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A COMPARATIVE EVALUATION OF ACUTE TOXICITY AND LOCOREGIONAL CONTROL BY CONCOMITANT CHEMORADIATION THERAPY WITH OR WITHOUT NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

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ABSTRACT

Introduction: Head and neck cancer is the commonest malignancy in India. Most of the cases present at a locally advanced stage. Concurrent chemoradiotherapy with or without neo-adjuvant chemotherapy are both viable treatment options in locally advanced cases. **Materials & Methods:** 30 biopsy proven cases of locally advanced head and neck cancer attending the Out Patient Department of Radiotherapy from August 2016 to May 2018, meeting specified Inclusion and Exclusion Criteria, willing to participate in the study were included. Patients were treated with neo-adjuvant chemotherapy followed by concurrent chemoradiation and followed for a minimum of 9 months. The toxicity and loco-regional control data were assessed. **Results:** At last follow-up Complete Response, Partial Response, Stable Disease and Progressive Disease was observed in 76.66%, 3.33%, 10% and 3.33% of cases respectively. Haematological toxicities like neutropenia (13.3%), thrombocytopenia (10%) and anaemia (20%) were seen. Acute toxicities like oral mucositis and skin reaction were observed in 33.3% and 30% cases respectively and late toxicity like xerostomia was observed in 40% of the cases. Hoarseness and dysphagia were observed in 30% and 56.66% respectively. **Conclusions:** Neo-adjuvant chemotherapy followed by concurrent chemoradiation gives good locoregional response, but increasing toxicity which is manageable. Thus, neo-adjuvant chemotherapy followed by concurrent chemoradiation is a good option in locally advanced head and neck cancer.

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INTRODUCTION

Head and neck cancer is the fifth most common malignancy among adults (Jemal, 2011). Overall 57.5% of global head and neck cancer occur in Asia especially in India (http://www.veedaoncology.com/PDF-Document/Head Neck %20Cancer%20In%20India.pdf). Over 200,000 cases of head and neck cancers occur each year in India (HEAD AND NECK CANCER, 2014). Oral cancer is the most common head and neck cancer for both sexes (Jemal, 2007). In India the incidence among males is 12.48 and females is 5.52 per 1, 00,000 population (Debrowsky, 2000).

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The mortality rates due to this cancer among males and females are 3.48 and 1.34 per 1, 00,000 population respectively (Debrowsky, 2000). Concurrent chemoradiation therapy (CRT) has become the standard of care in the nonsurgical management of most locally advanced head and neck cancer. Most randomized clinical trials show the superiority of combined RT and chemotherapy to RT alone for the treatment of locally advanced, non-metastatic HNC. A meta-analysis of individual patient data from >17,346 participants in 93 trials conducted from 1965 to 2000 [MACH-NC]) demonstrated that the use of radiotherapy and concurrent chemotherapy (CRT) resulted in a 19% reduction in the risk of death and an overall 6.5% improvement in 5-year survival compared to treatment with RT alone (Wolf, 1991). Neo-adjuvant chemotherapy (NACT) 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) (Paccagnella, 1994). 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 (Wolf, 1999 and Pointreau, 2009).

MATERIALS AND METHODS

Patients with locally advanced head and neck cancer attending the Radiotherapy Out Patient Department (OPD), SSKM and Institute of Postgraduate Medical Education and Research, Kolkata. from August 2016 to May 2018 , meeting specified Inclusion and Exclusion Criteria, willing to participate in the study were randomized into two groups or arms. Patients were treated with either neo-adjuvant chemotherapy followed by concomitant chemoradiation or concomitant chemoradiation alone and followed for a minimum of 9 months. Patients in Arm A were treated with Neo-Adjuvant Chemotherapy with Inj. Docetaxel 75 mg/m^2 IV infusion over 60 minutes, Inj. Cisplatin 75mg/ m^2 IV infusion over 60 minutes on day 1 and Inj. 5 FU 750 mg/ m^2/day continuous IV infusion starting from day 1 to day 5, administered for three cycles every 21 days.

