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Toxicity Outcome of Induction Chemotherapy Followed by Concurrent Chemoradiotherapy versus Concurrent Chemoradiotherapy Alone for Locally Advanced Hypopharyngeal Cancer

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Abstract **Original Research Article**

Background: Concurrent chemoradiation has emerged as a mainstay of treatment for locally advanced hypopharyngeal cancer (stage III to IVB). However, induction chemotherapy is still an area of ongoing interest in attempt to decrease the likelihood of emergence of distant metastases, improve loco-regional control and support organ preservation. ***Method:*** This quasi-experimental study was carried out among 86 patients of locally advanced hypopharyngeal cancer patients from November 2021 to October 2022 and distributed into two different groups. Group A received induction chemotherapy (IC) with Paclitaxel and Carboplatin followed by concurrent chemoradiotherapy (CCRT) and group B received CCRT alone. Patients were assessed in every 3 weeks during induction chemotherapy after each cycle and weekly during chemoradiotherapy to assess toxicities. ***Result:*** Final assessment was done at 12 weeks after completion of treatment. Most commonly observed toxicities were skin toxicity, oral mucositis, dryness of mouth and neurotoxicity. Patients in both groups mainly developed grade 2 skin toxicity and oral mucositis (44.2% vs 34.9% and 45.6% vs 39.5% in group A and B respectively). However, grade 2 dryness of mouth was observed among twenty patients in group A and eighteen patients in group B. Similarly, grade 1 neuropathy was mostly seen in both the group (41.86% vs 25.58% in group A and B respectively), but statistically not significant ($p>0.05$). 17(39.53%) and 05(11.63%) patients participated in group A developed grade 1 and grade 2 nephrotoxicity respectively, whereas 15(34.88%) and 03(06.98%) patients developed grade 1 and grade 2 nephrotoxicity respectively in group B. Statistically in significant ($p>0.05$). Hematological toxicity was also seen frequently in both the arms but statistically insignificant. ***Conclusion:*** All skin toxicity, oral mucositis, dryness of mouth, neurotoxicity and hematological toxicity were comparable between the two arms. The toxicities were acceptable and well tolerated.

Keywords: Toxicity outcome, hypopharyngeal cancer, cross-sectional study.

INTRODUCTION

Hypopharynx is one of the primary locations of head and neck cancer. Cancer of the upper aerodigestive tract, including the lips, oropharynx, larynx, oral cavity, hypopharynx, salivary glands, and Sino nasal cavities, is referred to as head and neck cancer. Since the majority of them (roughly 95%) originate from the surface epithelium, they are either squamous cell carcinomas or one of their variations [1].

The global burden of cancer incidence and death is constantly increasing. Head neck cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries [2]. The incidence of head and neck cancer was more than 931,931 cases with around 467,125 deaths in 2020. Among them, the total number of new cases of hypopharyngeal cancers was 84,254 and the number of new deaths was 38,599 [3]. Incidence of hypopharyngeal cancer varies by region, with the highest incidence in South-Central Asia [4]. In

Bangladesh, the estimated new cases of head and neck cancer in 2020 were around 32,337. Among them, the number of new cases of hypopharyngeal cancers was 13,401 and ranked 7th among all cancers [4]. There is no complete statistics of head and neck cancer in our country. According to the Hospital Cancer Registry Report, NICRH, Dhaka 2015-2017, the total number of new cases of hypopharyngeal was 173 in 2017 [5].

