



ORIGINAL RESEARCH PAPER

General Surgery

ASSESSMENT OF ROLE OF INDUCTION CHEMOTHERAPY IN MANAGEMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF ORAL CAVITY

KEY WORDS: Oral cavity squamous cell carcinoma, Head and Neck Squamous Cell Carcinoma, Induction chemotherapy.

Dr. Ashok Galande	Assistant Professor at Dept. of General Surgery, MGM Medical College and Hospital, Aurangabad, Maharashtra.
Dr. Hrushikesh D Mankar	Junior Resident at Dept. of General Surgery, MGM Medical College and Hospital, Aurangabad, Maharashtra.
Dr. Sor Prasad Totaram	Consultant & Director at Dept. of Onco-Surgery, Miramayee Cancer Speciality Hospital, Akola.
Dr. Ashwini Mahajan	Consultant Gynecologist At Dept. Of Obstertrics & Gynecology, Pentagon Hospital, Aurangabad.

ABSTRACT	<p>Background: Head and neck cancer is a heterogeneous disease, consisting of several subsites with differing pathologic and molecular characteristics, causative factors, therapeutic response, and prognosis. Systemic treatment is typically used in the management of head and neck squamous cell carcinoma (HNSCC). Theoretically, induction chemotherapy (IC) reduces the risk of distant metastasis and enables in vivo testing of responses and tumor biology. Thus, the purpose of this study was to investigate the efficacy, toxicity, and impact of IC in locally advanced squamous cell carcinoma (LA-SCC) of the oral cavity. Methodology: This prospective observational clinical study was conducted from March 2014 to April 2016. In this study, a total of 50 patients were enrolled. Among them, routine laboratory investigations including complete blood cell tests, chest x-ray, electrocardiogram (ECG), and computed tomography (CT) scan were investigated. Results: In the present study, 50 patients were included between the ages between 40 to 50 years. The prevalence of HNSCC was mostly found in males, with a male-to-female ratio of 2.12. IC results in organ preservation for approximately 50% of patients. Furthermore, findings show that, only 25% of cases were experienced both local and regional recurrence. Conclusion: IC was found to be the most effective method for the diagnosis of HNSCC, as it was well tolerated with no negative impact on radiotherapy or surgery.</p>
----------	--

INTRODUCTION:

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally, with more than 500,000 new cases diagnosed annually. Patients in the early clinical stages (I and II) are usually treated with surgery or radiation therapy, which generally results in excellent disease control and long-term survival. For patients with clinical stages III and IV, a sequential treatment approach is often necessary. This typically involves surgery and/or radiotherapy (RTX), with or without the addition of chemotherapy (CHT). Despite these treatments, the prognosis has not seen significant improvement. The five year survival percentage remains approximately 50% to 60%, and is even lower for patients in the later clinical stages.^[1]

Moreover, the frequency of HNSCC has been rising globally, especially in younger populations. By 2030, the incidence is expected to grow by 30% annually. Despite of the major occurrence of the disease worldwide, researchers all over the world are still not able to combat the treatment failure and recurrence of the disease.

Based on the location and the tumor's stage, validated treatment options include surgery, radiation therapy, or chemoradiotherapy (CRT).

Surgery is the preferred option for SCC of the oral cavity. However, in other sites, other approach is available. When the objective is to preserve organ function or when surgery is not feasible, an effective treatment involves combining CHT with RTX.^[2] In the field of oncology, Induction Chemotherapy (IC), alternatively termed neoadjuvant chemotherapy, stands as an essential therapeutic approach distinguished by its multifaceted advantages which are represented as follows:

i. IC serves as an effective strategy for the potential reduction or downstaging of HNSCC, effectively priming the tumor for subsequent treatment modalities.

ii. Through its implementation, IC facilitates an enhanced rate of organ preservation; thereby it prevents critical anatomical

structures and improves patient's functional outcomes.