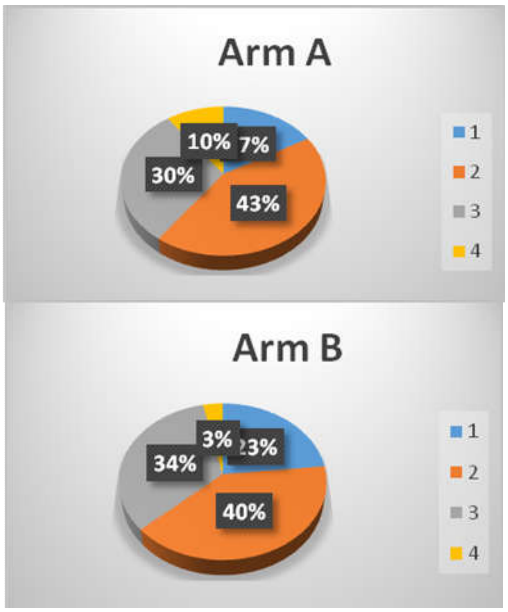
This was followed by Concomitant chemoradiation with 3 weekly Inj. Cisplatin 100mg/m^2 IV infusion (Vermorken, 2007), with necessary premedications and adequate hydration alongwith External Beam Radiation Therapy by Bhabatron 780 E CO 60 Telecobalt machine upto a total dose of 70Gy using standard fractionation. Concomitant chemoradiation was started 3 weeks after last neoadjuvant chemotherapy cycle.
Patients in Arm B were treated with concomitant chemoradiation with 3 weekly Inj. Cisplatin 100mg/m^2 IV infusion 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. Response was assessed using the Response assessment Criteria In Solid Tumors (RECIST) version 1.1. Acute and Late Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. During treatment patients were reviewed weekly. After treatment completion, patients were reviewed monthly for eight months.

RESULTS

This single institution study was conducted from August 2016 to May 2018. Total 82 patients were assessed for eligibility. Ultimately, 60 patients were included in the study and randomised into Arm A and Arm B. 1 patient in each arm expired during treatment and 1 patient in the study arm stopped treatment due to toxicity and subsequently was lost to follow up. Among the patients included In the study only 1 patient in the study arm was female. The age distribution and distribution of stage of disease were compared between the two arms. Then toxicities, namely, neutropenia, thrombocytopenia, anemia, mucositis, dermatitis, xerostomia, hoarseness, dysphagia, nephropathy, emesis were compared between the two arms. Finally, we compared outcome in the form of Complete response, Partial response, Stable disease and Progressive disease between two arms. Further, we performed stage-wise outcome comparison.

1. DISTRIBUTION OF AGE OF PATIENTS			
AGE GROUP	NO. OF PATIENTS (%)		
	ARM A	ARM B	P value
50-55 yrs	5 (16.7)	7 (23.3)	0.699
56- 60 yrs	13 (43.3)	12 (40)	
61-65 yrs	9 (30)	10 (33.3)	
66 – 70 yrs	3 (10)	1 (3.3)	
2. DISTRIBUTION OF STAGE OF DISEASE			
STAGE OF DISEASE	NO. OF PATIENTS (%)		
	ARM A	ARM B	P value
Stage III	16 (53.3)	22 (73.3)	0.108
Stage IV	14 (46.7)	8 (26.6)	