Management of hypopharyngeal cancer represents a significant treatment challenge. Because of the anatomic proximity to the larynx, and the desire to preserve respiratory, deglutition, and speech functions, additional consideration when choosing treatment modalities for patients with hypopharyngeal cancer is warranted. In early-stage disease, organ preservation with primary radiotherapy alone has been shown to yield acceptable results, with local control rates of 70–90% [6, 7]. The management of locally advanced hypopharyngeal cancer has evolved from initial approach with primary surgery and/or radiotherapy to modern multi-modality approaches using definitive concurrent chemoradiation [8]. Historically, the mainstay of treatment of tumors of the hypopharynx was surgical resection followed by adjuvant radiotherapy (RT). Concurrent chemoradiation has emerged as a mainstay in the treatment of hypopharyngeal cancer, mostly based on the extrapolation of evidence from other head-and-neck subsites. The use of CCRT for most stage III and IV (non-metastatic) hypopharyngeal cancer patients is based on the results of the meta-analysis of head and neck cancer (MACH-NC), which demonstrated a 4% absolute improvement in overall survival at 5 years from the use of CCRT compared to RT alone [9].

Recently, there has been renewed interest in the concept of induction chemotherapy approaches for patients with locoregionally advanced head and neck cancer including hypopharyngeal cancer. Several studies were carried out regarding the role of induction chemotherapy to decrease the likelihood of emergence of distant metastases, to improve loco-regional control and to support organ preservation with some positive results. The addition of induction chemotherapy remains an appropriate approach for advanced disease with high risk for local or distant failure [10]. Inclusion of induction chemotherapy is the first choice of treatment in hypopharyngeal carcinoma with cervical esophageal invasion to ensure laryngeal and esophageal preservation [11, 12]. Induction chemotherapy has role in organ preservation and in reducing distant metastases [13]. Induction chemotherapy can serve as a predictive tool and allow for the appropriate selection of the subsequent definitive management strategy. Patients responding to induction chemotherapy are also those who respond best to radiotherapy [14]. Paclitaxel-carboplatin induction chemotherapy may benefit patients with locally advanced HNSCC by facilitating adequate chemoradiation regimens that enhanced disease control [15].

The aim of the study was to compare toxicity outcome of Induction chemotherapy followed by concurrent chemoradiotherapy versus CCRT alone for locally advanced hypopharynx cancer (stage III to IVB).

METERIALS AND METHODS

This was a quasi-experimental study conducted in the department of clinical oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), oncology unit, Delta Hospital Ltd and Ahsania Mission Cancer and General Hospital (AMCGH) from November 2021 to October 2022. A total of 86 patients were selected for the purpose of this study following the inclusion and exclusion criteria. The inclusion criteria were Patients with histologically confirmed locally advanced hypopharyngeal squamous cell carcinoma (stage III to IVB) when surgery is not an option. Only patients who had given informed consent were included into the study. Those who did not give consent to the study or who were below 18 years and above 70 years, poor performance status (eastern Co-operative Oncology Group (ECOG) performance status score more than 2), history of double primaries, history of prior chemotherapy, radiotherapy or surgery, patients with other co-morbidities were excluded from the study. The selected patients were equally divided in two groups, group A and group B. Ethical approval for this study was obtained from the respective institutional ethical review committees. Enrolled patients of group A treated with induction chemotherapy with Injection Paclitaxel (175 mg/m² iv over 3 hours on day 1) and injection Carboplatin (AUC of 5-6 IV on day 1) every 3 weeks for 3 cycles. Patients received concurrent chemoradiation 21 days after the completion of chemotherapy. The patients participated in both arms were received concurrent chemoradiotherapy with 3DCRT, 66Gy in 2Gy daily fraction, 5 fractions per week. During whole length of radiotherapy period, weekly cisplatin 40mg/m² starting from first day of radiotherapy. Patient were assessed in every 3 weeks during induction chemotherapy after each cycle and weekly during chemoradiotherapy to assess the toxicities using the national cancer institute's ―Common Terminology Criteria for Adverse Events, v.5.0‖ published on November 27, 2017. All the relevant data were compiled on a master chart and then statistical analysis was done by using the SPSS (Statistical Package for Social Science) software program for Windows, version 26.0. Differences between two means were assessed by t test. The toxicity outcomes were compared by Chi square test. A $p<0.05$ in two tailed test was considered as statistically significant.

