



Assessment of the toxicity associated with the two regimens administered post-EBRT in locally advanced head and neck cancer

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Abstract: -

Background: The fractionation scheme in HNC patients is a complicated problem, as many factors are involved. In this case, the main concern would be minimizing overall treatment time without increasing acute reactions. **Aim:** To assess the toxicity associated with the two regimens administered post-EBRT in locally advanced head and neck cancer.

Methods: Quasi-experimental study was carried out in the Department of Oncology, Khwaja Yunus Ali Medical College and Hospital (KYAMCH) during the period October 2017 to March 2018 and the study done among a total of 60 patients with locally advanced head and neck cancer were included in this study and distributed 30 in A and 30 in arm B. **Result:** majority of the study subjects were from 50-59 years age group (Arm A 36.7%, Arm B 36.7%). The mean age of patients in Arm A was 52.97±9.07 years and in Arm B was 50.80±9.96 years. Moreover, in Arm A, 40% were from the lower class, 53.3% were from the middle class and 6.70% were from the upper class. The most common toxicity was Grade 2, and 3 neutropenia (26.7% and 13.3% respectively). Toxicities included Grade 2, 3 mucositis (26.7%, 6.7%), Grade 2 thrombocytopenia (6.7%), Grade 2 diarrhea (20.0%), Grade 2 nausea (33.3%) and Grade 2 vomiting (16.7%). The treatment response was not significant.

Conclusion: Various toxicities occurred in this study, the most common were mucositis, neutropenia, nausea, diarrhea, and alopecia but all those were manageable.

Keywords: Assessment, EBRT, mucositis, toxicities.

LIST OF ABBREVIATION

AJCC: American Joint Committee on Cancer	HNC: Head and Neck cancer
CBC: Complete Blood Count	IV: Intravenous
CCRT: Concurrent Chemo Radiotherapy	JAMA: Journal of the American Medical Association
CR: Complete Response	KYAMCH: Khwaja Yunus Ali Medical College and Hospital
CT: Computed Tomography	LFT: Liver Function Test
CTCAE: Common Terminology Criteria for Advanced Events	LFP: Leucovorin, 5-FU, Cisplatin
DCF: Docetaxel, Cisplatin, 5-FU	LRC: Locoregional Control
DFS: Disease Free Survival	MRI: Magnetic Resonance Imaging
ECOG: Eastern Cooperative Oncology Group	NCI: National Cancer Institute
EBRT: External beam radiotherapy	NADPH: Nicotinamide Adenine Dinucleotide Phosphate
5-FU: 5-Fluorouracil	NICRH: National Institute of Cancer research and Hospital
Gy: Gray	RFT: Renal Function Test
HPV 16: Human Papilloma Virus 16	TNM: Tumour Node Metastasis
H & N: Head and Neck	TPN: Total Parenteral Nutrition
HNC: Head and Neck cancer	USG: Ultrasonography

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Introduction:

The term “head and neck cancer” (HNC) refers to cancers of the upper aerodigestive tract, including the lips, oral cavity, oropharynx, sinonasal cavities, larynx, hypopharynx, and salivary glands^[1]. Head and neck cancers constitute approximately 10%^[2].

Cancers of the head and neck are further categorized by the area of the head or neck in which they begin. Among these areas, approximately one-fourth of all head and neck cancers originate in the larynx^[3]. The National Institute of Cancer Research and Hospital published the Cancer Registry Report- 2014 which provides information that a total of 18,856 newly diagnosed cancer patients attended the outpatient department in NICRH. Among them, lip, oral cavity, and pharyngeal cancer patients were 1,238 (11.1% of total patients). Total cheek/buccal mucosa malignancy patients were 245 (2.2%) which was the 9th top malignancy. In males, carcinoma of tongue patients were 148 (2.2% of total male patients) and carcinoma larynx patients were 108 (1.8%). In females, cheek/buccal mucosa patients were 140 (2.4 of the total female patients), which was 6th to malignancy.

Most head and neck malignant neoplasms arise from the surface epithelium and are SCC or one of its variants, including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma. Lymphomas and a wide variety of other malignant and benign neoplasms make up the remaining cases^[4]. Unfortunately, in our country, most of the patients with head and neck cancers attend the radiation oncology department in advanced stages, which may be due to ignorance, poverty, lack of a proper referral system, illiteracy, and some traditional beliefs. The head and neck region is the sole location of several functions, so-called special senses (vision, hearing, balance, taste, speech, and smell). Loss of function either by disease or by the treatment produces significant morbidity. Pronounced functional deficit and deformity associated with the disease heighten their relative importance.