Comparison between distribution of age of patients between two arms



Comparison between distribution of stage of disease between two arms

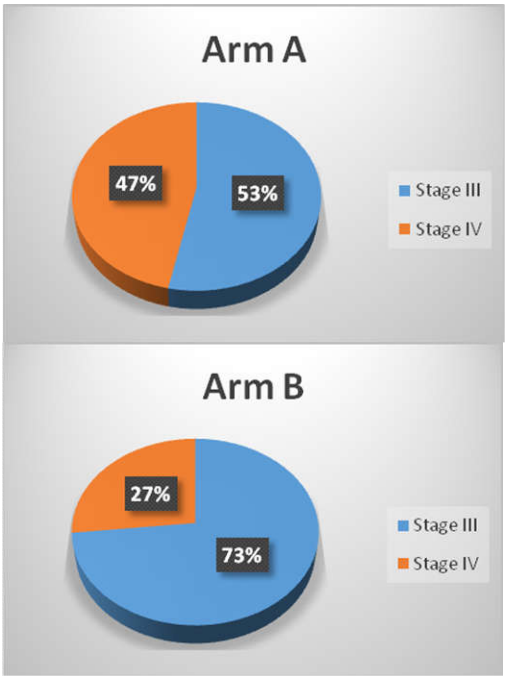
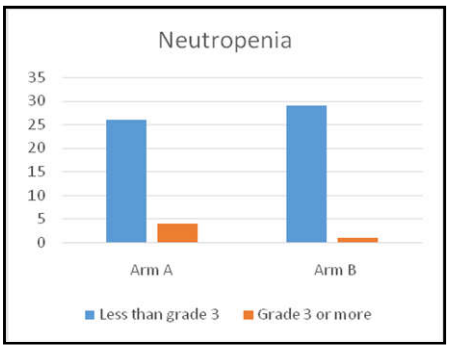
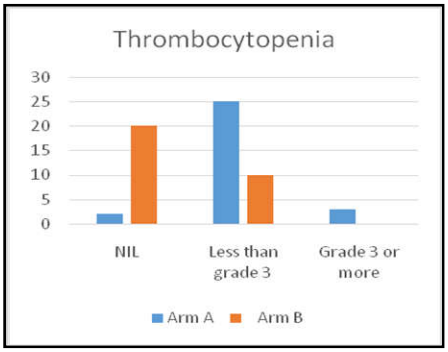


Table 2. Hematological toxicities

Incidence of highest grade of neutropenia at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	26 (86.7)	29	0.16
Grade 3 or more	4 (13.3)	1	
Incidence of highest grade of thrombocytopenia at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	25 (83.3)	10	0.00001
Grade 3 or more	3 (10)	0	
Incidence of highest grade of anemia at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than Grade 3	24 (80)	29	0.044
Grade 3 or more	6 (20)	1	





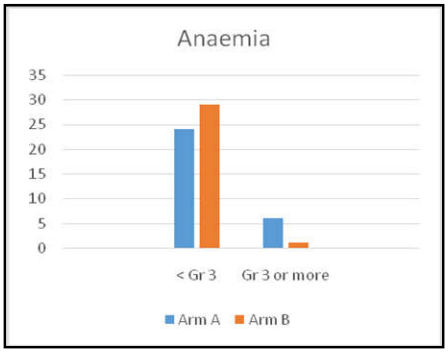
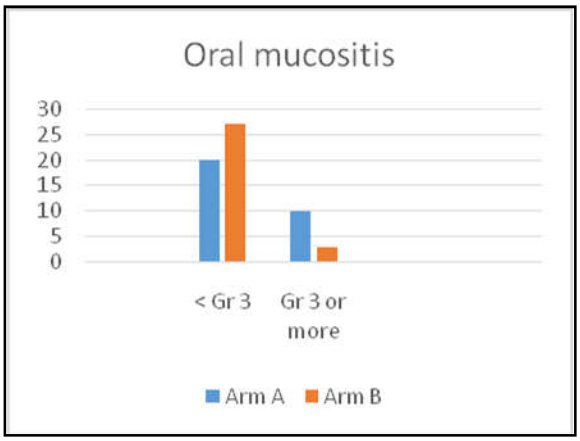
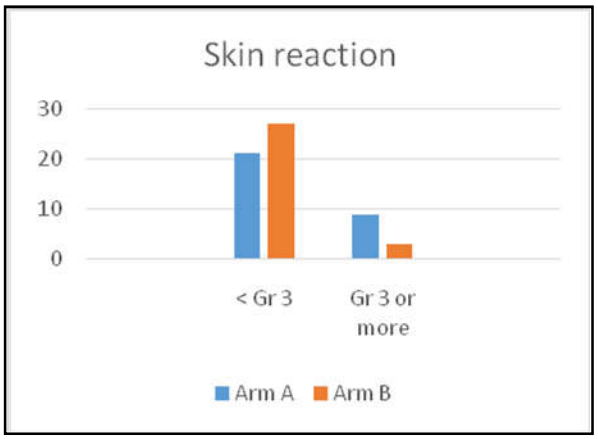
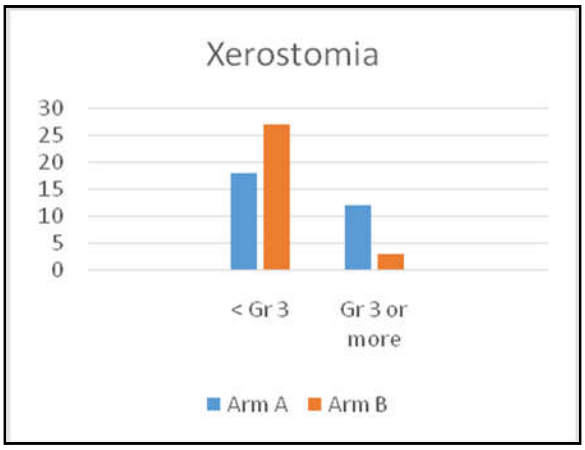


