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Original Research

Comparative Efficacy of Induction Chemotherapy Followed by Concurrent Chemoradiotherapy versus Chemoradiotherapy Alone in Inoperable Locally Advanced Head and Neck Cancer: A Quasi-Experimental Study

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Introduction: Head and neck cancer is a common oncological problem in Bangladesh. Most of the head and neck cancers present with a locally advanced stage. Concurrent chemoradiotherapy (CCRT) is the current standard for inoperable locally advanced head and neck cancer (LAHNC). Several studies explored the induction chemotherapy (ICT) option before CCRT and found promising outcomes. Objective: The study aimed at assessing the complete response rate and toxicity of CCRT with or without ICT in inoperable LAHNC.

Materials and Methods: This quasi-experimental study enrolled 140 patients from June 2018 to July 2019. Participants were included based on the inclusion and exclusion criteria and equally divided between the two arms: 70 patients in Arm A (ICT plus CCRT) and 70 patients in Arm B (CCRT). ICT and CCRT were given to Arm A, while CCRT alone was given to Arm B. Three months following completion of the treatment, the final outcomes were assessed.

Results: At the final follow-up, Arm A showed a statistically higher complete response rate compared to Arm B (58.57% versus 32.85%, p-value = 0.002). Treatment-related toxicities, such as mucositis, xerostomia, dermatitis, anemia, neutropenia and renal toxicity, were similar in both arms.

Conclusion: Patients who received ICT before CCRT had a significantly higher complete response rate compared to those who received CCRT alone with comparable toxicities. Therefore, ICT may improve locoregional control when added before CCRT in inoperable LAHNC.

Introduction

Head and neck cancers can develop in various locations and structures within the head and neck region, such as the pharynx, oral cavity, larynx, paranasal sinuses, nasopharynx, salivary glands or

nasal cavity. The most prevalent pathology is squamous cell carcinoma (> 90%) [1]. In 2018, Head and neck cancers had a global annual incidence of over 887,000 cases, representing 5.2 percent of all newly diagnosed cancer cases, with approximately 453,000 fatalities [2]. In Bangladesh, the estimated incidence of head and neck cancers in 2018 was over 30,000 [3]. Approximately 60% of head and neck cancers patients presented with advanced stages [4]. Concurrent chemoradiotherapy (CCRT) is the accepted standard treatment option for inoperable locally advanced head and neck cancer (LAHNC) [5]. The use of induction chemotherapy (ICT) before CCRT in LAHNC was heavily investigated. According to previous clinical trials, ICT accompanied by CCRT improves overall survival, progression-free survival and loco-regional control [6-10]. Haddad et al. [11] suggested that for advanced diseases that have a significant risk of failure, either local or distant, ICT is still a viable option. Additionally, ICT can be used to assist with the correct selection of a future management strategy. Patients who respond well to ICT respond well to radiotherapy as well [12]. According to Bangladesh's perspective, there are more cancer patients than radiation machine slots, which results in long waiting periods. During treatment waiting periods, induction chemotherapy (ICT) may reduce tumor size, prevent the progression of the disease and enhance locoregional control prior to CCRT. The objective of this study was to assess the complete response rate and toxicity of CCRT with or without ICT in LAHNC.

Materials and Methods

Sample size calculation

For determination of sample size, the following formula was applied:

$$n = [(Z\alpha/2 + Z\beta)^2 \times (P_1(1-P_1) + P_2(1-P_2))] / (P_1 - P_2)^2$$

In this equation, $P_1 = 0.21$ (21.2%), $P_2 = 0.50$ (50%), $Z\alpha = 1.96$, and $Z\beta = 1.645$ [7]. The final sample size was 70 in each arm after allowing 10% dropout cases.

Patients

Between June 2018 and July 2019, 140 patients with inoperable LAHNC participated in this quasi-experimental study. Patients over the age of 18 were eligible if they had stage III/IVA/IVB inoperable LAHNC; an Eastern Cooperative Oncology Group (ECOG) performance status below 3; and no prior treatments such as chemotherapy, radiotherapy, or surgery.

Study design and treatment

This quasi-experimental study was carried out at the National Institute of Cancer Research and Hospital's (NICRH) Department of Radiotherapy and the Bangladesh Medical University's (BMU) Department of Clinical Oncology in Dhaka, Bangladesh. At first, a total of 163 patients were evaluated for eligibility, and after applying inclusion and exclusion criteria, 140 patients were enrolled in this study. Purposive sampling was used to divide participants into two groups: arm A (ICT plus CCRT arm) and arm B (CCRT arm). Randomization controlled trial was not feasible within the available funding and infrastructure. To reduce allocation bias, we followed strict inclusion and exclusion criteria and ensured that two groups of patients had comparable baseline characteristics. Arm A received ICT followed by CCRT, while Arm B received only CCRT (Figure 1).

