



## THE EFFICACY AND TOXICITY OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED HEAD AND NECK CARCINOMA.

### Oncology

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### ABSTRACT

Loco-regionally advanced head and neck cancer is the common presentation in more than half of the cases and different treatment approaches can be considered. Patients attending the Out Patient Department (OPD) of Radiotherapy from December 2018 to September 2020, meeting specified Inclusion and Exclusion Criteria, willing to participate in the study were included. After completion of treatment, overall complete response is 82%, partial response 11%, stable disease 4% and progressive disease 3%. In case of STAGE III Complete response was 86%, Partial response 13% and other form of response 1% and in case of STAGE IVA and IVB disease complete response 74%, partial response 24%, and other form of response 2% respectively. Acute toxicities like oral mucositis and skin reaction were observed in 33% and 30% cases respectively and late toxicity like xerostomia was observed in 40% of the cases.

### KEYWORDS

Neoadjuvant Chemotherapy, Concurrent Chemoradiation, Locally Advanced Head And Neck Cancers.

### INTRODUCTION

Head and neck cancers (HNCs) are malignant tumours of the upper aerodigestive tract including oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx.<sup>[1][2]</sup> Every year, over 650,000 head and neck cancer (HNC) cases are diagnosed, and they account for more than 330,000 deaths worldwide<sup>[3]</sup>. Over 200,000 cases of head and neck cancers occur each year in India<sup>[4]</sup>. Among them, Oral cancer is the most common head and neck cancer for both sexes<sup>[5]</sup>. In India the incidence among males is 12.48 and females is 5.52 per 1, 00,000 population<sup>[6]</sup>. The possible reasons for the higher incidence of HNCs in India include extensive use of tobacco, pan masala (which include betel quid, areca nuts, and slaked lime), and gutkha. Risk factors associated with HNC include tobacco use, alcohol consumption, and poor oral hygiene, human papillomavirus infection, and precancerous lesion.

Concurrent chemoradiation therapy (CRT) has become the standard of care in the nonsurgical management of most locally advanced head and neck cancer. Neo-adjuvant chemotherapy followed by concurrent chemoradiation is effective in locally advanced head and neck cancer. Neo-adjuvant chemotherapy for locally advanced HNSCC has also shown high overall responses rate (RR), including complete response (CR)<sup>[7]</sup>. Neo-adjuvant chemotherapy (NACT) can help reducing the initial bulk of disease, reducing the rate of distant metastasis, improving Overall survival, resulting in better organ preservation and thereby improving symptoms and quality of life.<sup>[8][9]</sup>

### MATERIALS AND METHODS

All biopsy proven cases of locally advanced head and neck cancer attending the Out Patient Department (OPD) of Radiotherapy, meeting specified Inclusion and Exclusion Criteria who are willing to participate in the study.

#### (I) Timeline :

The accrual period was from December 2018 to September 2020 and the minimum follow-up was for 9 months.

#### (II) definition Of Population:

All biopsy proven cases of locally advanced squamous cell carcinoma of head and neck attending the Department of Radiotherapy, OPD.

#### (III) Inclusion Criteria :

- Adult patients (Age 50 to 70 years)
- Cytologically/Histologically confirmed patients of squamous cell carcinoma of head and neck; stage IVA&B
- ECOG Performance Status 0 – 2
- Normal baseline complete blood counts, liver function test, renal functions test,

- Signed informed consent to participate in the study.

#### (IV) Exclusion Criteria

- Malignancies originating from oral cavity, nasopharynx, paranasal sinus, salivary gland, thyroid and External auditory canal.
- Malignant neck node enlargement with unknown primary.
- Prior radiation/surgery (excepting neck node biopsy)/chemotherapy.
- Preexisting co-morbid medical conditions.
- Pregnancy or lactation.
- Participation in any other study on head and neck cancer
- No other synchronous or metachronous primary malignancy.
- History of prior radiation therapy or cytotoxic chemotherapy.
- Patient's refusal

#### (V) Sample Size:

90 patients

**(VI) Method Of Data Collection:** By history taking, physical examination, keeping all investigation reports and treatment records.