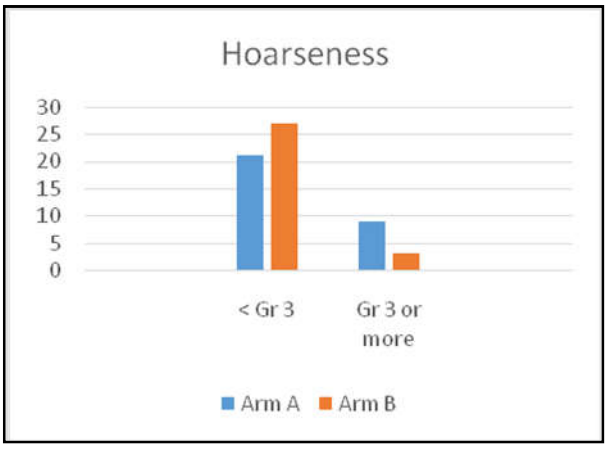
Table 3. Other Toxicities

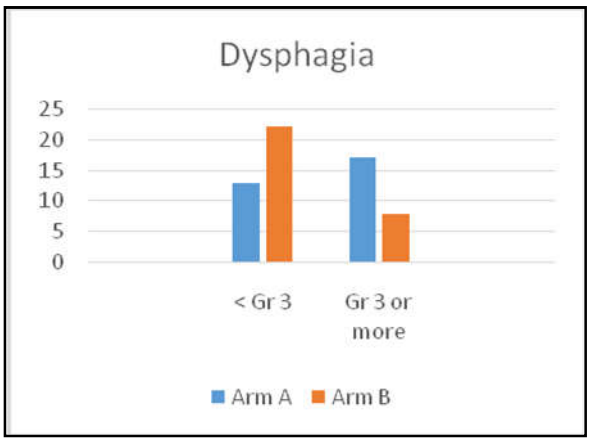
Incidence of highest grade of Oral Mucositis at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	20 (66.7)	27 (90)	0.028
Grade 3 or more	10 (33.3)	3 (10)	
Incidence of highest grade of Skin reaction at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	21 (70)	27 (90)	0.052
Grade 3 or more	9 (30)	3 (10)	
Incidence of highest grade of Xerostomia at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	18 (60)	27 (90)	0.0073
Grade 3 or more	12 (40)	3 (10)	
Incidence of highest grade of Hoarseness at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	21 (70)	27 (90)	0.052
Grade 3 or more	9 (30)	3 (10)	
Incidence of highest grade of Dysphagia at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	13 (43.3)	22 (73.3)	0.018
Grade 3 or more	17 (56.7)	8 (26.6)	
Incidence of highest grade of Nausea and vomiting at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	21 (70)	27 (90)	0.03
Grade 3 or more	8 (26.7)	0 (0)	
Incidence of highest grade of weight loss at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	21 (70)	23 (76.6)	0.34
Grade 3 or more	9 (30)	7 (23.3)	
Incidence of highest grade of Renal dysfunction at any point of time during treatment			
Grade	No. of patients (%)		
	ARM A	ARM B	P value
Less than grade 3	21 (70)	10 (33.3)	0.008
Grade 3 or more	1 (3.3)	0 (0)	