Figure 1. Consort Flow Chart of the Participants. We analyzed every participant, including lost-to-follow- up

patients, according to intention-to-treat analysis.

ICT was given only in Arm A, along with cisplatin 100 mg/m^2 intravenously on day 1 and 5-fluorouracil 1000 mg/m^2 intravenously daily for 5 days, from day 1 to day 5. This is a three-week schedule that was repeated three times [13]. After 1 month following ICT, all patients in Arm A received CCRT. On the other hand, Arm B received CCRT alone. The CCRT dose schedule was similar in both arms. Over a 6.5-week period, all patients in both arms received external beam radiotherapy, 66 Gray (33 fractions), 5 days per week. During the radiotherapy period, both arms also received chemotherapy with inj. cisplatin 30 mg/m^2 per week [14]. Radiotherapy was given with a two-dimensional (2D) technique using a 6-megavoltage linear accelerator (LINAC) machine. Simulation was done in a supine position with their head on a customized headrest and spine as flat as possible. The head was immobilized by a thermoplastic musk. Orthogonal simulation was used for the treatment plan, and field boundaries were established using bony landmarks based on the stage and location of the disease. Two parallel opposed fields were chosen. Reduction of lateral fields was done after 44 Gy to keep the spinal cord tolerance limit by X-ray simulation. Electron was used to boost the posterior cervical chain node after 44 Gy when required. Toxicities were managed according to the grade of particular toxicity. Basic oral and skin care were given to all patients to prevent mucositis and dermatitis, respectively. Hematological toxicities, such as anemia and neutropenia, were managed with transfusion and growth factor, respectively. Hydration was maintained according to institutional cisplatin protocol. Modification of chemotherapy dose was performed in few patients due to higher toxicity grade. With the right supportive measures, most patients were treated as outpatients.

Assessment and data collection

Patients were evaluated after each cycle during ICT and once a week during CCRT. For evaluation of treatment response, Response Evaluation Criteria in Solid Tumors (RECIST) criteria were utilized [15]. Toxicities were assessed using Radiation Therapy Oncology Group (RTOG) scoring criteria [16]. Finally, they were evaluated 1.5 months and 3 months after finishing treatment. To assess treatment responses and treatment-related toxicities, relevant clinical examinations and investigations were performed. Data were collected using a data collection.

Statistical analysis

For statistical analysis, IBM SPSS software version 25 was used. The intent-to-treat principle was used in this study. For missing data, the last observation carried forward imputation method was used. Lost to follow-up participants were included in the analysis using their last available data. The chi-square test was used to compare categorical data, while t-test was employed to analyze continuous variables. A multivariate logistic regression analysis was done to assess predictors of complete response. A p-value of less than 0.05 was defined as statistical significance.

Ethical considerations

The BMU Institutional Review Board (IRB) granted ethical approval (No. BSMMU/2018/5655 dated 28- 05-2018). Permission was also taken from NICRH, Mohakhali, Dhaka. The Helsinki Declaration and good clinical practice recommendations were followed during this study. An explanation about the study was given to all the participants. It was also explained to them that they have the right to refuse or accept to enroll in this study. Each participant in this study gave their written informed consent. The data of all patients were kept confidential.

Results

The mean age of the patients between the two arms was comparable (57.27 versus 56.03 years). Nearly three- quarters of the participants were male. In both arms, the majority of patients had an ECOG score of zero. The most common primary location was the oral cavity. Almost half of patients had tumors that were moderately differentiated. The majority of the patients were in stage IVA/B. Overall, the patient characteristics at baseline were comparable in both arms (Table 1).