iii. Notably, IC significantly mitigates the risk of locoregional or distant recurrence, thereby culminating in superior treatment outcomes characterized by prolonged disease-free intervals and increase overall survival rates.^[3]

On the basis of previous investigations, Cisplatin and 5 Fluorouracil, along with taxanes and mitomycin have most extensively used as chemotherapy regimen because it is proven as effective treatment for advanced head and neck carcinomas. It is well known that, above mentioned novel drugs exhibit high activity, achieving partial remission in 60% to 90% of patients who have not received treatment before. However, prior randomized trials have not shown a definitive effect on local tumor control or overall survival. The format of induction treatment also serves as a valuable tool for assessing new drug regimens. Utilization of chemotherapy offers the potential for improved control over both regional and distant tumors.

The concurrent use of chemotherapy and radiation has had a notable effect on treating advanced HNSCC. Multimodality management has arisen with significant additional objectives, including organ preservation and function, cosmesis enhancement, and improved quality of life.

Based on previous studies, the incidences of HNSCC and mortality rate among such patients were found to be very high. Therefore, to reduce such type of life-threatening conditions, IC has been proven to an effective for the management of HNSCC.

Thereby, objective of the present study was to evaluate the role of IC in HNSCC. Despite the small patient sample size and the results being derived from a single institution, this study provides valuable insights into the efficiency of IC for LA-SCC of the oral cavity.

MATERIALS AND METHODOLOGY

This prospective observational clinical study was performed in the Department of Surgical Oncology, at a tertiary health care center in Kolkata during March 2014 to April 2016. In this study, 50 patients with LA-SCC confirmed by histopathology examination who had not received any treatment were included.

Criteria of Inclusion:

- Patients belonging to the age group of 20 to 70 years.
- The Eastern Cooperative Oncology Group (ECOG) performance status should be < or equal to 2.
- Patients who have not undergone previous treatment and have been histologically confirmed to have SCC of the oral cavity.
- Patients who were willing to accept all three treatment modalities, i.e., surgery, chemotherapy, and radiotherapy.
- Participants with primary tumors located in the oral cavity, including the tongue, cheek, soft or hard palate, lip, buccal mucosa, alveolus, or oropharynx.

Criteria of Exclusion:

- Patients with a history of significant neurologic or psychiatric disorders, including dementia or seizures, and radiotherapy.
- Patients with active peptic ulcer, chronic obstructive pulmonary disease, immunosuppression, and collagen vascular diseases.
- Pregnant women
- Patients who were not fit for chemotherapy were excluded.

Methodology:

A comprehensive clinical analysis including tumor staging, complete blood cell (CBC) test, and radiographic examination such as ECG, X-ray, and CT scan (if required), were performed by a multidisciplinary committee of surgical, medical and radiation oncologists.

After clinical examination, patients were underwent induction chemotherapy. In this therapy, patients received 3 cycles of TPF (docetaxel 75 mg/m2 on day 1, cisplatin 80 mg/m2 on days 1 and 2, and 5FU 750 mg/m2 on days 1, 2, and 3) following the evaluation of their suitability for chemotherapy (using the ECOG performance status, nutritional status, CBC, urea, creatinine, and liver function test (LFT)).

Thereafter, patients were treated based on their responses, following response categorization from IC. Radiotherapy was then performed, in which 66Gy to 70Gy a definitive curative radiation dose was administered to the primary tumor, administered as a fraction of 1.8 to 2Gy per 5 days/week. At least 50 Gy of radiation was given to the uninvolved lymph node, and 60–70 Gy was given to the involved lymph node. At last, follow-up of the patients were taken for 2 years, all patients underwent through clinical and radiological examinations in every two to three months and then every six month (if necessary).