**(VII) Experiment Design:** Prospective randomized open label single-institutional trial.

#### (VIII) Parameters:

Outcomes were studied clinically and by means of laboratory tests and comparison were done in following parameters

1. Assessment of symptom relief
2. Toxicity – early and late
3. Response rate

#### (IX) Study Tools

- History
- Detailed physical examination
- Otorhinolaryngological Examination findings
- Investigations
  - Complete Blood Counts & Biochemistry
  - Cytological/Histological proof from primary/metastatic site
  - Chest X-Ray
  - USG Whole Abdomen
  - CT scan of head and neck region
  - Indirect/Direct laryngoscopy
  - Fiber optic laryngoscopy (if possible)
- machine Bhabatron 780E Isocentric <sup>60</sup>Co Teletherapy machine
- Assessment of loco-regional response using RECIST v1.1
- Gradation of toxicities using CTCAEv4.0 during treatment and follow up

**(X) Treatment**

Patients treated with Neo-Adjuvant Chemotherapy with (TPF) Inj. Docetaxel 75 mg/m<sup>2</sup> IV infusion over 60 minutes, Inj. Cisplatin 75mg/m<sup>2</sup> IV infusion over 60 minutes on day 1 and Inj. 5 FU 750 mg/ m<sup>2</sup>/day continuous IV infusion starting from day 1 to day 5, administered for three cycles every 21 days.

This was followed by Concomitant chemoradiation with 3 weekly Inj. Cisplatin 100mg/m<sup>2</sup> IV infusion<sup>(10)</sup> with necessary premedications and adequate hydration alongwith External Beam Radiation Therapy by Bhabatron 780 E CO 60 Telecobalt machine upto a total dose of 70Gy using standard fractionation. Concomitant chemoradiation was started 3 weeks after last neoadjuvant chemotherapy cycle. Response was assessed using the Response assessment Criteria In Solid Tumors(RECIST) version 1.1<sup>(11)</sup> Acute and Late Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0<sup>(11)</sup> During treatment patients were reviewed weekly. After treatment completion, patients were reviewed monthly for eight months.

**RESULT**

Haematological and renal toxicity are the main adverse events of induction TPF. The baseline characteristics, toxicities, namely, neutropenia, thrombocytopenia, anaemia, mucositis, dermatitis, xerostomia, hoarseness, dysphagia, emesis and responses were reported. Moreover, we performed stage-wise outcome analysis. In case of STAGE III complete response was 86%, partial response 13% and other form of response 1% (Stable disease and Progressive disease) and in case of STAGE IVA and IVB disease complete response 74%, partial response 24%,and other form of response 2% (Stable disease and Progressive disease)

**Distribution Of Age Of Patients**

Age of the patients included in the study within 50 to 70 years.