RESULTS

From November 2021 to October 2022, a total number of 86 patients with locally advanced squamous cell carcinoma of hypopharynx (stage III to IVB) were included in this study. Among the 86 patients, 43 were taken in each group. The patients of group A were treated with induction chemotherapy followed by concurrent chemoradiotherapy and group B were treated with concurrent chemoradiotherapy alone. Table 1 shows the mean age of the patients participated in this study was 54.74(±7.72) years for group A and 54.09(±7.66) years for group B. Histologic differentiation of tumor observed in this study has been shown in Table 1. The most prevalent histologic differentiation was moderately differentiated, with 58.14% in group A and 72.09% in group B.

Table1: Patient characteristics.

Characteristics	Group A (n=43) N (%)	Group B (n=43) N (%)
Age (meand±SD) years	54.74±7.72	54.09±7.66
Age groups (years)		
31-40	02(4.65%)	01(2.33%)
41-50	05(11.63%)	08(18.6%)
51-60	27(62.79%)	24(55.81%)
61-70	09(20.93%)	10(23.26%)
Clinical stage (%)		
III	18 (41.86%)	17(39.53%)
IVA	19(44.19%)	21(48.84%)
IVB	06(13.95%)	05(11.63%)
Histological differentiation (%)		
Well differentiated	11(25.58%)	07(16.28%)
Moderately differentiated	25(58.14%)	31(72.09%)
Poorly differentiated	07(16.28%)	05(11.63%)

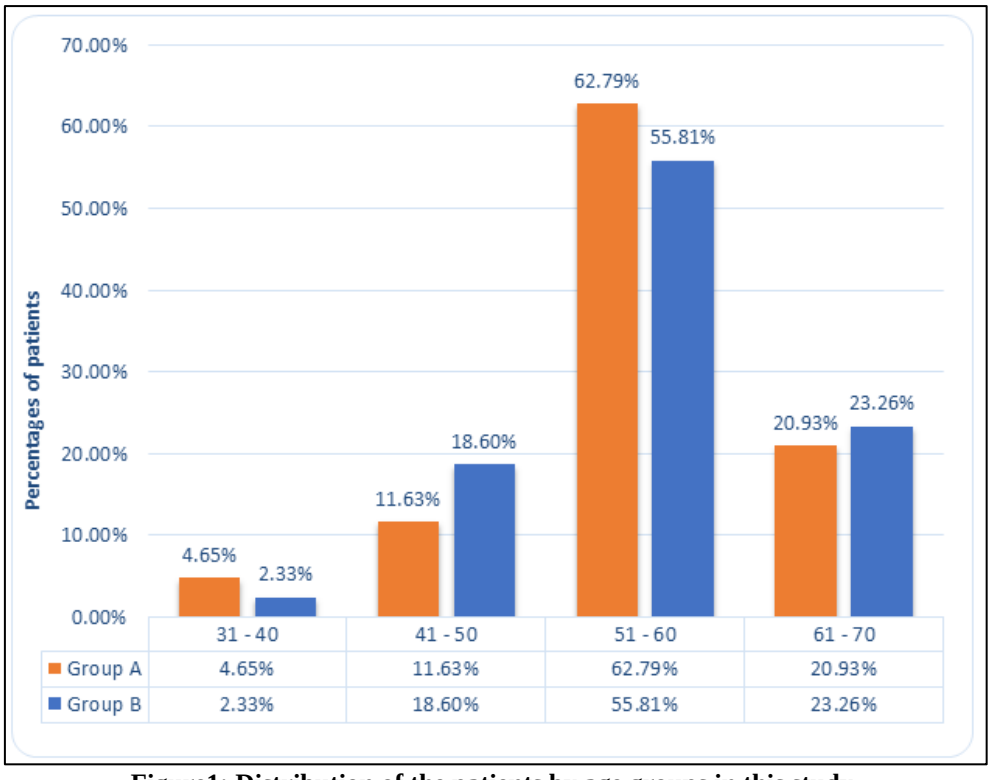

Figure1: Distribution of the patients by age groups in this study.