RESULT:

In this research, total 50 patients were included. The predominant age group was 40-50 years, with a median age of 45.5 years. The male population exhibited a higher prevalence, showing the ratio of male and female of 2.12. Clinical manifestations indicated that, ulceration and trismus were the most prevalent symptoms, observed in approximately 86% and 48% of cases, respectively, with median duration of 3 months. The most frequently encountered lesion was characterized by ulceration with trismus, displaying a median diameter of 5 cm. Nearly all patients, except for five, reported some form of addictive habits, with tobacco abuse being the most prevalent (46% for chewing and 44% for smoking). Other identified habits included betel nut use in 30% and alcohol abuse in 22%. Co-existing conditions were noted, with 20% of patients has

diabetes mellitus, 16% hypertension, and 2% chronic obstructive pulmonary disease (COPD). Furthermore, four patients had previously been diagnosed with leukoplakia, with duration of 8 months during the analysis of leukoplakia and the subsequent identification of cancer, as documented in previous records.

The buccal mucosa emerged as the most prevalent subsite, accounting for the highest number of patients at 38%, with a total of 19 individuals diagnosed with oral cancer in this area. Following closely, the tongue constituted the second most affected subsite, comprising 20% of the cases, involving 10 patients. The retromolar trigone exhibited oral cancer in 14% of the patients, with a total of 7 cases. Both the lip and hard palate presented with a similar incidence, each contributing 8% to the overall distribution, encompassing 4 patients each. Additionally, the floor of the mouth and the alveolar region shared a 6% occurrence rate, with three patients diagnosed in each subsite (Table-1).

Table-1: Distribution Of Subsite.

Sub Site	Number of patients	Percentage
Buccal mucosa	19	38
Tongue	10	20
Retromolar trigone	7	14
Lip	4	8
Hard palate	4	8
Floor of the mouth	3	6
Alveolus	3	6

Table-2 represents distribution of grade and stages. In terms of tumor grade, the majority of cases exhibited moderate differentiation, constituting 68% of the cohort, followed by well-differentiated cases at 28%, and poorly differentiated cases at 4%. The T stage distribution reveals that, 34% of cases were classified as T3, 60% as T4a, and 6% as T4b, indicating varying degrees of tumor invasion. Regarding regional lymph node involvement (N stage), 12% of cases were classified as N0 (no lymph node involvement), while 32% each were categorized as N1, N2a, N2b, and 10% as N2c.

Table-2: Distribution Of Grade, T Stage And N Stage.

Grade	Number (%)
Well differentiated	14(28%)
Moderate differentiated	34(68%)
Poorly differentiated	2(4%)
T stage	
T3	17(34%)
T4a	30(60%)
T4b	3(6%)
N stage	
N0	6(12%)
N1	16(32%)
N2a	7(14%)
N2b	16(32%)
N2c	5(10%)
N3	nil

In terms of treatment-related toxicities, the most prevalent adverse event was vomiting, occurring in 42% of cases, followed by diarrhea in 18% of cases. Hematological issues, specifically neutropenia, were observed in 4% of cases, while infections and mucositis were reported in 8% and 12% of cases, respectively. Pulmonary and renal complications, each accounting for 4% of cases, were also noted.

Complications arising from surgery were categorized, with partial mucosal dehiscence occurring in 16.6% of cases, wound infections in 13.3%, and pulmonary infections in 3.3% of cases. Additionally, partial flap necrosis was observed in 10% of cases, while oro-cutaneous fistula and bleeding were each reported in 3.3% of cases.

The recurrence patterns noted among the included cases

show that, 37.5% of cases experienced local recurrence. Also, 37.5% cases had regional recurrence and 25% exhibited both local and regional recurrence as mentioned in Table-3.

Table-3: Toxicity, Complications Of Surgery And Recurrence Pattern Of Patients.

