

## Original Article



# Induction Chemotherapy Followed by Radiotherapy Versus Induction Chemotherapy Followed by Chemoradiotherapy in Locally Advanced Squamous Cell Carcinoma of Head and Neck

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### Abstract

**Background:** Radiotherapy and chemotherapy are practiced widely for the treatment of locally advanced squamous cell carcinoma of head and neck. **Objectives:** To compare the effectiveness and toxicities between induction chemotherapy followed by radiotherapy alone and concurrent chemoradiotherapy. **Materials and Methods:** A quasi experimental study was carried out from January 2014 to December 2014. Total sixty patients with locally advanced squamous cell carcinoma of head and neck origin were included and allocated into the arm A and B alternatively. Induction chemotherapy by Cisplatin and 5-Fluorouracil was given to the patient of both arms. Injection Cisplatin was given concurrently during the whole length of radiotherapy period in Arm A while patient in Arm B received radiotherapy alone. The patients were evaluated up to 30 weeks following the completion of the treatment. **Results:** In this study, male to female ratio was 4:1 and mean age at diagnosis was  $60 \pm 5$  years. Overall complete response was 90% (27/30) and 53.3% (16/30) for the Arm A and Arm B respectively at 30 weeks after completion of treatment. During induction chemotherapy only 5% (3/60) of patients suffered from Grade 3 diarrhoea in both arms. In Arm A Grade 3 and 4 mucositis was observed in 36.66% (11/30) and 3.33% (1/30) of patients respectively whereas in Arm B it was 33.33% (10/30) and 3.33% (1/30) respectively. **Conclusion:** Induction chemotherapy followed by concurrent chemoradiotherapy is more effective than induction chemotherapy followed by radiotherapy alone in loco-regional control of locally advanced squamous cell carcinoma of head and neck origin.

**Keywords:** Concurrent Chemoradiotherapy, Head and Neck cancer, Induction Chemotherapy, Squamous Cell Carcinoma.

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### Introduction

Varieties of malignant tumors develop in the head and neck region, majority being squamous cell carcinoma or one of its many variants including malignant tumor arising from larynx, pharynx, oral cavity, nasopharynx, paranasal sinus, nasal cavity, salivary gland etc.<sup>1</sup> Cancers of brain, eye, esophagus, thyroid gland, scalp, skin, muscles, and bones of head and neck, are not usually classified as head and neck cancers.<sup>2</sup> Although surgery has been widely advocated but non-operative strategies i.e., radiation and chemotherapy are practiced especially for larger lesions (>T3) with comparable satisfactory result. Considering the result of treatment, morbidity and mortality of surgery, preservation of organ and cosmesis, radiotherapy is preferred to surgery.<sup>3-6</sup> Based on the

results of meta-analysis of chemotherapy in head and neck cancer (MACH-NC), which demonstrated a 6.2% absolute improvement in the overall survival at 5 years with the use of concurrent chemoradiotherapy compared to radiotherapy alone with manageable toxicity.<sup>6</sup>

### Materials and Methods

This was a Quasi Experimental study to compare the treatment outcome between induction chemotherapy followed by radiotherapy alone versus concurrent chemoradiotherapy for the treatment of locally advanced squamous cell carcinoma of head and neck region. The study was conducted at Department of Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Department of Radiation Oncology, National