Advances in surgical techniques continue to improve operative outcomes, the overall morbidity associated with resection of advanced head and neck cancer remains substantial. Non-operative treatment strategies involving radiation and chemotherapy continue to evolve^[5]. The basic principle of radiotherapy is to cure patients with minimal functional and structural impairment. Small primary lesions (T1 and T2) with negative cervical nodes are generally treated with a single modality^[6]. Small lesion nodal involvement requires surgery and irradiation for control of neck disease. Large primary lesions (T3 and T4) and/or extensions to the cervical node usually need both surgery and radiotherapy^[7]. Sometimes surgery is not possible due to certain anatomical sites and some associated medical co-morbidities in that case choice of treatment is radiotherapy and chemotherapy. But nowadays considering the goal of treatment, radiotherapy has some advantages over surgery which includes the following-(a) the complication of major surgery can be avoided. Surgical mortality of 1-2% seems high to the patients compared with no such mortality in radiation therapy, (b) does not require removal of tissue. In surgery, even the excision of small lesions may produce functional and cosmetic defects and (c) prophylactic irradiation of the lymph nodes carries a little morbidity whereas surgical procedures can cause higher morbidity with elective neck dissection.

Since radiation therapy or concurrent chemoradiotherapy has the advantage of preserving anatomical integrity, sequential chemotherapy followed by radiotherapy, which has been studied for several decades, remains quite popular in many regions. Induction chemotherapy was developed clinically based on the following rationale^[8].

The biological basis of combined modality therapy such as the Prevention of the emergence of resistant clones by the interaction of chemotherapy and radiotherapy is that cell cycle alteration induced by chemotherapy leaves cells in a state in which they are more sensitive to radiation.

Decreased toxicity due to initial tumor shrinkage by giving chemotherapy may result in the adequacy of smaller irradiation fields, which in turn, results in decreased toxicity from radiation therapy. This may not be the only advantage of initial chemotherapy. Reduced tumor size may enhance blood flow, improve oxygenation, and increase radiosensitivity. Treatment decisions are mainly based on an appraisal of the patient's tumors, but the patients often play an important role. Emphasis is given to host factors. So far, our knowledge goes no substantial work has been carried out previously regarding the effectiveness with the LFP chemotherapy regimen in Bangladesh. The study may give us to assess the toxicity associated with the two regimens administered post-EBRT in locally advanced head and neck cancer.

Methods:

This Quasi-experimental study was conducted in the Department of Oncology, Khwaja Yunus Ali Medical College and Hospital, Enayetpur, Sirajgonj from October 2017 to March 2019. Two groups of 60 patients were studied – Every alternately thirty patients were enrolled in this arm and treated with induction chemotherapy by LFP regimen followed by radiotherapy. Another thirty patients were enrolled in this arm and treated with induction chemotherapy by DCF regimen followed by radiotherapy. In this study induction chemotherapy policy is adopted for both arms as per the following schedule-

In arm A, the LFP regimen (Inj. Leucovorin 30 mg/m² I/V D1-D3, Inj. 5-FU 750 mg/m² I/V continues infusion D1-D5 and Inj. Cisplatin 75 mg/m² I/V D1) at 3 weekly cycles for 3 cycle. In arm B, DCF regimen (Inj. Docetaxel 75 mg/m² I/V D1, Inj. 5-FU 750 mg/m²/d I/V continues infusion D1-D5 and Inj. Cisplatin 75 mg/m² I/V D1) at 3 weekly cycle for 3 cycle.

Hydration is needed for patients subjected to chemotherapy with cisplatin. So proper hydration was done. Pre and post-chemotherapy medication with antiemetics, steroids, and other necessary drugs were given before and after chemotherapy.

Toxicity was assessed before and one week after each cycle of chemotherapy was completed by clinical and relevant routine blood investigations (CBC, serum creatinine, liver function test). Patients with at least a partial response of the primary tumors and neck received definitive radiation.