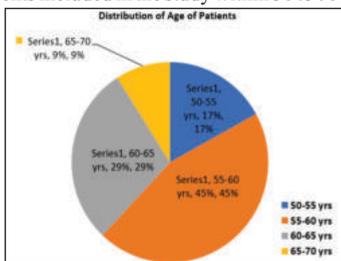


Fig 1: Distribution Of Age Of Patients

**Distribution Of Stage Of Disease**

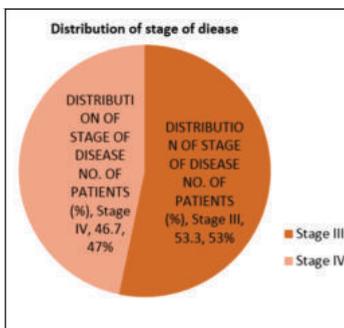


Fig 2: Distribution Of Stage Of Disease

**Incidence of Neutropenia**

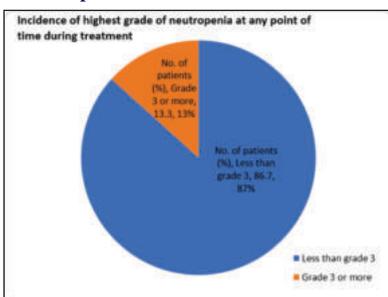


Fig 3: Incidence Of Neutropenia

**Incidence of Thrombocytopenia**

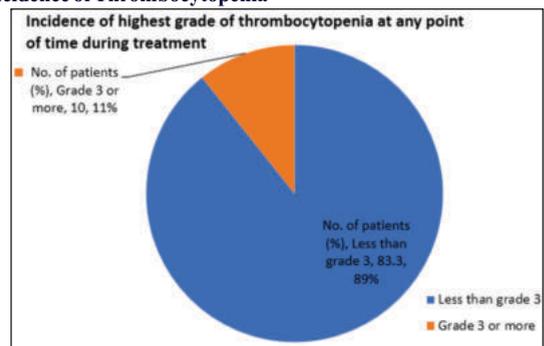


Fig 4: Incidence Of Thrombocytopenia

**Incidence of Anaemia**

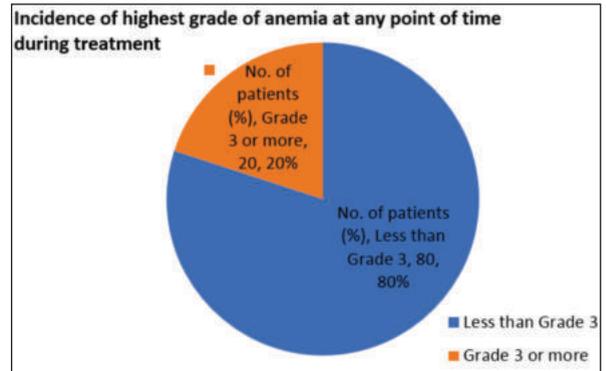


Fig 5: Incidence of Anaemia

**Incidence of Oral Mucositis**

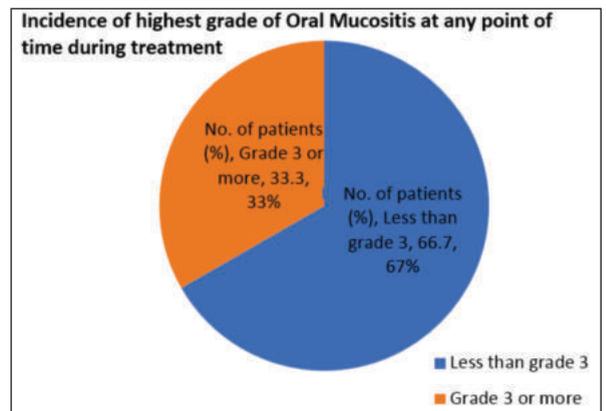


Fig 6: Incidence of Oral Mucositis

**Incidence of Skin Reaction**

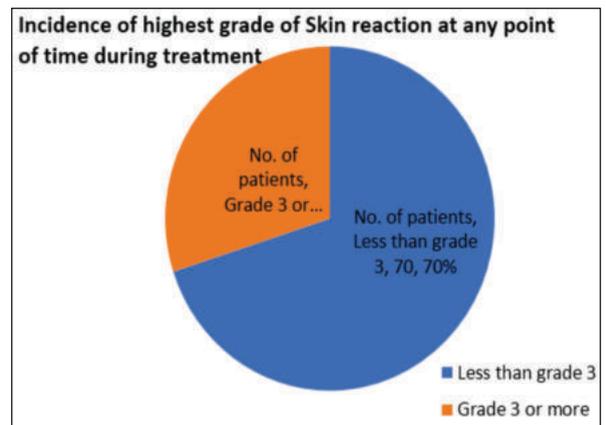
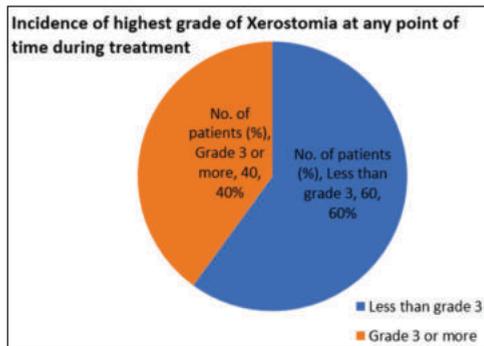