Most of the patients (62.79%) of group A were 51 – 60 years of age. In group B, 55.81% of patients were in that age range (figure 1).

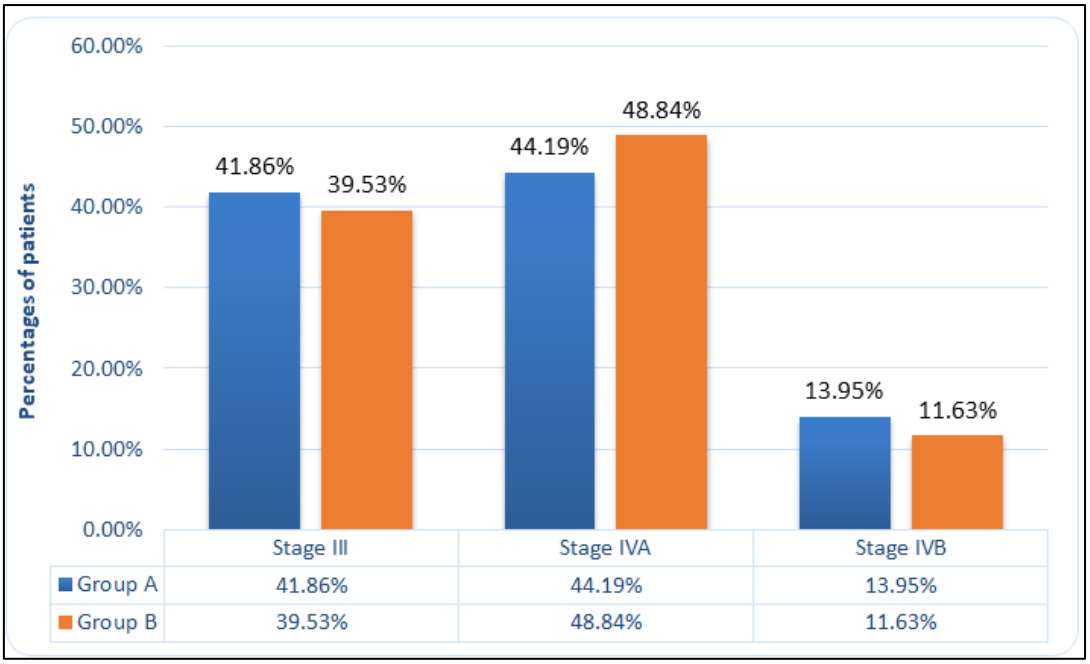

Figure2: Distribution of the patients according to the stage of the disease.

Percentage of patients with stage IVA disease a little bit higher in both groups (44.19% in group A and 48.84% in group B). Six patients of group A and five patients of group B had stage IVB disease (figure 2).

Regarding toxicity profile, concurrent chemoradiotherapy patients of both groups were assessed weekly for toxicity. Oral mucositis, skin toxicities, and dryness of mouth were frequently observed during this period. In group A, 20 (45.6%) and 06 (14.0%) patients developed grade 2 and 3 oral mucositis respectively. In group B, 17 (39.5%) and 05 (11.6%) patients developed grade 2 and 3 oral mucositis respectively. These differences were not statistically significant (p>0.05) (table 2). Skin toxicity was observed in the radiation field in both groups. In group A, 19 (44.2%) and 08 (18.6%) patients developed grade 2 and 3 skin toxicity respectively. In group B, 15 (34.9%) and 06 (14.0%) patients developed grade 2 and 3 skin toxicity respectively (table 2). These differences were not statistically significant (p>0.05). Dry mouth was a common complication of RT and no patient was spared from it. In group A, 23 (53.49%) and 20 (46.51%) patients developed grade 1 and 2 dry mouth respectively. In group B, 25 (58.14%) and 18 (41.86%) patients developed grade 1 and 2 dry mouth respectively (table 2). This difference was not statistically significant (p>0.05).

