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IP Journal of Diagnostic Pathology and Oncology

Journal homepage: https://www.jdpo.org/

Original Research Article

Neo adjuvant chemotherapy in locally advanced oral cancers -A prospective study at a tertiary cancer care hospital

Deepa Shunmugam[1]*, SS Sundaram[1], Arumugam Velappar[1], Anitha Gandhi[1], MJ Murali Kannan[1], Ganesh Babu V[2], Karthik Manohar[1]

[1]*Dept. of Surgical Oncology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India*
[2]*The Tamil Nadu Dr M.G.R. Medical University, Chennai, Tamil Nadu, India*

ARTICLE INFO

Article history:
Received 21-07-2023
Accepted 24-01-2024
Available online 31-01-2024

Keywords:
Neo adjuvant Chemotherapy
Target lesion
Progressive disease
Partial response
Complete response
Stable disease

ABSTRACT

Introduction: Oral squamous cell carcinoma (OSCC) is the most prevalent type of cancer found in the oral cavity. Approximately 30% of these tumours are detected at an early stage, while the majority are diagnosed as locally advanced tumours.

Background: Extensive research has been conducted on neoadjuvant chemotherapy (NACT) in head and neck cancers, aiming to reduce surgical margins, decrease distant metastasis rates, and improve overall outcomes.

Materials and Methods : In this prospective study conducted at the Department of surgical oncology, Tirunelveli Medical College, 60 patients with unresectable locally advanced oral cancers were staged based on the AJCC TNM (8th edition). The period of study was from October 2018 to March 2023. Here the selected patients are examined both clinically and radiologically, measurements of the target lesions are made. These patients are subjected to neoadjuvant chemotherapy (TPF regimen) upto three cycles based on the clinical response after each cycle. reassessment done prior to surgery as done during the prechemotherapy. Adjuvant therapy post-surgery is based on the histopathology.

Results: Among the 60 patients enrolled in this study, 33 of 60 (55.0 %) were males and 27 of 60 (45%) were females. Based on age distribution 8.3% of patients were less the 40 years of age, 41.7% were between 51 to 60 years. The common risk factors were tobacco / pan chewing in 66.7% of patients, smoking in 40% of patients and alcoholism in 38.3% of patients. All the 60 patients received TPF regimen as a neo-adjuvant chemotherapy for two or three cycles and the clinical responses were recorded after NACT prior to definitive therapy (surgery vs RT. The mean and median of survival was calculated in 33 patients who had completed treatment by 2021 in view of the follow up period of at least for 24 months were mandatory to analyse the treatment outcome and disease free survival. The overall survival in surgery group was 35.1 months and RT group was 21.8 months. The disease free survival in surgery group was 28 months whereas in RT group was 16 months.

Conclusion: Patients who have oral cavity cancers that cannot be surgically amenable up-front may experience a response rate of approximately 25% when treated with an aggressive three-drug regimen (TPF) and these patients may derive benefits from subsequent surgical treatment.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most prevalent type of cancer found in the oral cavity. Approximately 30% of these tumours are detected at an early stage, while

* *Corresponding author*.
E-mail address: oncodeepa@gmail.com (D. Shunmugam).

https://doi.org/10.18231/j.jdpo.2024.006

the majority are diagnosed as locally advanced tumours.[1] Unfortunately, locally advanced OSCC is associated with a relatively poor prognosis, with 5-year survival rates ranging from less than 50% to 60%.[2]

Currently, the standard treatment approach for resectable locally advanced OSCC involves surgical clearance of the primary along with neck dissection, followed by postoperative radiotherapy or chemoradiotherapy, depending on the presence of intermediate- or high-risk features.[3] The primary mode of treatment failure for oral cancer is at the local or regional level.

Addressing locally advanced OSCC often requires extensive surgical procedures, which can result in significant cosmetic deformities and functional morbidity. However, advancements in reconstruction techniques have made it possible to perform wider resections while minimizing the impact on functional and cosmetic outcomes.[4] Nonetheless, achieving resectability of the tumour must involve a delicate balance between ensuring negative surgical margins and preserving acceptable functional abilities and cosmetic appearance.

Extensive research has been conducted on neoadjuvant chemotherapy (NACT) in head and neck cancers, aiming to reduce surgical margins, decrease distant metastasis rates, and improve overall outcomes.[5] A meta-analysis involving 31 trials and over 5000 patients examined the effect of chemotherapy on head and neck cancer. However, this analysis did not find a significant survival advantage following induction chemotherapy.[6] Nevertheless, trials that utilized a combination of 5-fluorouracil (5-FU) and cisplatin as part of the NACT regimen demonstrated a notable overall survival (OS) benefit compared to other combinations and single-agent NACT. It is worth noting that these trials did not specifically focus on oral cavity cancers and had limited representation of patients with oral squamous cell carcinoma (OSCC).