Toxicity	No. of cases (%)
Vomiting	21(42%)
Diarrhea	9(18%)
Hematological (neutropenia)	2 (4%)
Infections	4(8%)
Mucositis	6(12%)
Pulmonary	1(4%)
Renal(raised urea and creat)	1(4%)
Complications of surgery	No. of cases (%)
Partial Mucosal dehiscence	5(16.6%)
Wound Infection	4(13.3%)
Pulmonary infection	1(3.3%)
Partial flap necrosis	3(10%)
Oro-Cutaneous Fistula	1(3.3%)
Bleeding	1(3.3%)
Recurrence pattern	No. of cases (%)
Local	37.5%(3)
Regional	37.5%(3)
Both	25%(2)
Distant	0%

In the current investigation, other findings revealed, IC led 25(50%) patients to organ preservation (12 patients in total with bimodality treatment i.e. chemotherapy and radiation, and 13 PR patients with trimodality treatment). Patients with organ preservation (mandible) had good masticatory functions and good cosmesis. Plus it made 17(34%) patients operable who were initially thought to be inoperable.

In the Buccal Mucosa (BM) group of 19 patients, one achieved complete response (CR), 16 exhibited partial response (PR), two had stable disease (SD), and no cases reported progressive disease (PD). However, six patients experienced recurrences. The Tongue group (10 patients) saw two CRs, eight PRs, and one recurrence. The retromolar trigone (RMT) group (7 patients) had no CRs, two PRs, three SDs, and two PDs, with one recurrence. In the Lip and Hard Palate groups (4 patients each), one achieved CR in each, with the majority showing PR. The Floor of the Mouth and Alveolus groups (3 patients each) exhibited varying responses, including PR and SD, with one recurrence in the Alveolus group (As shown in Table-4).

Table-4: Subsite Analysis:

Site	No of patients	CR	PR	SD	PD	Recurrences
BM	19	1	16	2	-	6
Tongue	10	2	8	-	-	1
RMT	7	-	2	3	2	1
Lip	4	1	3	-	-	-
Hard palate	4	-	3	1	-	-
Floor of mouth	3	-	3	-	-	-
alveolus	3	-	3	-	-	-

DISCUSSION:

In the current analysis, we used IC to reduce the cancer to accomplish surgical resections with negative margins. There are no reports that have been made regarding the use of IC in a patient population whose oral cavity tumors alone are marginally resectable.

In this study, a total 50 patients were included. Chewing tobacco use was one of the most common habits reported among almost all study populations. According to a histological analysis, the majority of the tumors belonged to the moderate differentiation category.

The present study demonstrated that, the male population showed a higher prevalence than women and nearly all patients had additive habits with 46% for chewing and 44% for smoking tobacco. Similar research findings were found in the study conducted by Kukreja et al., who investigated that, the 92.5% population was of male patients and alcohol and tobacco usage were the reasons for the cause.^[4]

In the current analysis, following IC, 38 out of 50 patients (70%) had PR and 4 patients (8%) had CR to IC. Also, 2 patients (4%) had PD and 6 patients (12%) had SD despite three cycles. Similar findings were reported by Shen et al., according to them, the CR, PR, and SD were 10.0%, 46.7%, and 43.3% respectively.^[5] Li et al., also reported that, 23.1% represent CR and 61.5% represent PR which shows similarity with the present study.^[6]

In the recent study, we noted that in terms of regional lymph node involvement (N stage), 12% of cases were designated as N0 (no lymph node involvement), while 32% each were classified as N1, N2a, N2b, and 10% as N2c. In contrast, Andersson et al., reported different proportions: N0 contributed 60%, N1 contributed 14.6%, and N2 and N3 together contributed 34.7% and 20.30% respectively. These findings show varied results with our study regarding to the distribution of regional lymph node involvement stages.^[7]

In the present study, the recurrence site was seen equally with local and regional recurrence (3 patients each with 37.5%) and only 2 patients (25%) had recurrence at both sites. According to Hanna et al., 22% of the cases experienced local recurrence, and distant recurrence was noted only in 2 % of cases. This study shows slight variation from the present study.^[8]

According to the Leon et al., patients who were treated with IC and radiotherapy achieved an organ preservation frequency of 62%. This finding found to be similar to the present study, where a 50% organ preservation rate was observed.^[9]

Based on the present study findings, oral tumors that became resectable after induction chemotherapy were present in 34% of patients undergoing induction chemotherapy scans. Logistically, it was preferable to employ taxanes, the other drug with platinum, rather than 5-FU in earlier investigations.