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Institute of Cancer Research and Hospital (NICRH), Dhaka from January 2014 to December 2014. Ethical approval was taken from the Institutional Review Board (IRB) of BSMMU on 23-11-2013. Calculated sample size was to be 30 in each arm. Inclusion criteria for this study was, clinically diagnosed and histopathological proven squamous cell carcinoma of head and neck region, TNM stage III to IVA with ECOG performance status 0-2, any sex and with no history of prior chemotherapy and or radiotherapy. Informed written consent was taken from all participated patients. A total of 60 patients were included in the study and the patients were allocated in two different arms: Arm A and Arm B in alternate manner. Arm A consisted of 30 patients who received the induction chemotherapy followed by concurrent chemoradiotherapy and Arm B included another 30 patients who received induction chemotherapy followed by radiotherapy alone. Induction chemotherapy was adopted for both the Arms A and B with Injection Cisplatin 100 mg/m<sup>2</sup>/day IV on day 1 and Injection 5-FU, 1000 mg/m<sup>2</sup>/day IV on day 1 to 4, 3-weekly cycle for 3 cycles. Following induction chemotherapy all patients of both the Arms were evaluated clinically and radiologically. The patients of Arm A were treated with concurrent chemoradiotherapy with weekly Cisplatin 30 mg/m<sup>2</sup> IV along with Radiotherapy, 66 Gray in 33 daily fractions over 6.5 weeks while Arm B had radiotherapy alone, by same dose and fractionization over 6.5 weeks. Premedication (Ondansetron, Dexamethasone and Ranitidine) was given and at least 1 to 3 liters of 0.9% sodium chloride solution depending on the dose of Cisplatin was given to all the patients for hydration. The patients were also asked to take plenty of fluid before and after Cisplatin infusion. Every patient was evaluated after each cycle of chemotherapy and thereafter weekly. They were also evaluated at 6, 18 and 30 weeks after completion of treatment. Evaluation was done on the basis of subjective and clinical response. Complete blood count, renal function tests, liver function tests were done to see the toxicities. All the information's were recorded in prescribed data sheet, analyzed in Statistical Package for Social Sciences (SPSS) version 21 A p-value of less than 0.05 was accepted as statistically significant. The chi-square test was used to compare the results.

**Result**

In this study, male to female ratio was 4:1 observed (male 48/60 and female 12/60) and mean age at diagnosis was 60 ± 5 years. Among total patients enrolled 35 patients were found in Stage III and 25 patients were in Stage IVA. In Arm A, 17 and 13 patients were in stage III and IVA respectively similarly in Arm B 18 and 12 patients were in stage III and IVA respectively. Common site of Head and Neck cancer were larynx and oropharynx followed by cancers of oral cavity and hypopharynx. More than 80 % of patients were at ECOG performance status 1 (49/60, 81.66%) followed by 2 (10/60, 16.66 %) and 0 (1/60, 1.66 %) (Table 1).

**Table I.** Clinical Characteristics of patients enrolled in the study.

Clinical Characteristics	Arm A n = 30	Arm B n = 30
<b>Gender</b>		
Male	27	21
Female	03	09
<b>Clinical stage</b>		
Stage III	17	18
Stage IV A	13	12
<b>Histological differentiations</b>		
Well differentiated	15	
Moderately differentiated	11	
Poorly differentiated	04	
<b>Site of primarytumors</b>		
Oral cavity	05	06
Oropharynx	10	10
Hypopharynx	06	03
Larynx	09	11
<b>ECOG Performance status</b>		
0	00	01
1	26	23
2	04	06

After 3 cycles of induction chemotherapy all the patients were clinically and radiologically evaluated. Complete response was seen in 2/30 (1%) patients in Arm A and 1/30 (3.33%) patient in Arm B. 28/30 (93.3%) patients in Arm A and 29/30 (96.6%) patients in Arm B had partial response (table 2).

**Table II.** Clinical response after 3rd cycle of induction chemotherapy observed in Arm A (n=30) and Arm B (n=30).

Response Evaluation	Arm A (n = 30)	Arm B (n = 30)	P value
Complete response	02 (1%)	01 (3.33%)	0.554
Partial response	28 (93.3%)	29 (96.6%)	
Stable disease	00	00	
Progressive disease	00	00	

At the end of treatment (after 30 weeks of completion of treatment) all the patients were reevaluated with relevant investigations. In Arm A complete response was observed in 16 out of 17 patients (94.1%) and 11 out of 13 patients (84.6%) for stage III and IVA respectively. In Arm B, it was observed in 11 out of 18 patients (61.1%) and 5 out of 12 patients (41.7%) for stage III and IVA disease respectively. Partial response was seen in 1/17 patient (5.9%) and 2/13 patients (15.4%) for stage III and IVA disease in Arm A while in Arm B partial response was seen in 7/18 patients (38.9%) and 7/12 patients (58.3%) for stage III and IVA disease respectively (table 3).

**Table III.** Clinical response after completion of the treatment observed at 30 weeks of therapy in Arm A (n=30) and Arm B (n=30).