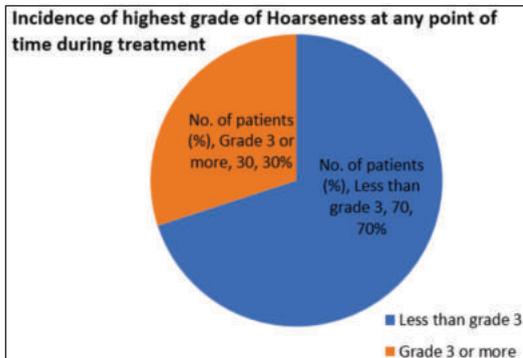
Fig 7: Incidence Of Skin Reaction

**Incidence of Xerostomia**



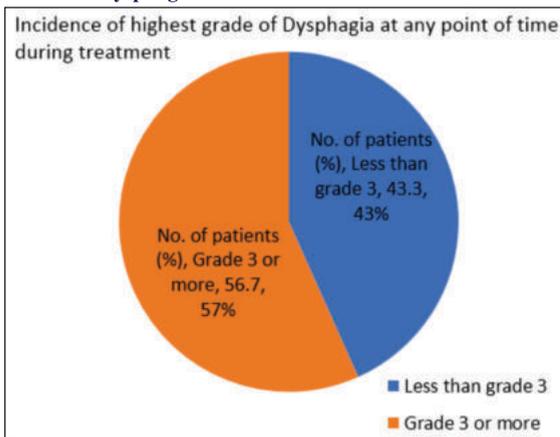
**Fig 8:** Incidence of Xerostomia

**Incidence of Hoarseness of Voice**



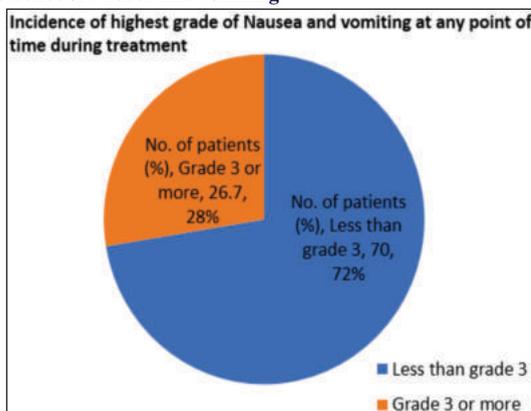
**Fig 9:** Incidence of Hoarseness of Voice

**Incidence of Dysphagia**



**Fig 10:** Incidence of Dysphagia

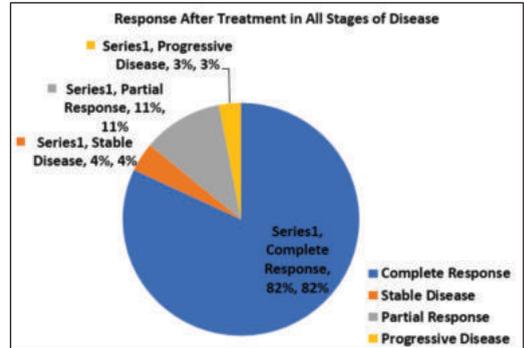
**Incidence of Nausea and Vomiting**



**Fig 11:** Incidence of Nausea and Vomiting

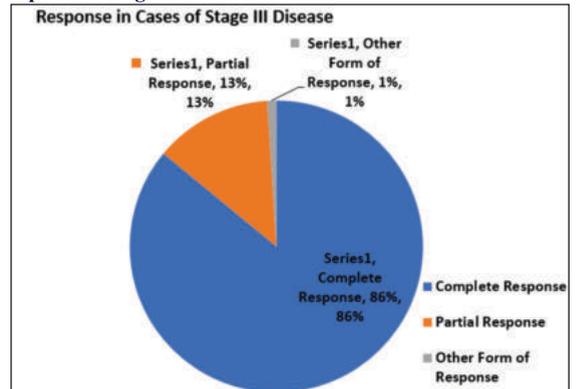
**Response after Treatment-All Stages of Disease**

After completion of treatment, overall complete response is 82%, partial response 11%, stable disease 4% and progressive disease 3%.