All data obtained during the study period from the patient remain confidential. The ethical committee granted permission. After cleaning and editing, all the relevant data were compiled on a master chart. SPSS obtained statistical analysis of the results for Windows (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, IBM Corp.). Categorical data were expressed as

numbers and percentages and were compared via the Chi-squared test and Fischer’s exact tests. Continuous data were expressed as mean ± SD and were compared by the student “t” test. Two-tailed p-value<0.05 was considered significant.

Selection of Patients:

A. Inclusion Criteria:

- 1. Clinically diagnosed and histo-pathologically proved locally advanced head and neck carcinoma.
- 2. Stage III or IVA, B disease without distant metastasis.
- 3. Age: 18 to 70 years.
- 4. Any sex.
- 5. Patients having ECOG performance status score up to scale 2.
- 6. Patients willing to be included in this study.

B. Exclusion criteria:

- 1. Age below 18 years and above 70 years.
- 2. Poor performance status (ECOG score >2)
- 3. Patients with distant metastasis.
- 4. Patients with synchronous primaries.
- 5. Patients with a history of prior chemotherapy or radiotherapy for head and neck region.
- 6. Initial surgery (excluding diagnostic biopsy) of the primary site.
- 7. Pregnant or lactating woman.
- 8. Patient with uncontrolled infection.
- 9. Those who are not willing to be included in the study.

Result:

Sociodemographic characteristics of the respondents (n=60)

Figure 1: Age distribution of the respondents (n=60):

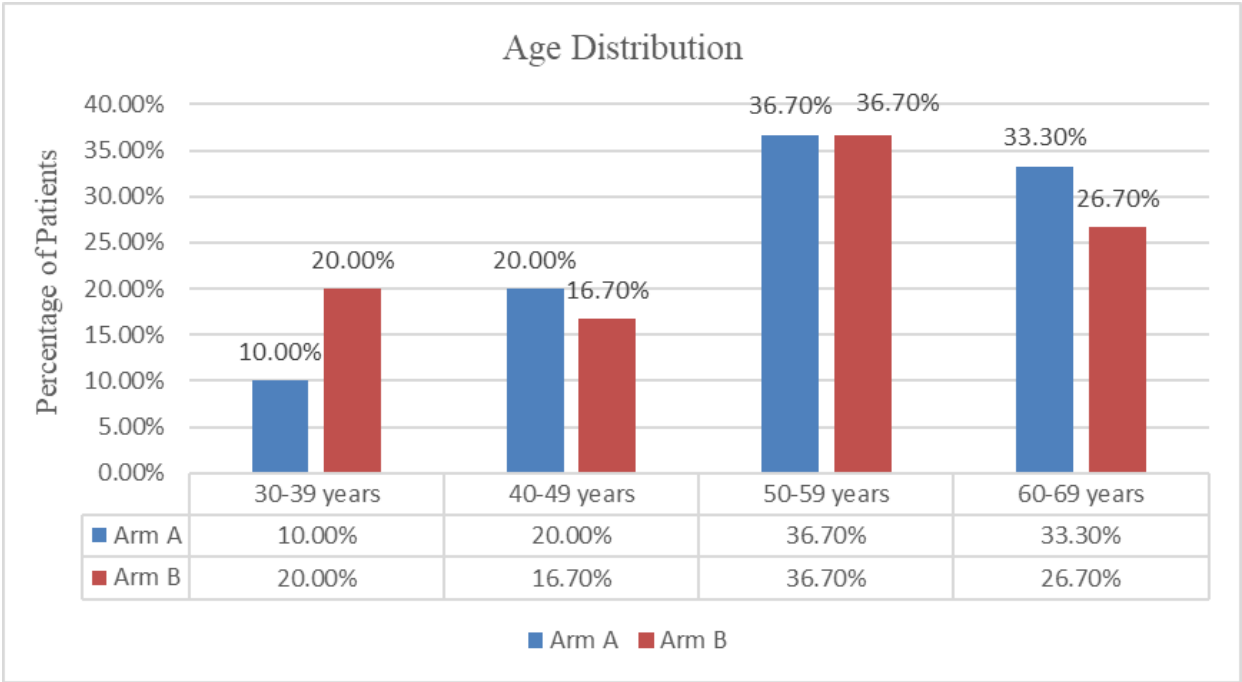


Figure 1 illustrates age distribution showing a majority of the study subjects were from 50-59 years age group (Arm A 36.7%, Arm B 36.7%). The mean age of patients in Arm A was 52.97± 9.07 years and in Arm B was 50.80±9.96 years. Only 10.0 % and 20 % of patients were in 30-39 age group for Arm A and B respectively.