Stage Group	Arm A n=30	Arm B n=30	P value
Stage III	17 (56.7%)	18 (60.0%)	0.02
	CR: 16 (94.1%) PR: 01 (5.9%)	CR: 11 (61.1%) PR: 07 (38.9%)	
Stage IVA	13 (43.3%)	12 (40.0%)	0.025
	CR: 11 (84.6%) PR: 02 (15.4%)	CR: 05 (41.7%) PR: 07 (58.3%)	
Overall	30 (100%)	30 (100%)	0.001
	CR: 27(90%) PR: 3(10%)	CR: 16(53.3%) PR: 14(46.6%)	

CR = Complete response, PR = Partial response.

Toxicities observed during induction chemotherapy for both Arms are represented in Table 4. Only three patients developed Grade 3 diarrhea and one patient showed Grade 2 nephrotoxicity.

**Table IV.** Toxicities observed during induction chemotherapy in both Arms.

Variables	Arm A n=30	Arm B n=30
<b>Mucositis</b>		
Grade 1	04 (13.33%)	07 (23.33%)
Grade 2	14 (46.66%)	12 (40.00%)
Grade 3	11 (36.66%)	10 (33.33%)
Grade 4	01 (03.33%)	01 (03.33%)
<b>Skin reaction</b>		
Grade 1	10 (33.33%)	15 (50.00%)
Grade 2	12 (40.00%)	12 (40.00%)
Grade 3	08 (26.66%)	03 (10.00%)
<b>Nausea</b>		
Grade 1	12 (40.00%)	09 (30.00%)
Grade 2	03 (10.00%)	01 (03.33%)
<b>Anemia</b>		
Grade 1	02 (06.67%)	05 (16.67%)
Grade 2	06 (20.00%)	03 (10.00%)
Grade 3	02 (06.67%)	02 (06.67%)
Grade 4	01 (03.33%)	
<b>Xerostomia</b>	11 (36.66%)	10 (33.33%)
<b>Loss of taste sensation</b>	14 (46.66%)	11 (36.66%)
<b>Weight loss</b>		
Grade 1	02 (06.67%)	05 (16.67%)
Grade 2	02 (06.67%)	02 (06.67%)

Toxicities during and immediately after radiotherapy were also assessed (table 5) which showed Grade 3 mucositis was observed in 11 patients in Arm A and 10 patients in Arm B. 2 patients one from each arm developed Grade 4 mucositis.

**Table V:** Toxicities observed in both the Arms during and after radiotherapy

Adverse effects	Total patients (n=60) (Arm A and Arm B)
<b>Mucositis</b>	
Grade 1	30 (50.00%)
Grade 2	07 (11.66%)
<b>Nausea</b>	
Grade 1	28 (46.67%)
Grade 2	08 (13.33%)
<b>Vomiting</b>	
Grade 1	15 (25.00%)
Grade 2	17 (28.33%)
<b>Anaemia</b>	
Grade 1	06 (10.00%)
Grade 2	08 (13.33%)
<b>Neutropenia</b>	
Grade 1	02 (03.33%)
Grade 2	01 (01.67%)
<b>Diarrhoea</b>	
Grade 1	13 (21.67%)
Grade 2	14 (23.33%)
Grade 3	03 (05.00%)
<b>Alopecia</b>	
Grade 1	20 (33.33%)
Grade 2	04 (06.67%)
<b>Nephrotoxicity</b>	
Grade 1	05 (08.33%)
Grade 2	01 (01.67%)