Characteristics	Arm A (ICT + CCRT) (%)	Arm B (CCRT) (%)	p-value
	(n = 70)	(n = 70)	
Age (mean± SD)	57.27±9.23	56.03±8.48	0.40 (NS)
Sex			
Male	48 (68.57)	53 (75.71)	0.34 (NS)
Female	22 (31.43)	17 (24.29)	
Male: Female	2:01	3:01	
Clinical stage			
Stage III	27 (38.57)	23 (32.86)	0.48 (NS)
Stage IVA and B	43 (61.43)	47 (67.14)	
Differentiation			
Well	18 (25.71)	21 (30.00)	0.70 (NS)
Moderate	37 (52.86)	32 (45.71)	
Poor	15 (21.43)	17 (24.29)	
Primary sites			
Oral cavity	27 (38.57)	23 (32.86)	0.62 (NS)
Larynx	15 (21.43)	16 (22.86)	
Oropharynx	10 (14.29)	15 (21.43)	
Hypopharynx	18 (25.71)	17 (24.29)	
ECOG Performance			
0	33 (47.14)	27 (38.57)	0.28 (NS)
1	21 (30.00)	19 (27.14)	
2	16 (22.86)	24 (34.29)	

Table 1. Characteristics of the Participants.

NS, Not significant

Final follow-up was given after 3 months of therapy and treatment responses were evaluated using RECIST criteria. In this study, ICT plus CCRT arm had higher complete response rate than CCRT arm (58.57% versus 32.85%). This result was statistically significant between the two arms (p-value = 0.002) (Table 2).

Response	Arm A (ICT + CCRT)	Arm B (CCRT)	p-value
	(n = 70)	(n = 70)	
Complete response (CR)	41 (58.57%) 95% CI: 46.5-70%	23 (32.85%) 95% CI: 21.9-44.6%	0.002
Partial response (PR)	16 (22.86%)	26 (37.14%)	
Stable disease (SD)	07 (10.00%)	12 (17.14%)	
Progressive disease (PD)	06 (08.57%)	09 (12.86%)	

Table 2. Treatment Outcomes at Final Follow-up.

According to multivariate analysis, ICT plus CCRT was the independent predictor of CR (β = +1.18,

p = 0.0018). Patient characteristics, such as age, sex, stage, differentiation and ECOG performance, were not statistically significant predictors in our study.

During concurrent chemoradiotherapy, both chemotherapy- and radiotherapy-related toxicities, such as mucositis, xerostomia, dermatitis, anemia, neutropenia and renal toxicity, were observed. Only in the oral mucosa, grade 4 toxicity was seen. In ICT plus CCRT arm, 4 patients developed grade 4 oral mucositis, while in CCRT arm, 2 patients developed grade 4 oral mucositis. Treatment-related toxicity differences were not statistically significant between the two arms (p-value > 0.05) (Table 3).

Toxicities	Arm A (ICT + CCRT) (%)	Arm B (CCRT) (%)	p-value
	(n = 70)	(n = 70)	
Oral mucositis			
Grade 1	28 (40.00)	34 (48.57)	
Grade 2	20 (28.57)	21 (30.00)	0.556 (NS)
Grade 3	18 (25.71)	13 (18.57)	
Grade 4	04 (05.71)	02 (02.86)	
Dermatitis			
Grade 1	39 (55.71)	43 (61.43)	
Grade 2	22 (31.43)	15 (21.43)	0.378 (NS)
Grade 3	09 (12.86)	12 (17.14)	
Xerostomia			
Grade 1	52 (74.29)	46 (65.71)	0.268 (NS)
Grade 2	18 (25.71)	24 (34.29)	
Neutropenia			
Grade 1	19 (27.14)	22 (31.43)	
Grade 2	12 (17.14)	09 (12.86)	0.452 (NS)
Grade 3	03 (04.29)	01 (01.43)	
Anaemia			
Grade 1	14 (20.00)	17 (24.29)	0.382 (NS)
Grade 2	05 (07.14)	03 (04.29)	
Nephrotoxicity			
Grade 1	26 (37.14)	22 (31.43)	
Grade 2	17 (24.29)	14 (20.00)	0.406 (NS)
Grade 3	09 (12.86)	03 (04.29)	

Table 3. Treatment-related Toxicities of the Participants.

NS, Not significant

In our study, 83% of patients in Arm A got full course of ICT, while 17% required reduction of chemotherapy dose or delay of treatment due to toxicities. During CCRT, 24 % of participants in ICT plus CCRT arm and 17% of in CCRT arm required treatment interruptions due to radiation-induced grade 3 or 4 toxicities. Four patients in Arm A and 2 patients in Arm B required hospitalization.

