional relapse rates were higher in patients with stage II and N0 tumors receiving induction therapy. The type of surgery performed, the response to chemotherapy as per the T stage, the impact of effective chemotherapy and the adequacy of surgical margins achieved have not been reported [23]. The TA X 323 trial has reported on the use of induction chemotherapy in unresectable head and neck cancers[16].

Different approaches have been tried to improve outcome of these patients. At our institute, NACT is used in patients where lesions are deemed unresectable due to their anatomic spread. The intent of treatment is to make the lesions amenable to resection with adequate margins. An interesting hypothesis in this regard could be the potential difference in the biological activity of oral cavity tumors compared with other sites in the head and neck region. Yeole *et al*. have demonstrated that the response of oral cavity cancers especially buccal mucosa cancers to radiation is inferior when compared with pharyngeal cavity cancers [24]. Hence, surgery upfront or following chemotherapy should conceivably be the preferred paradigm of therapy. Further, this approach seems promising as patient undergoing surgery had a survival advantage in our analysis. There are limitations to our study. This is a retrospective analysis and there is no randomization or a comparator arm to decide the true benefit of NACT. In our study, 65 % of patients receiving three drug regimen and 21.4 % of patients receiving 2 drug regimen had cancers of the oral cavity that became resectable following induction chemotherapy. Three-drug regimen was more effective than 2-drug regimens.The overall response rate seen in our study is lower when compared to that reported for 2 drug and 3 drug regimens in the TAX 323 and TAX 324. However, it should be noted that less than 15% of patients in these trials had oral cavity cancers.[16,17.] Though objective criteria were used as much as possible along with discussion in a multidisciplinary clinic, inherently the assessment of resectability is dependent on the surgical skills available in any center. Hence, our results need to be validated by different centers.

An intriguing finding from our study is the unexpectedly weak association of the response evaluation criteria in solid tumor criteria with the achievement of resectability. Many patients had stable disease on imaging which implies a change of < 30% in the sum of longest diameters. Such a decrement might often be sufficient for a surgeon to achieve resection with adequate margins especially where the lesion was border line to begin with. Thus, a discussion with the radiologist and surgical oncologist in a multidisciplinary clinic is essential in all cases. Another important finding relates to the selection of patients and the protocol for induction chemotherapy.Further, regimens containing 3 drugs appear to be better The OS advantage demonstrated in our analysis from use of surgical modality post neoadjuvant treatment is encouraging. However, it should be considered that patient in whom there was tumor regression could only undergo surgery as response to induction chemotherapy is a known important prognostic factor in head and neck cancers [22,25,26]. The likely benefit of

this approach has also been pointed out by Paterson *et al* [27]. Our results prior to use in clinical practice need prospective randomized evaluation where in patients post induction chemotherapy are considered resectable, undergo a randomization between surgery versus radical chemo radiation.

V. Conclusion

The use of induction chemotherapy in T4b unresectable cancer delays the progression of disease, gives partial response macroscopically , is safe and feasible and may lead to This approach is likely to lead to a survival advantage in patients who undergo surgery. 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 unresectable oral malignancies.