Table 2 resembles the sociodemographic characteristics of the respondents. According to gender, in both arms, males were more

prevalent than females. In arm A, males were 24 (80.0%), and in arm B males were 17 (56.7%). In Arm A and Arm B, females were 06 (20.0%) and 13 (43.3%) and Male to female ratio was 4:1 and 1.3:1 in Arm A and B respectively. On the other hand, In Arm A, 40% were from the lower class, 53.3% were from the middle class and 6.70% were from the upper class. In Arm B, 4 (13.3%) were from the lower class, 20 (66.7 %) were from the middle class and 5 (16.7%) were from the upper class.

Distribution of the patients according to the gender (n=60)			
Gender	Arm A N (%)	Arm B N (%)	Total (N= 60)
Male	24 (80.0%)	17 (56.7%)	41 (68.3%)
Female	06 (20.0%)	13 (43.3%)	19 (31.7%)
Economic Condition	Arm A	Arm B	Total
Per month income	(N=30) (%)	(N=30) (%)	(N = 60)
<12,260 Taka	12 (40.0%)	04 (13.3%)	16 (26.7%)
12,260-31,640 Taka	16 (53.3%)	20 (66.7%)	36 (60.0%)
>31,640 Taka	02 (6.7%)	05 (16.7%)	07 (11.7%)

Figure 2: Distribution of the patients according to the performance status (n=60)

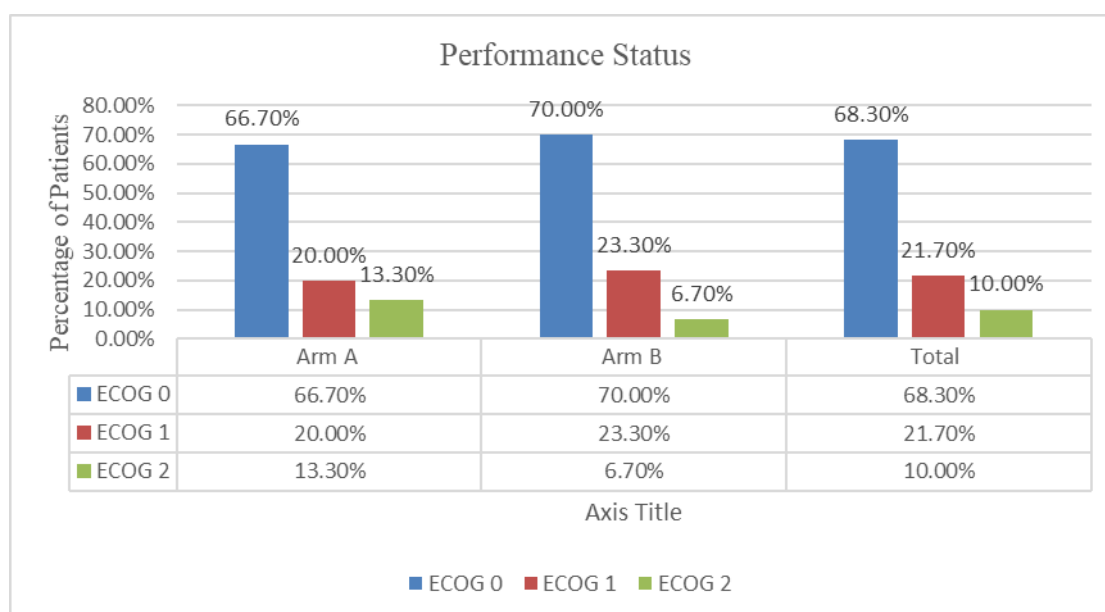


Figure 1 illustrates the distribution of the patients according to their performance status. In Arm A, 40% were from the lower class, 53.3% were from the middle class and 6.70% were from the upper class. In Arm B, 4 (13.3%) were from the lower class, 20 (66.7 %) were from the middle class and 5 (16.7%) were from the upper class.

Table 2: Distribution of patients according to risk factors in both arms

Table 2 Tobacco smoking was the dominant prevailing risk factor which was 35 (58.3%) of patients were smokers, 50 (83.3%) of patients were betel-nut user and 19 (31.7%) of patients had a habit of tobacco-chewing in both arms.