Table2: Distribution of patients by common toxicities

Variables	**Arm A** n = 43		**Arm B** n = 43		**Total** n = 86		χ^2 **value**	**p value**
	Number	%	Number	%	Number	%		
Skin toxicity								
Grade 1	**16**	37.2	**22**	51.2	**38**	44.19	1.7	**0.427**
Grade 2	**19**	44.2	**15**	34.9	**34**	39.53		
Grade 3	**08**	18.6	**06**	14	**14**	16.27		
Oral mucositis								
Grade 1	**17**	39.5	**21**	48.8	**38**	44.19	0.76	**0.686**
Grade 2	**20**	45.6	**17**	39.5	**37**	43.02		
Grade 3	**06**	14	**05**	11.6	**11**	12.79		
Dryness of the mouth								
Grade 1	**23**	53.49	**25**	58.14	**48**	55.81		**0.828**
Grade 2	**20**	46.51	**18**	41.86	**38**	44.18		

Other toxicities like nausea, vomiting, anemia, neutropenia, thrombocytopenia, nephrotoxicity and neurotoxicity were also observed between two groups but no statistically significant differences were found (p>0.05) (Table 3).

Table3: Distribution of the patients by common toxicities

Variables	Arm A n = 43		Arm B n = 43		Total n = 86		χ^2 value	p value
	Number	%	Number	%	Number	%		
Nausea								
Grade 1	**23**	53.49	**19**	44.19	**42**	48.83		
Grade 2	**17**	39.53	**20**	46.51	**37**	43.02	0.77	**0.681**
Grade 3	**03**	06.98	**04**	09.30	**07**	08.14		
Vomiting								
Grade 0	**16**	37.21	**23**	58.49	**39**	45.35		**0.316**
Grade 1	**20**	46.51	**15**	34.88	**35**	40.67	2.3	
Grade 2	**07**	16.28	**05**	11.63	**12**	13.95		
Neutropenia								
Grade 0	**19**	42.22	**20**	44.44	**39**	45.35		
Grade 1	**15**	34.88	**17**	39.53	**32**	37.2		**0.861**
Grade 2	**06**	14	**04**	09.3	**10**	11.62	0.775	
Grade 3	**03**	07	**02**	04.7	**05**	05.81		
Anemia								
Grade 0	**17**	39.53	**17**	39.53	**34**	39.53		**0.805**
Grade 1	**19**	44.19	**21**	48.84	**40**	46.51	0.43	
Grade 2	**07**	16.28	**05**	11.63	**12**	13.95		

Variables	Arm A n = 43		Arm B n = 43		Total n = 86		χ^2 value	p value
	Number	%	Number	%	Number	%		
Thrombo cytopenia								
Grade 0	**16**	37.21	**23**	53.49	**39**	45.35	2.419	0.298
Grade 1	**19**	44.19	**15**	34.88	**34**	39.53		
Grade 2	**08**	18.6	**05**	11.63	**13**	15.12		
Nephrotoxicity								
Grade 0	**21**	48.84	**25**	58.14	**45**	52.33		
Grade 1	**17**	39.53	**15**	34.88	**32**	37.21	0.973	0.615
Grade 2	**05**	11.63	**03**	06.98	**08**	09.30		
Neuropathy								
Grade 0	**17**	39.53	**27**	62.79	**44**	51.16		0.098
Grade 1	**18**	41.86	**11**	25.58	**29**	33.72	4.655	
Grade 2	**08**	18.60	**05**	11.63	**13**	15.12		