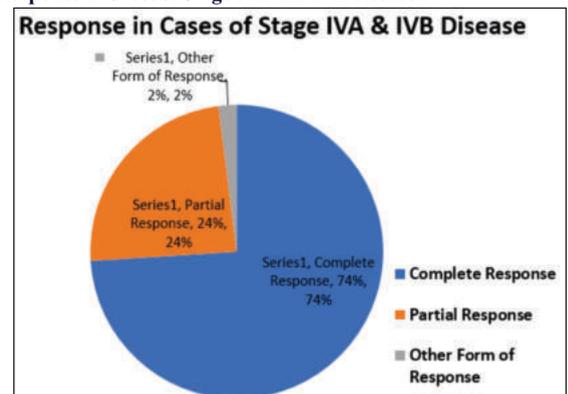
**Fig 12:** Response After Treatment - All Stages Of Disease

**Response to Stage III disease**



**Fig 13:** Response to Stage III disease

**Response in Cases of Stage IVA and IVB disease**



**Fig 14:** Response in Cases of Stage IVA and IVB disease

**DISCUSSION**

Head and neck carcinoma is one of the commonest malignancy in India. In our present study we tried to assess the toxicity and locoregional control in case of induction chemotherapy followed by chemoradiation therapy in Stage III and IVA , IVB Squamous cell carcinoma of head and neck.

TPF is less toxic and more effective than the historical therapy PF (cisplatin 100 mg/m<sup>2</sup> and fluorouracil 1,000 mg/m<sup>2</sup>/day for five consecutive days). However, in some studies treatment-related mortality has been reported to be as high as 6%. In addition, quality of life was improved with TPF vs. PF in the TAX 323 trial<sup>[12]</sup> and the cost-utility analysis of both the TAX 323 and 324 studies showed benefit in quality-adjusted life-years in favor of TPF<sup>[13]</sup>. On assessing individual toxicity, it was seen that incidence of Grade 3 or more neutropenia was present in 13% of patients. In the study conducted by R. Hitt et al showed incidence of febrile neutropenia was more in TPF group.<sup>[14]</sup> Grade 3 or more thrombocytopenia and anemia was present in 11% and

20% of the patients respectively. Grade 3 or more oral mucositis, skin reaction and xerostomia was found in 33%, 30% and 40% of the patients. Grade 3 or more nausea and vomiting was found in 28% of patients. A similar study conducted by Nikam B M et al on Indian patients showed similarly higher rate of oral mucositis, emesis and bone marrow toxicity in patients treated with neoadjuvant chemotherapy<sup>[15]</sup>.

At last follow-up .Complete Response, Partial Response, Stable Disease and Progressive Disease was observed in 82%, 11%, 4% and 3% of cases respectively. This result closely resembles the result obtained in similar study on Indian population conducted by Jain P. et al. where taxane combined to cisplatin and 5 FU have been proved to be effective in locoregional control in locally very advanced head neck carcinoma.<sup>[16]</sup>

The best compliance to concomitant treatment reported in the Italian trial<sup>[17]</sup> vs. the Spanish trial<sup>[18]</sup> might be attributable to the schedule and doses of TPF and to the concomitant regimen adopted (2 cycles of concurrent cisplatin plus 5FU). It should be noted that in the GSTTC trial the cisplatin total dose in the sequential arm was 400 mg/m<sup>2</sup> vs. >500 mg/m<sup>2</sup> in the Spanish trial. Because of toxicities, intensive care and nutritional support are required during treatment to avoid interruptions and discontinuations.

## CONCLUSION

In the present study it was observed that in locally advanced squamous cell carcinoma of head and neck , neo-adjuvant chemotherapy with Docetaxel, Cisplatin and 5 Fluorouracil followed by conventional chemoradiotherapy showed good locoregional response. Use of neoadjuvant chemotherapy was associated with significantly increased haematological, gastrointestinal and mucosal toxicity, which was manageable. Neo-adjuvant chemotherapy (NACT) can help reducing the initial bulk of disease, reducing the rate of distant metastasis, improving Overall survival ,resulting in better organ preservation and thereby improving symptoms and quality of life. Thus, neo-adjuvant chemotherapy followed by concurrent chemoradiation is a good option in locally advanced head and neck cancer, which is to be administered weighing the pros and cons of the therapy on an individualised basis. We may have a satisfactory result of good control of locally advanced squamous cell carcinoma of head and neck with NACT followed by concurrent chemo-radiation in comparison to concurrent chemo-radiation alone. But this may also increase toxicity. So this study is aimed to find whether more satisfactory tumour control can be achieved with tolerable toxicity.

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