Risk Factors	Arm A (N %)	Arm B (N %)	P-Value
Smoking Habits	20 (66.7%)	15 (50.0%)	1.714
Betel-Nut user	24 (80.0%)	26 (86.7%)	0.480
Tobacco-chewing	10 (33.3%)	9 (30.0%)	0.077

Table 3: Distribution of patients according to common various clinical features in both arms.

Table 3 shows the distribution of patients according to common various clinical features in both arms. It is evident that, Arm A 50% patients were presented with oral ulcerative lesion and difficulty in taking food, 43.3 % with neck nodes, 33.3 % with

difficulty in deglutition and 20.0% had pain in throat or pain in oral cavity and 3.3% were presented with weight loss whereas, in arm B 33.3 % patients presented with oral ulcerative lesion and difficulty in taking food, 26.7 % presented with neck nodes, 53.3 % with difficulty in deglutition, 26.7 % with pain in throat or pain in oral cavity and 6.7 % had weight loss.

Presenting complaints	Arm A	Arm B	Total
	N (%)	N (%)	(N = 60)
Oral Ulcerative Lesion Difficulty in Deglutition Neck Nodes	15 (50.0%)	10 (33.3%)	24 (41.7%)
Pain in throat and or oral cavity Difficulty in taking food Hoarseness of Voice	10 (33.3%)	16 (53.3%)	26 (43.3%)
Weight Loss Neck Swelling	13 (43.3%)	08 (26.7%)	21 (35.0%)
Salivation and or Bleeding	06 (20.0%)	08 (26.7%)	14 (23.3%)
	15 (50.0%)	10 (33.3%)	25 (41.7%)
	0 (0.0%)	03 (10.0%)	03 (5.0%)
	01 (3.3%)	03 (10.0%)	4 (6.7%)
	0 (0.0%)	02 (6.7%)	02 (3.3%)
	01 (3.3%)	0 (0.0%)	01 (1.7%)

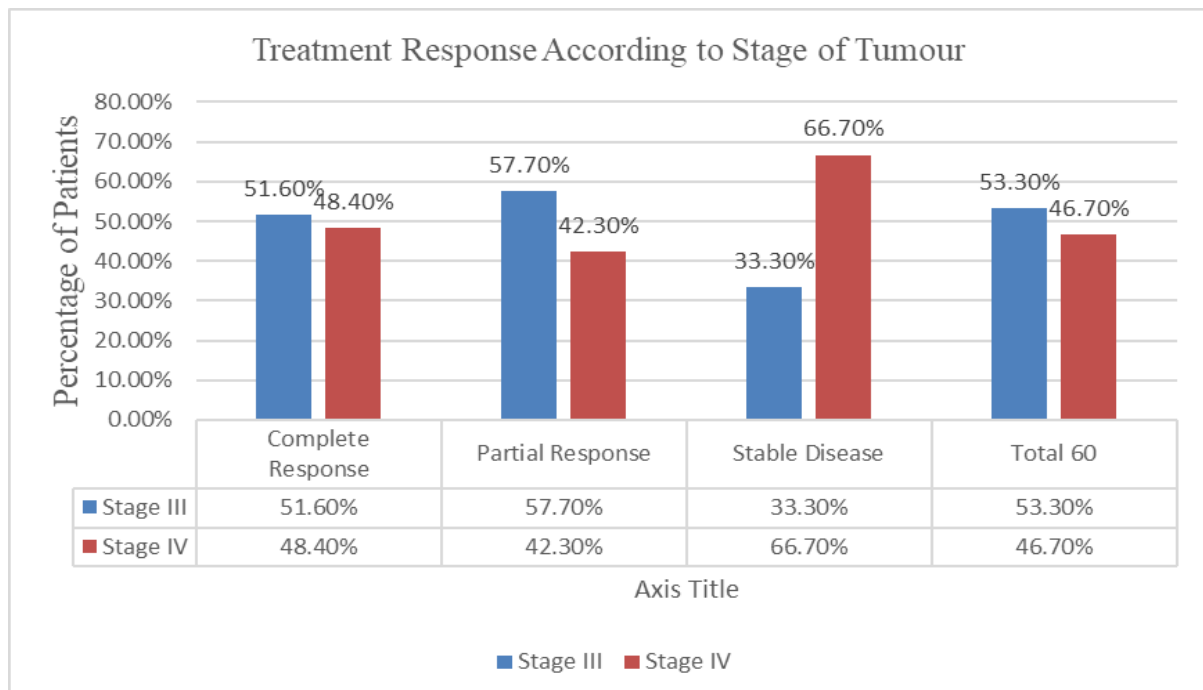
Figure 3: Radiotherapy-induced Grade III Skin Toxicity according to the respondents (n=60)

Figure 3 resembles radiotherapy-induced Grade III Skin toxicity according to the respondents' bar diagram showing the response of treatment based on the staging of the tumor after the completion of 3rd cycle of induction chemotherapy. In Arm A complete response was revealed 51.60% and 48.40% was for Arm B.