The present study, mainly focused on organ preservation and patient operability and effectively illustrated the viability of induction chemotherapy with respectable outcomes. However, our current study recommends that, before this induction technique can be legitimately incorporated into standard care surgical, medical, and radiation oncologists must elaborate the studies related to this technique.

LIMITATIONS OF THIS STUDY:

- 1) The study was completed in a constrained amount of time
- 2) The population was not very large.
- 3) Due to financial and logistical limitations, there was no control data for this.
- 4) Follow-up was done for a short while.

CONCLUSION:

When the tumor's T stage increases, the likelihood of achieving pathologically negative margins decreases noticeably, particularly in cases where the tumor has involved pterygoid muscles, soft tissues, and a large amount of skin edema. Also, in cases where definitive surgery was needed or if it was challenging to identify the disease's margin because of wet, oedematous boundaries, IC produces a high response rate. Combination chemotherapy can be quite effective in organ preservation when combined with radiotherapy.

This study highlights, the administration of induction chemotherapy, which is well tolerated and has no apparent

adverse impact on subsequent definitive treatments, including surgery or radiotherapy.

REFERENCES

1. Ma J, Liu Y, Yang X, Zhang CP, Zhang ZY, Zhong LP. Induction chemotherapy in patients with resectable head and neck squamous cell carcinoma: a meta-analysis. *World journal of surgical oncology*. 2013;11(1):1-7.
2. Ferrari D, Ghi MG, Franzese C, Codecà C, Gau M, Fayette J. The slippery role of induction chemotherapy in head and neck cancer: myth and reality. *Frontiers in oncology*. 2020;10:7.
3. de Bree R, Wolf GT, de Keizer B, Nixon IJ, Hartl DM, Forastiere AA, Haigentz Jr M, Rinaldo A, Rodrigo JP, Saba NF, Suárez C. Response assessment after induction chemotherapy for head and neck squamous cell carcinoma: From physical examination to modern imaging techniques and beyond. *Head & neck*. 2017;39(11):2329-49.
4. Kukreja D, Akhtar N, veravolu Resu A, Mahajan D, NIRANJAN P, CHAKRABARTI D, SRIVASTAVA K, GUPTA R, BHATT M. Impact of induction chemotherapy on Resectability in Locally advanced oral cavity Carcinomas. *Medical Research Archives*. 2023;11(7.1).
5. Shen P, Qiao B, Jin N, Wang S. Neoadjuvant immunoradiotherapy in patients with locally advanced oral cavity squamous cell carcinoma: a retrospective study. *Investigational New Drugs*. 2022;40(6):1282-9.
6. Li X, Fang Q, Du W, Zhang X, Dai L, Qiao Y. Induction chemotherapy combined with immunotherapy in locally advanced head and neck squamous cell carcinoma. *BMC cancer*. 2021;21(1):1-9.
7. Hanna GJ, Woo SB, Li YY, Barletta JA, Hammerman PS, Lorch JH. Tumor PD-L1 expression is associated with improved survival and lower recurrence risk in young women with oral cavity squamous cell carcinoma. *International journal of oral and maxillofacial surgery*. 2018;47(5):568-77.
8. Anderson EM, Luu M, Balzer BL, Scher KS, Mita AC, Lu DJ, Shiao SL, Clair JM, Ho AS, Zumsteg ZS. Variations in the association of grade with survival across the head and neck cancer landscape. *Head & Neck*. 2021;43(4):1105-15.
9. León X, López-Pousa A, De Vega M, Orús C, De Juan M, Quer M. Results of an organ preservation protocol with induction chemotherapy and radiotherapy in patients with locally advanced laryngeal carcinoma. *European Archives of Oto-Rhino-Laryngology and Head & Neck*. 2005;262:93-8.