## Discussion

The incidence of the Head neck cancer is increasing in the developing country and is the 6<sup>th</sup> most common cancer worldwide.<sup>7</sup> It is one of the most common cancers in Southeast Asian countries. In contrast they constitute only 1%-4% of all cancers in the Western world.<sup>8</sup> As per WHO oropharynx, oral cavity cancer are predominant forms of head and neck squamous cell cancer (HNSCC) in Bangladesh<sup>9</sup> whereas oropharyngeal and tongue cancers are common in the Western world. These differences in site of disease may be related to the prevalent habits in the respective regions. In our study 18 to 70 years age group was considered. Majority of our cases were Carcinoma of oropharynx and larynx. Larynx, oral cavity, oropharyngeal and hypopharyngeal cancer are the commonly involved sub-sites of supraglottic which is comparable study done by Bhattacharjee et al.<sup>10</sup> Most of the patients in this study were male and male to female ratio was 4:1. 95% patients were diagnosed after 40 years of age.<sup>11</sup> Since the prognosis of patients with locally advanced squamous cell cancer of the head and neck is poor with the current standard therapy of surgery and/or radiation. Attempts to improve the results is going on. The concept of a multi-modality approach using induction systemic chemotherapy before definitive therapy is gaining wider use in the management of these patients. Induction chemotherapy for loco-regionally advanced head and neck cancers has been investigated for the last two decades. There are some trials and studies which supports the role of induction chemotherapy in locally advanced head and neck cancer. Study by Rooney et al. demonstrated response rate of 93% in patients receiving induction chemotherapy with cisplatin and 5-FU.<sup>12</sup> MACH-NC group (meta-analysis of chemotherapy in head and neck cancer), recommended that the use of chemotherapy in non-metastatic HNSCC can enhance survival.<sup>6</sup> This meta-analysis consisted of 63 randomized trials including 10741 patients performed between 1965 and 1993. Trials included patients treated for non-metastatic HNSCC by chemotherapy in addition to locoregional treatment.<sup>13</sup> With the use of chemotherapy there was a survival benefit of 4% at 5 years. The study also suggested that maximum benefit of chemotherapy was observed when given concomitantly with radiotherapy.<sup>6</sup> Promising result of this meta-analysis were updated in 2009 including 93 trials (17 493 patients). This meta-analysis compared all the treatment modalities indirectly. 4.5% absolute benefit was observed when chemotherapy was added to other loco regional treatment at the periods of 5 years. For the same period the benefit was 6.5% for concomitant chemotherapy.<sup>14</sup> In another study, the benefit of chemotherapy was explored in all tumor's locations.<sup>15</sup> Results were consistent in all tumor locations. Similarly, Perez et al. showed that the absolute benefit of induction chemotherapy is 2.4%.<sup>16</sup> A preliminary report by Hitt and Lopez-Pousa from

their study of induction CT followed by CCRT compared with CCRT alone suggested a benefit for the induction arm.<sup>17</sup> Various drug regimen either three drugs or two drugs regimen are used for induction chemotherapy. In this study cisplatin and 5-FU were used for induction chemotherapy because most of the patients in Bangladesh are poor and as well Taxane containing regimen causes more complication, which were described in TAX 32/ EORTIC and TAX 324 trails and also correlates with Posner et al, where locoregional control, overall survival and median survival increased in Docetaxel, Cisplatin and 5-FU arm than Cisplatin and 5-FU arm but 25% patients cannot receive radiotherapy due to toxicity.<sup>18</sup> In this study, the complete response rate was 94.1% for Stage III and 84.6% for Stage IV disease in patients receiving CCRT. On the other hand, it was 61.1% and 41.7% respectively in patients receiving RT. Complete response was higher in patients receiving CCRT than RT only (90% versus 53.3%). Suggesting that the addition of concurrent chemotherapy could lead to better response in advanced head and neck cancer. This implies that, there is a role of induction chemotherapy in head and neck cancer. In induction group, most common chemotherapy related early were mucositis 61.66%, nausea 60%, vomiting 53.33%, diarrhea 50%, alopecia 40% and anemia 23.33%. All the toxicities were limited to Grade 1 and Grade 2 except three patients who suffered from Grade 3 diarrhoea. No hospitalization was needed for toxicity management. Mucositis was observed more commonly in patients receiving CCRT (46.66% - Grade 2 and 36.33% - Grade 3) than patients receiving RT only (40% - Grade 2 and 33.33% - Grade 3). Similarly, skin reactions were also frequently observed in patients receiving CCRT. None of the patients experienced life threatening events. In the study by Vokes et al. found 54% Grade 3/4 mucositis, 60% leucopenia and 5 patients died due to toxicity of drugs.<sup>6</sup> In this study the toxicity profile of concurrent modality was limited in Grade 1 (48%), Grade 2 (34%), Grade 3 (17%) and Grade 4 (1%).

## Conclusion

Induction chemotherapy followed by concurrent chemoradiotherapy is more effective than induction chemotherapy followed by radiotherapy alone in loco-regional control of locally advanced squamous cell carcinoma of head and neck origin with acceptable toxicity.

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