Table 4: Toxicities Grading (Mucositis, Nausea, Vomiting, Anaemia, Neutropenia and Thrombocytopenia, Diarrhoea, Alopecia, Weight Loss, Skin Toxicity, and Renal impairment) after completion of 3rd cycle of induction chemotherapy (n=60)

Table 4 illustrates toxicities Grading (mucositis, nausea, vomiting, anemia, neutropenia and thrombocytopenia, diarrhea, Alopecia,

Weight Loss, Skin Toxicity, and Renal impairment) after completion of 3rd cycle of induction chemotherapy. None of the patients needed hospitalization for toxicity management. The dose of 5-FU was reduced to 50% in one patient in arm A and one patient in arm B. Different kinds of toxicities presented in patients of both arms during treatment. The most common toxicity was Grade 2, and 3 neutropenia (26.7% and 13.3% respectively). Toxicities included Grade 2, 3 mucositis (26.7%, 6.7%), Grade 2 thrombocytopenia (6.7%), Grade 2 diarrhea (20.0%), Grade 2 nausea (33.3%) and Grade 2 vomiting (16.7%). However, there was no treatment-related death. P-value pulled from chi-square test.

Variables of Toxicity	Arm A N (%)	Arm B N (%)	Total (N = 60)	P-Value
Mucositis Grade 1	10 (33.3%)	14 (46.7%)	24 (40.0%)	0.619
Grade 2	8 (26.7%)	05 (16.7%)	13 (21.7%)	
Grade 3	2 (6.7%)	03 (10.0%)	05 (8.3%)	
Nausea Grade 1	20 (66.7%)	20 (66.7%)	40 (66.7%)	0.608
Grade 2	10 (33.3%)	10 (33.3%)	20 (33.3%)	
Vomiting Grade 1	12 (40.0%)	10 (33.3%)	22 (36.7%)	0.773
Grade 2	05 (16.7%)	07 (23.3%)	12 (20.0%)	
Anaemia Grade 1	10 (33.3%)	13 (43.3%)	23 (38.3%)	0.696
Grade 2	05 (16.7%)	05 (16.7%)	10 (16.7%)	
Neutropenia Grade 1	18 (60.0%)	18 (60.0%)	36 (60.0%)	0.710
Grade 2	08 (26.7%)	06 (20.0%)	14 (23.3%)	
Grade 3	04 (13.3%)	06 (20.0%)	10 (16.7%)	
Thrombocytopenia Grade 1	09 (30.0%)	08 (26.7%)	17 (28.3%)	0.686
Grade 2	02 (6.7%)	04 (13.3%)	06 (10.0%)	
Diarrhoea Grade 1	09 (30.0%)	07 (23.3%)	16 (26.7%)	0.298
Grade 2	06 (20.0%)	04 (13.3%)	10 (16.7%)	
Grade 3	0.0 (0.0%)	03 (10.0%)	03 (5.0%)	
Alopecia Grade 1	17 (56.7%)	15 (50.0%)	32 (53.3%)	0.866
Grade 2	04 (13.3%)	05 (16.7%)	09 (15.0%)	
Weight Loss Grade 1	08 (26.7%)	07 (25.0%)	15 (25.0%)	0.946
Grade 2	08 (26.7%)	07 (25.0%)	15 (25.0%)	
Grade 3	02 (6.7%)	03 (8.3%)	05 (8.3%)	
Skin toxicity Grade 1	07 (23.3%)	08 (26.7%)	15 (25.0%)	0.938
Grade 2	06 (20.7%)	06 (20.0%)	12 (20.0%)	
Grade 3	02 (6.7%)	03 (10.0%)	05 (8.3%)	
Renal impairment Grade 1	07 (23.3%)	08 (26.7%)	15 (25.0%)	0.781
Grade 2	01 (3.3%)	02 (6.7%)	03 (5.0%)	

Table 6: Distribution of patients according to response pattern at 3rd (final) follow-up after completion of treatment

Table 6 shows this study's final result at 3rd follow-up (at week 30).