Most of the trials included in the meta-analysis were conducted before the era of taxanes, and the impact of taxane-based regimens in the neoadjuvant setting was not addressed. Recent studies, such as TAX 323 and 324, have reignited interest in NACT by incorporating taxane (specifically docetaxel) along with fluorouracil and cisplatin (TPF) in the induction regimen.[7] The TPF regimen has shown improved survival outcomes in advanced head and neck squamous cell carcinoma (HNSCC) compared to patients receiving cisplatin and fluorouracil (PF) alone as induction therapy.[8] However, it should be noted that these trials included various subsites within the head and neck region and were not exclusively designed for OSCC.

The aim of this paper is to critically review the current evidence for NACT in locally advanced OSCC and suggest an algorithmic approach to the patient population who might benefit from NACT for OSCC.

The decision of unresectability is a contentious matter that is influenced by subjective factors, leading to potential variations. Technical unresectability encompasses various complex factors such as the disease's status, anatomical site involvement, surgical expertise, quality of life considerations, and the ability to achieve complete tumour removal (R0 resection). According to Patil et al., the following criteria have been defined to identify technical unresectability:[9]

1. Buccal mucosa primary tumours with diffuse margins, peritumoral edema extending up to or above the level of the zygomatic arch, and the absence of satellite nodules.
2. Tongue primary tumours (anterior 2/3rd) with tumour extension up to or below the level of the hyoid bone.
3. Extension of tumour originating in the anterior two-thirds of the oral tongue to the vallecula.
4. Tumour extension into the high infratemporal fossa, as determined by the tumour extending above an axial plane passing through the level of the sigmoid notch.
5. Extensive infiltration of the skin, hindering the achievement of negative margins.

2. Materials and Methods

In this prospective study conducted at the Department of surgical oncology, Tirunelveli Medical College, 60 patients with technically unresectable locally advanced oral cancers were staged based on the AJCC TNM (8th edition). The period of study was from October 2018 to March 2023. The patients were subjected to clinical examination and measurements of the concerned primary and nodal disease were recorded as target I and target II lesions. These patients were also subjected to contrast studies of the local part (a contrast-enhanced computerised tomography (CECT) of the base of skull to sternal notch for all oral cavity primaries except for tongue which required magnetic resonance imaging) and CECT Chest for metastatic work up. All patients underwent a formal ENT examination with video laryngoscopy and diagnostic nasal endoscopy was done and the size of the target lesions were recorded prior to the commencement of the neoadjuvant chemotherapy (NACT). The chemotherapeutic regimen preferred was docetaxel 80 mg/m^2, cisplatin 75 mg/m^2 and 5 fluro uracil 750 mg/m^2(TPF). The response assessment was done clinically after completion of each cycle of chemotherapy. Based on the clinical response, the patients were subjected upto two to three cycles of chemotherapy. After completion of the final cycle of chemotherapy the same imaging which was used prior to induction of chemotherapy was done with a clinical and radiological assessment of the target lesions were recorded. The standard World Health Organization (WHO) RECIST1.1 criteria were used to evaluate the response after

NACT.

Complete response: The disappearance of all target lesions (any pathological lymph node must have a reduction in short axis to <10mm.

Partial response: 30% or > 30% decrease in the sum of the longest diameter of the target lesions, taking as a reference, the baseline sum of the diameters.

Stable disease: Neither sufficient decrease to qualify for a partial response nor sufficient increase to qualify for progressive disease.

Progressive disease: 20% or >20% increase in the sum of the longest diameter of the target lesions

In tumours with complete or partial response or in some cases of stable disease surgery was performed. If progressive or stable disease, these patients were subjected to definitive radiotherapy. In patients showing a complete response or a partial response, surgical interventions with or without reconstructions were performed and adjuvant therapy in the form of radiotherapy was planned as per oncological indications. These patients had a monthly follow up during the 1^{st} year, two monthly follow up during the second year and three monthly follow-up during third year followed by biannual follow-up there after.

2.1. *Inclusion criteria*

1. Patients with good performance status.
2. Patients with extensive soft tissue involvement.
3. Patients with skin edema.
4. Patients with tumour extension to posterior third of tongue.
5. Lesions crossing midline (in tongue / floor of mouth primaries).
6. Infra temporal fossa involvement.