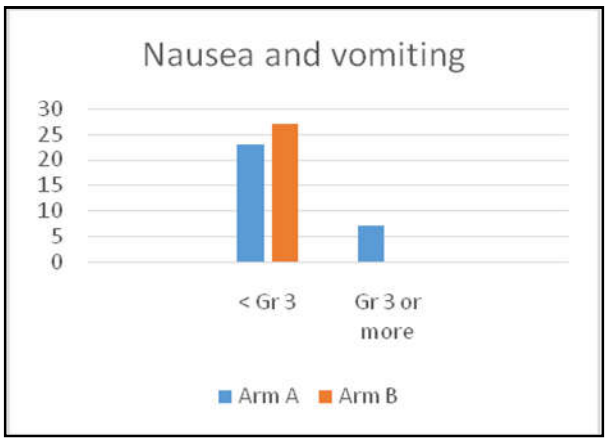

Oral mucositis
30
25
20
15
10
5
0
< Gr 3
Gr 3 or more
Arm A
Arm B

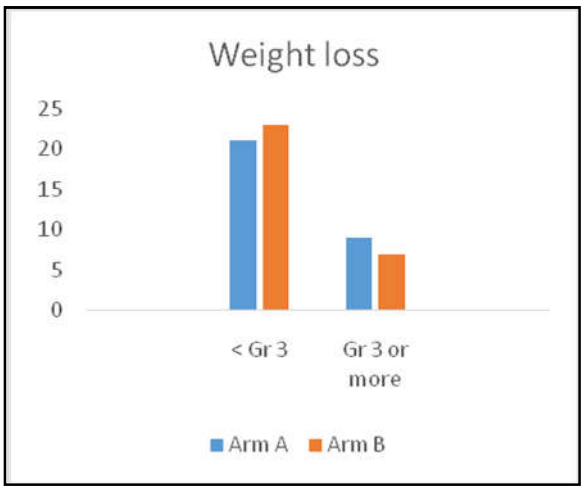

Skin reaction
30
20
10
0
< Gr 3
Gr 3 or more
Arm A
Arm B

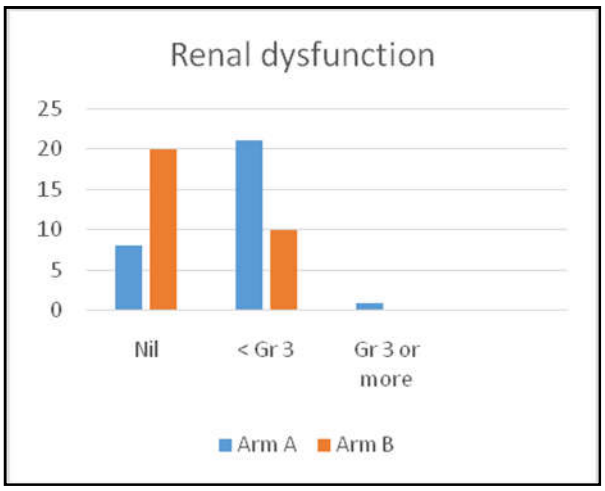

Xerostomia
30
25
20
15
10
5
0
< Gr 3
Gr 3 or more
Arm A
Arm B


Hoarseness
30
25
20
15
10
5
0
< Gr 3
Gr 3 or more
Arm A
Arm B


Dysphagia
25
20
15
10
5
0
< Gr 3
Gr 3 or more
Arm A
Arm B

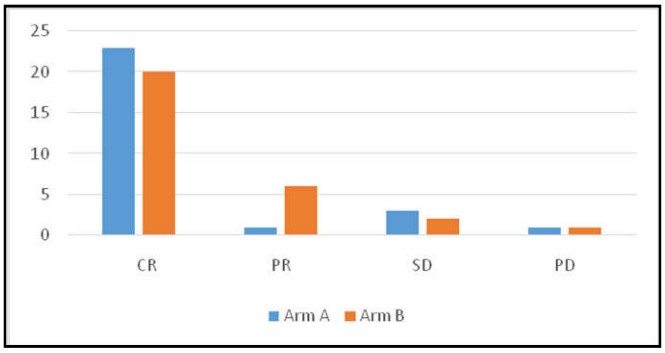

Nausea and vomiting
30
25
20
15
10
5
0
< Gr 3
Gr 3 or more
Arm A
Arm B

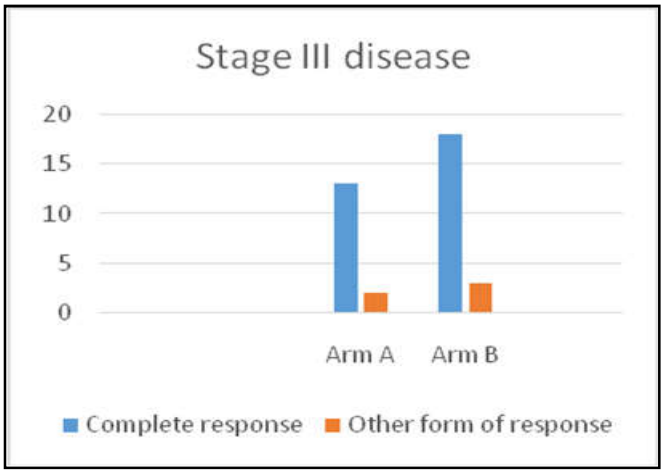

Weight loss
25
20
15
10
5
0
< Gr 3
Gr 3 or more
Arm A
Arm B

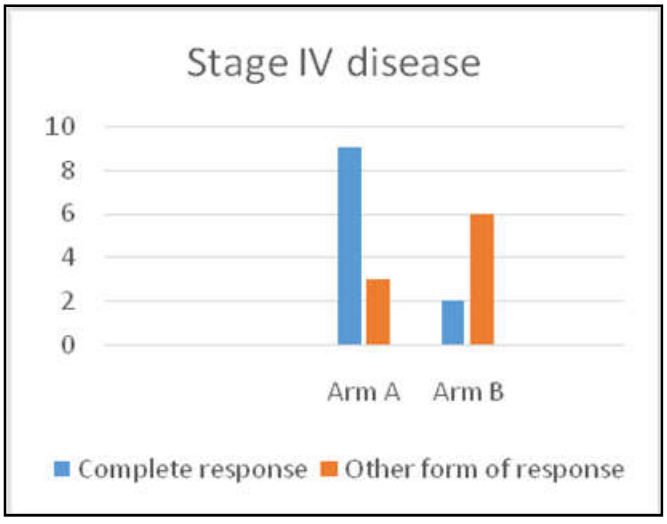

Renal dysfunction
25
20
15
10
5
0
Nil
< Gr 3
Gr 3 or more
Arm A
Arm B

Response to Treatment

Response to Treatment			
Type of response		No. of patients (%)	
	ARM A	ARM B	P value
Complete Response (CR)	23 (76.6)	20 (66.6)	0.265
Partial Response (PR)	1 (3.3)	6 (20)	
Stable Disease (SD)	3 (10)	2 (6.6)	
Progressive isease (PD)	1 (3.3)	1 (3.3)	
STAGE-WISE RESPONSE			
Response in cases of Stage III disease			
Response		No. of patients (%)	
	ARM A	ARM B	P value
Complete Response	13 (81.2)	18 (81.8)	0.93
Other form of response	2 (12.5)	3 (13.6)	
Response in cases of stage IVA and IVB disease			
Response		No. of patients (%)	
	ARM A	ARM B	P value
Complete Response	9 (64.3)	2 (25)	0.027
Other form of response	3 (21.4)	6 (75)	