Treatment Group	Complete Response	Progressive Disease	χ^2 Value	P-Value
Arm A	24 (80.0%)	06 (20.0%)	0.111	0.50
Arm B	25 (83.3%)	05 (16.7%)		

Discussion:

In this study 60 patients who were enrolled, were histologically or cytologically proven to have locally advanced (Stage III or Stage IVA, B) Head-Neck Cancer. The tumor was at inoperable state and had not received any definitive oncologic treatment. The patients were studied randomly in two different arms, Arm A and Arm B. Arm A was given treatment with chemotherapy with LFP (Leucovorin, 5-FU, Cisplatin) regimen and DCF (Docetaxel, Cisplatin, 5-FU) regimen in arm B followed by EBRT in locally advanced Head-Neck cancer. Most of the patients in this study were male and the female ratio is 4:1 in arm A and 1.3:1 in arm B. In arm A, 24 (80.0%), in arm B 17 (56.7%). In arm A, female 06 (20.0%), in arm B, female was 13 (43.3%). The usual time of diagnosis is after the age of 40, except for salivary gland and nasopharyngeal cancer (NPCs), which may occur in the younger age group (Devita Jr et al., 2014) this age group and gender percentage were correlated with Devita Jr et al (2014) and Brady et al (2007) [10,11].

Most of the patients in this study belong to the low to middle-class population group, where 16 (26.7%) patients came from the poor economic class and 36 (60.0%) patients came from the middle class. These results correlate with the study [12]. The reason for the higher number of low to middle-class patients may be due to having cost-efficient treatment here and the higher-class patients would prefer or can afford the private sector or abroad for getting costly treatments which is not possible for low to middle-class patients.

Bomford et al (2003) and describe tobacco use as the greatest risk for head and neck cancer in the Indian subcontinent. Different kinds of acute toxicities were observed in the patients of both arms during induction chemotherapy. All toxicities among the two arms showed no statistically significant differences [13].

Alopecia grade 2 in Arm A was 04 (13.3%) and in Arm B was 05 (16.7%). In Arm A and B grade 2 anemia occurred in 05 (16.7%), grade 3 neutropenia in Arm A 04 (13.3%) and 06 (20.0%) in this study but neutropenia was grade 3 or 4 in 41% and 18% of patients, respectively. Thrombocytopenia grade 2 was 02 (6.7%) in arm A and 04 (13.3%) in arm B. Mucositis grade 3 in arm A, 2 (6.7%) and 03 (10.0%) in arm B but Grade 3 or 4 mucositis was noted in 7% and 3% of patients, respectively. In the current study, after completion of 3rd cycle induction chemotherapy, a complete response was observed in 06 (20%) patients. Partial response was seen in 20 (66.7%) and stable disease was 04 (13.3%) in subjects

In arm A complete response was 80% and progressive disease was seen in 10% of enrolled patients. In arm B those were 83.3% and 16.7% respectively. The treatment response was not significant (P-value 0.50).

with LFP regimen. In those patients receiving DCF regimen, complete response was revealed in 05 (16.7%) subjects, partial response in 18 (60.0%) and stable disease was 11 (23.3 %) although statistically overall treatment responses were not significant in two groups. In a comparable study by Psyrri et al, (2004), it was seen that complete response was observed in 10 (24%) patients, partial response was seen in 22 (52%) and stable disease was 05 (12%) in subjects with LFP receiving. In almost similar study by Dreyfuss et al. (1990), complete response was observed in 23 (66 %) patients, partial response was seen in 05 (14 %) subjects with LFP receiving [14].

In this study, induction chemotherapy with LFP regimen showed similar tumor control with acceptable toxicities in comparison to DCF regimen. But the LFP regimen is low priced as well as cost effective than that of DCF regimen.

Further studies with a larger sample size and a longer duration of study with well financial backup are recommended to observe treatment outcomes in terms of survival benefit in two treatment regimen groups.

Conclusion:

LFP induction chemotherapy produced an equivalent complete response rate and almost similar local tumor control and acute toxicities in comparison to the DCF regimen. Further studies are needed to confirm the activity of LFP and to determine its potential impact on local tumor control and disease-free and overall survival.

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