2.2. *Exclusion criteria*

1. Poor performance status.
2. Metastatic disease.
3. Involvement of the skull base.
4. Encasement of the carotids.
5. Involvement of the masticator space.

2.3. *Statistical analysis*

The data were presented as median, interquartile range, frequency and percentage. Continuable variables were compared using Mann-Whitney U-test. Categorical variables were compared using Pearson Chi-square test. The Kaplan-Meier curve is constructed by plotting the survival function against time. Significance was defined by P values less than 0.05 using two-tailed test. Data analysis was performed using IBM-SPSS version 21.0 (IBM-SPSS Science Inc., Chicago, IL).

3. Results

Among the 60 patients with locally advanced oral cancers enrolled in this study, 33 of 60 (55.0%) were males and 27 of 60 (45%) were females as depicted in Table 1.

Table 1: Sex distribution

Gender	No. of patients	Percentage
Male	33	55.0%
Female	27	45.0%

Based on age distribution 8.3% of patients were less the 40 years of age, 41.7% were between 51 and 60 years and only three patients were above 70 years, as depicted in Table 2.

Table 2: Age distribution

Age group	No. of patients	Percentage
<40	5	8.3%
41-50	14	23.3%
51-60	25	41.7%
61-70	13	21.7%
>71	3	5.0%

The common risk factors were tobacco / pan chewing in 66.7% of patients, smoking in 40% of patients and alcoholism in 38.3% of patients as depicted in Table 3.

Table 3: Risk factors

Risk factors	No. of patients	Percentage
Tobacco/Pan chewer	40	66.7%
Smoker	24	40.0%
Alcoholic	23	38.3%

Based on the affected subsite in oral cavity among the 60 patients, 34 patients had involvement of buccal mucosa, 17 had involvement of lower alveolus, 4 patients with lesion in the tongue, 3 patients with floor of mouth and 2 had involvement of upper alveolus as depicted in Table 4.

Table 4: Subsites

Subset	Number	Percentage (%)
Buccal mucosa	34	56
Lower alveolus	17	28
Tongue	4	6.6
Floor of mouth	3	5
Upper alveolus	2	3.3

The response rate to TPF regimen was 25%. This includes both complete response of 5% and partial response of 20% as shown in Table 5. Patients with stable disease were either

allotted to surgery or radiotherapy arm based on clinical assessment.

Table 5: Response after NACT

Response	No. of patients	Percentage
Progressive disease	32	53.30%
Partial response	12	20%
Complete response	3	5%
Stable disease	13	21.70%

The number of patients who underwent surgery were 18, whereas 35 patients received radical RT and the remaining 7 patients were lost to follow up as shown in Table 6.

Table 6: Surgery vs RT group

Surgery group	RT group
18	35

The mean and median of survival was calculated in 33 patients who had completed treatment as on December 2021 in view of the follow up period of at least for 24 months were mandatory to analyse the treatment outcome and disease free survival. The median overall survival in surgery group was 35.1 months and radiotherapy group was 21.8 months as depicted in Table 7. The disease free survival in surgery group was 28 months whereas in RT group was 16 months. The overall survival rate in surgery group was 50 % and RT group was 25 %(P value – 0.824). The overall mortality rate in surgery group was 22.2 % and RT group was 73.7 % (P value – 0.01).

Table 7: Mean and median for survival time

Treatment	Mean Estimate (months)	Median 95% Confidence Interval
RT	21.893	14.870
Surgery	35.143	25.048
Overall	25.586	19.084

The resectability rate was 30% (18 of 60 patients) and there were no margin positive resection. Two patients had a pathological complete response following surgery, hence deferred adjuvant RT was deferred and are on regular follow up.Figure 1

4. Discussion

The management strategy for stage I and II cancers of the oral cavity involves a single modality approach, while stage III and IV diseases requires a multimodality approach.[10] The advancement of radiation techniques, particularly intensity-modulated radiation therapy (IMRT), has resulted in better control of the tumour at the local-regional level.[11]