DISCUSSION

Sqaumous cell carcinoma of head and neck is one of the commonest malignancy in India. In our present study we tried to compare the toxicity and locoregional control between induction chemotherapy followed by chemoradiation therapy and chemoradiation alone in Stage III and IVA, IVB Sqaumous cell carcinoma of head and neck. The study included a population predominantly male and belonging to the elderly group. One patient in each arm died during the course of treatment. As age distribution is concerned there was no significant difference (p value 0.699). There was also not statistically significant difference in stage distribution between these arms (p value 0.108) making these two arms comparable. On comparing individual toxicity, it was seen that incidence of Grade 3 or more neutropenia is significantly more in the neo-adjuvant group (p value 0.16). In the study conducted by R. Hitt *et al* showed incidence of febrile neutropenia was more in TPF group. The incidence of grade 3 or more anemia was significantly more in the neo-adjuvant chemotherapy group (p value 0.044). The incidence of grade 3 or 4 oral mucositis was more in the TPF group (p value 0.028). In both the group all incidence of grade 3 or 4 xerostomia was noted from 5th week of radiotherapy onwards. However, the incidence is significantly more in TPF group (p value 0.0073). The incidence of grade 3 and 4 dysphagia occurred in both the arms after the 4th week of radiotherapy. In TPF arm it was noted in 17 patients (56.66%), whereas, in the CTRT alone group in 8 patients (26.66%) (p value 0.018). 22 patients (73.33%) in the TPF group had some grade of renal dysfunction during treatment. One patient in this group developed grade 3 nephropathy during the third cycle of chemotherapy. On the control arm, 10 patient (33.33%) had some grade of nephropathy during CTRT (p value 0.008). However, all nephropathies occurred in control group were grade 1 and 2.This observation was in accoradance with the study conducted by R. Hitt *et al* that showed grade 3–4 nephropathy was higher at TPF-CCRT (8.4%), than CCRT alone arms (5.1%).On comparing incidence of emesis , In the TPF group grade 3 emesis happened in 8 patients(26.66%) and all cases happened during neoadjuvant chemotherapy and on day 2 onwards. In the control group only one patient (3.33%) (p value 0.030) developed grade 3 vomiting after the 5th week of concurrent chemotherapy. 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 (Nikam, 2014). Some sort of skin reaction occurred in all patients belonging to either arms. Grade 3 or more neutropenia seen in 9 patients (30%) of the study arm and 3 (10%) patients of the control arm. The difference is, however, statistically not significant (p value 0.052). Similarly, some grade of hoarseness , commonly after the 4th week of radiotherapy was universal to both the arms. Grade 3 or more hoarseness seen in 9 patients (30%) in study arm, as opposed to 3 patients (10%) in control arm but the difference in not statistically significant. On analysing the pattern of response, it was noted that among the TPF group the number of patients having complete response was 23 (76.66%), partial response 1 (3.33%), stable disease 3 (10%) and progressive disease 1 (3.33%). On the other hand, in the chemoradiation alone arm complete response was seen in 20 patients (66.66%), partial response in 6 patients (20%), stable disease in 2 patients (6.66%) and progressive disease in 1 patient (3.33%). But this difference is statistically not significant (p value 0.265).

As stage wise response assessment was carried out it was seen that for stage III disease, 13 patients (86.7%) in the study arm had complete response and 2 patients (13.7%) had poorer response. In the control arm 18 patients of stage III (85.7%) had complete response and 3 patients (14.3%) had poorer response. Again the difference did not attend statistical significance (p value 0.93). But in the case of stage IV disease, that is the group with locally very advanced disease the result is something different. In this stage group 9 patients (75%) in the neoadjuvant chemotherapy arm had complete response and 3 patients 25%) did not get complete response. Whereas, in the chemoradiortherapy arm 2 patients (25%) had complete response and all other 6 patients (75%) had partial response, stable disease or progressive disease. This difference is statistically significant with a p value of 0.027. This results 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.[12]Similar result was obtained in the study conducted by Malik G. *et al* on North Indian patient showing NACT followed by concomitant chemoradiation is a better treatment protocol as compared to accelerated RT or conventional radiotherapy (Malik, 2017).

Conclusion

In our study it was observed that in locally advance squamous cell carcinoma of head and neck, addition of neoadjuvant chemotherapy with Docetaxel, Cisplatin and 5 Fluorauracil to conventional chemoradiotherapy significantly improved locoregional response in stage IVA and IVB disease, but not in case of stage III cancer. Use of neoadjuvant chemotherapy was associated with significantly increased haematological, gastrointestinal, mucosal and renal toxicity, which being manageable, were not associated with increased mortality.

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