Discussion

Pignon et al. [17] conducted a meta-analysis that showed CCRT has a major survival benefit in LAHNC and has now become the standard treatment. In different clinical trials, the addition of ICT to CCRT in the treatment of LAHNC was investigated. Two previous clinical studies found no survival benefit for additional ICT prior to CCRT [11, 18]. In contrast, three recent clinical trials

have demonstrated that addition of ICT with CCRT improves survival and locoregional control when compared to CCRT alone [7-9]. This quasi-experimental study was designed to observe and compare the treatment response and toxicity of ICT followed by CCRT versus CCRT alone in inoperable LAHNC.

Patients with inoperable LAHNC were included in our study. In this study, we found that the complete response (CR) rate was significantly higher in ICT plus CCRT arm than in CCRT arm. A complete response was observed in 41 (58.57%) of patients in ICT plus CCRT arm, but only 23 (32.85%) of patients in CCRT arm (p-value=0.002). Previous studies correlated with our result and found that ICT accompanied by CCRT resulted in a statistically significant complete response as compared to CCRT alone [7-9]. A phase II randomized study conducted by Paccagnella et al. [7] with a total of 101 patients (51 in the ICT plus CCRT arm and 50 in the CCRT alone arm) found that CR rates were 21.2% in the ICT plus CCRT arm versus 50% in the CCRT arm (p-value: 0.004), which nearly correlates with our study finding. According to Ghi et al. [6], more CR rates were observed in the ICT plus CCRT arm (42.5%) compared to the CCRT alone arm (28%), which is in line with our findings. In our study, we found comparatively more CR rates may be due to evaluation time. We assessed treatment response after 3 months following CCRT, whereas Ghi et al. evaluated after 2 months, so that the tumor got more time to regress in our study. However, the DeCIDE trial demonstrated much lower CR rates compared to our findings: 26% in the ICT plus CCRT arm and 21% in the CCRT arm. This difference may be due to variations in patient characteristics, particularly the stage of the disease. In our study, we included both stage III and IVA/B, while the DeCIDE trial included higher stage IVA/B only [18].

In this study, patients were evaluated for toxicity on a weekly basis during concurrent chemoradiotherapy, as well as after treatment. During this time, both arms showed chemotherapy- and radiotherapy-related toxicities. However, treatment-related toxicity differences between the two arms were not statistically significant (p-value > 0.05). Mucositis, dermatitis and xerostomia were among the most common during this time period. Grade 4 toxicity was observed only in the oral mucosa. 04 patients (05.71 percent) developed grade 4 oral mucositis in ICT plus CCRT arm, while 02 patients (02.86 percent) developed grade 4 oral mucositis in CCRT arm. Other toxicities were also observed between the two arms, including anemia, neutropenia, and renal toxicity. However, the side effects were well tolerated and manageable. Both Paccagnella et al. [7] and Nikam et al. [8] also found that the toxicities of the two groups were comparable.

In the low-resource countries like Bangladesh, radiotherapy machines are inadequate compared to the patients' load. Therefore, there is a long delay in starting CCRT, and ICT may play a vital role in this regard. As ICT showed a higher complete response rate, it may prevent the progression of the disease during the waiting period prior to CCRT.

The study has limitations. As the study was a non- randomized quasi-experimental study, it failed to prevent selection bias. Due to the short study period, late toxicities and survival data could not be assessed.

In conclusion, ICT followed by CCRT resulted in a significantly higher complete response rate than CCRT alone in inoperable LAHNC with comparable toxicities. This suggests that ICT may improve locoregional control for inoperable LAHNC patients who will undergo CCRT. Although this result is encouraging, it should be interpreted cautiously because long-term outcomes were not assessed and randomization was not used in this study. To verify whether this improvement in tumor response results in improved overall survival, randomized controlled trials with longer follow-up are required. While complete response is a vital initial surrogate marker reflecting locoregional control of disease, survival and quality of life outcomes are crucial for translating these results into clinical practice.

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• The authors declare no conflict of interest.

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Clinical trial registration

Not applicable

Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding authors per reasonable request.

Code availability

No custom code was used.

Authors' contributions

Sajib Kumar Talukdhar, MD. Zillur Rahman Bhuiyan and Sarwar Alam contributed to the conception, design, and final drafting of the manuscript. Sajib Kumar Talukdhar, Moumita Ghosh and Mohammad Jahan shams contributed to data collection. All authors contributed to the primary drafting of the manuscript. Sarwar Alam supervised the study. All authors approved the final version for submission.

Ethics approval

This study was approved by the Institutional Review Board (IRB) of Bangladesh Medical University, Dhaka, Bangladesh.

Consent to participate

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Declaration on generative AI and AI-assisted technologies in the writing process

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