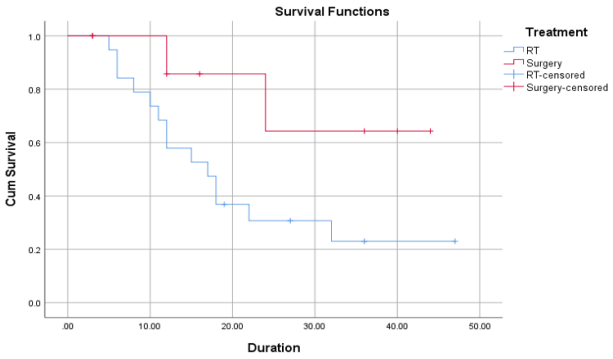

Figure 1: Kaplan Meier survival curve

However, it has been observed that distant recurrences increasingly affect overall survival. To address this issue, researchers hypothesized that administering induction or neoadjuvant chemotherapy before definitive radiation-based therapy or surgery could reduce the occurrence of recurrent and metastatic disease, thereby improving survival rates.[12] Phase 3 trials investigating the addition of a taxane agent, namely docetaxel or paclitaxel, to induction cisplatin and 5-fluorouracil (5-FU) therapy have demonstrated enhanced response rates, disease-free survival, and overall survival in patients who received this triplet induction chemotherapy.[13]

The demography of our study, shows that the males were the dominant gender (55%) and the female comprised of 45%. The common age group was between 51 - 60 years. According to the study on the "Socio demographic profile of oral cancer patients residing in Tamil Nadu", the males were more commonly affected in the study as comparable to our study.[14] In the same study 44.5% were smokers and 39.8 % were alcoholics which was also comparable to our study as 40 % of smokers and 38 % of alcoholics respectively.

Patil et al. published a retrospective study of 123 patients with technically unresectable locally advanced oral cavity cancers.[15] The patients were given NACT with TPF or TP and assessed for resectibility. The response rate with the three drug was 32.00% which was comparable to our study.

A study was conducted by Dhruv Patel et al., in which 32 patients with locally advanced oral cancers, who received three cycles of TPF (docetaxel, cisplatin, 5FU) followed by response assessment prior to surgery.[16] In this study, 12 out of 32 patients (37.5%) were good responders including two patients (6.2%) who had a Complete Response (CR). Our study comprised of patients with response rate of 25 % was comparable.

In a study conducted by Joshi et al, the patients with locally advanced oral cancers received two cycles of neoadjuvant chemotherapy had a resectability rate of 30.9 %, whereas TAX 324 study showed a resectability rate of 30 % which was comparable to our study.[17]

In TAX 324 study, an open label phase 3 trial comparing the survival benefit for 3 cycles TPF vs 3 cycles of PF in

patients with locally advanced oscc (stage III and stage IV) showed a better outcome in TPF group where the survival rate was 50%. This was comparable to our study which recorded median overall survival of 35 months in surgery group with a survival rate of 50%.[18]

In a study conducted by Zhong et.al, 109 patients with technical unresectability received two cycles of TPF regimen as a neoadjuvant therapy followed by surgery followed by adjuvant radiotherapy, where estimated 2-year OS was 68.2%.[19] In our study the overall survival of 50 % and a disease free survival of 48 % respectively were recorded.

The following limitation in our study may be a factor – Only those patients who are good responders to the neoadjuvant chemotherapy are taken up for surgery, so naturally the survival in such patients may be better as the disease biology is favourable.

Patients who have oral cavity cancers that are not surgically amenable up-front, after receiving neoadjuvant chemotherapy with TPF regimen can achieve a resectability rate of 30 % and a survival rate of 50 %. Based on the clinical response and the patient's outcome we recommend that the neoadjuvant chemotherapy can be a safe and feasible option leading to R_0 surgical resection.[20] This approach also has the potential to improve survival in patients who undergo surgery and may be considered the standard of care in this context.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Author biography

Deepa Shunmugam, Associate Professor https://orcid.org/0009-0003-1594-5760

SS Sundaram, Professor & HOD https://orcid.org/0000-0003-4591-460X

Arumugam Velappar, HOD https://orcid.org/0009-0007-2601-926X

Anitha Gandhi, Assistant Professor https://orcid.org/0000-0002-2451-9806

MJ Murali Kannan, Assistant Professor https://orcid.org/0000-0001-8230-1568

Ganesh Babu V, Senior Resident https://orcid.org/0009-0002-9226-3176

Karthik Manohar, Senior Resident https://orcid.org/0009-0007-2059-647X

Cite this article: Shunmugam D, Sundaram SS, Velappar A, Gandhi A, Kannan MJM, Ganesh Babu V, Manohar K. Neo adjuvant chemotherapy in locally advanced oral cancers -A prospective study at a tertiary cancer care hospital. *IP J Diagn Pathol Oncol* 2024;9(1):34-39.