DISCUSSION

There are several reasons why hypopharynx cancer patients who are technically resectable may not undergo primary surgery. Curative-intent chemoradiation is often pursued in these settings. The role of induction chemotherapy remains controversial. Several studies were carried out regarding the role of induction chemotherapy in locally advanced head and neck cancer including hypopharyngeal with some positive results. The aim of this study was to compare the toxicity of induction chemotherapy followed by concurrent chemoradiotherapy and concurrent chemoradiotherapy alone in locally advanced hypopharyngeal cancer (stage III to IVB). This study was conducted from November 2021 to October 2022. After meeting the inclusion and exclusion criteria, a total number of 86 patients were allocated in this study and were divided into two groups, A and B respectively. The mean age of the patients participated in this study was 54.74(±7.72) years for group A and 54.09(±7.66) years for group B. Jyoti *et al.,* 2019, observed that the mean age of the patients was 58.1 years.[16] Most of the patients (62.79%) of group A were 51 – 60 years of age. In group B, 55.81% of patients were in that age range. This observation correlates with Islam *et al.*, 2015 and Samsujjamn K *et al.*, 2023, who observed that most of the patients were between the fifth and sixth decade of life [17-22]. The most prevalent histologic differentiation was moderately differentiated, with 58.14% in arm A and 72.09% in

arm. This observation nearly correlates with Islam *et al.*, 2015, who observed that most common differentiation was moderately differentiated (50%) [17]. Percentage of patients with stage IVA disease a little bit higher in both arms (44.19% in arm A and 48.84% in arm B). According to Halperin *et al.*, 2018, the majority of hypopharyngeal cancer patients have advanced local or regional disease, with around 25% having clinical stage III disease and 50% having clinical stage IV disease [18]. The patients in group B tolerated the concurrent chemoradiotherapy compatibly well. There was no interruption of treatment due to toxicity. All the observed toxicities were managed accordingly. In both groups oral mucositis and skin toxicity and dryness of the mouth were frequently observed. In Arm A, 20 (45.6%) and 06 (14.0%) patients developed grade 2 and 3 oral mucositis respectively. In Arm B, 17 (39.5%) and 05 (11.6%) patients developed grade 2 and 3 oral mucositis respectively. These differences were not statistically significant ($p>0.05$) which nearly correlates with Paccegnella *et al.*, 2009, where grade 3 mucositis is slightly higher in induction chemotherapy followed by concurrent chemoradiotherapy group [19]. Skin toxicity was observed in the radiation field in both groups. In group A, 19 (44.2%) and 08 (18.6%) patients developed grade 2 and 3 skin toxicity respectively. In group B, 15 (34.9%) and 06 (14.0%) patients developed grade 2 and 3 skin toxicity respectively. These differences were not statistically significant ($p>0.05$) which nearly co-relates with Hitt *et al.* ,2005 [20]. Dry mouth was a common complication of radiotherapy and no patient was spared from it. In group A, 23 (53.49%) and 20 (46.51%) patients developed grade 1 and 2 dry mouth respectively. In group B, 25 (58.14%) and 18 (41.86%) patients developed grade 1 and 2 dry mouth respectively. This difference was not statistically significant ($p>0.05$). Other toxicities like nausea, vomiting, anemia, neutropenia, thrombocytopenia, nephrotoxicity and neurotoxicity were also observed between two groups but no statistically significant differences were found ($p>0.05$). Paccagnella *et al.*, 2009 and Nikam *et al.*, 2014, also did not find any statistically significant difference of toxicities between two groups [19-21].

Limitations

The study was conducted with a very small sample size, the results may not represent the whole demography. As this was a quasi-experimental study, further research with larger sample size and duration of follow up was necessary.

CONCLUSION

In conclusion, treatment related toxicities were slightly higher in induction chemotherapy followed by concurrent chemoradiotherapy group, which were manageable and acceptable. In Bangladesh, with high disease burden of locoregionally advanced squamous cell carcinoma of hypopharyngeal region and inadequate number of radiotherapy centers, long queue in the radiotherapy department, waiting for radiation treatment. Induction chemotherapy was found to be useful for patients who would have a delay in starting concurrent chemoradiotherapy with acceptable toxicities.

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Conflict of Interest: *None declared*

Ethical Approval: *The study was approved by the Institutional Ethics Committee*

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