References

[1]. Kademani D. Oral cancer. Mayo ClinProc 2007;82:878-87.
[2]. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29
[3]. Neville BW,Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002;52:195-215.
[4]. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
[5]. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers, Version 1; 2012.
[6]. Corry J, Peters LJ, Costa ID, Milner AD, Fawns H, Rischin D, *et al*. The 'QUAD SHOT' - A phase II study of palliative radiotherapy for incurable head and neck cancer. RadiotherOncol 2005;77:137-42.
[7]. Pearson RA, Bannister-Young RH, Ivison D, Kelly CG, Chatterjee S. Split-course hypofractionated palliative radiotherapy for patients with head and neck squamous cell carcinoma-A worthwhile treatment schedule in the UK? ClinOncol (R CollRadiol) 2010;22:890-1.
[8]. Mohanti BK, Umapathy H, Bahadur S, Thakar A, Pathy S. Short course palliative radiotherapy of 20 Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study. RadiotherOncol 2004;71:275-80.
[9]. Agarwal JP, Nemade B, Murthy V, Ghosh-Laskar S, Budrukkar A, Gupta T, *et al*. Hypofractionated, palliative radiotherapy for advanced head and neck cancer. RadiotherOncol 2008;89:51-6.
[10]. Al-mamgani A, Tans L, Van rooij PH, Noever I, Baatenburg de jong RJ, Levendag PC. Hypofractionated radiotherapy denoted as the "Christie scheme": An effective means of palliating patients with head and neck cancers not suitable for curative treatment. ActaOncol 2009;48:562-70.
[11]. Ghoshal S, Mallick I, Panda N, Sharma SC. Carcinoma of the buccal mucosa: Analysis of clinical presentation, outcome and prognostic factors. Oral Oncol 2006;42:533-9.
[12]. Pathak KA, Gupta S, Talole S, Khanna V, Chaturvedi P, Deshpande MS, *et al*. Advanced squamous cell carcinoma of lower gingivobuccal complex: Patterns of spread and failure. Head Neck 2005;27:597-602.
[13]. Pradhan SA. Surgery for cancer of the buccal mucosa. SeminSurgOncol 1989;5:318-21.
[14]. Liao CT, Ng SH, Chang JT, Wang HM, Hsueh C, Lee LY, *et al*. T4b oral cavity cancer below the mandibular notch is resectable with a favorable outcome. Oral Oncol 2007;43:570-9.
[15]. Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, *et al*. Survival in squamous cell carcinoma of the oral cavity: Differences between pT4 N0 and other stage IVA categories. Cancer 2007;110:564-71.
[16]. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, *et al*. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695‑704.
[17]. Lorch JH, Goloubeva O, Haddad RI, Cullen K, Sarlis N, Tishler R, *et al*. Induction chemotherapy with cisplatin and fluorouracil alone or incombination with docetaxel in locally advanced squamous‑cell cancer ofthe head and neck: Long‑term results of the TAX 324 randomised phase3 trial. Lancet Oncol 2011;12:153‑9.
[18]. Patil VM, Noronha V, Joshi A, Muddu VK, Gulia S, Bhosale B, *et al*. Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: Does it make a difference? Indian J Cancer 2013;50:1-8.
[19]. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7 th ed. Bangalore: Springer;2009.
[20]. Edge S, Byrd DR, Compton CC. Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7 th ed. Bangalore: Springer; 2009.
[21]. Nair MK, Sankaranarayanan R, Padmanabhan TK. Evaluation of the role of radiotherapy in the management of carcinoma of the buccal mucosa. Cancer 1988;61:1326-31.
[22]. Licitra L, Grandi C, Guzzo M, Mariani L, Lo Vullo S, Valvo F, *et al*. Primary chemotherapy in resectable oral cavity squamous cell cancer: A randomized controlled trial. J ClinOncol 2003;21:327-33
[23]. Okura M, Hiranuma T, Adachi T, Ogura T, Aikawa T, Yoshioka H, *et al*. Induction chemotherapy is associated with an increase in the incidence of locoregional recurrence in patients with carcinoma of the oral cavity: Results from a single institution. Cancer 1998;82:804-15.
[24]. Yeole BB, Ramanakumar AV, Sankaranarayanan R. Survival from oral cancer in Mumbai (Bombay), India. Cancer Causes Control 2003;14:945-52.
[25]. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 1991;324:1685-90.
[26]. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: Preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890-9.
[27]. Paterson C, Robertson AG, Grose D, Correa PD, Rizwanullah M. Neoadjuvant chemotherapy prior to surgery in head and neck cancer. ClinOncol (R CollRadiol) 2012;24:79-80

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