OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Oncology**

Comparison of Outcome of Concurrent Chemoradiotherapy and Sequential Chemoradiotherapy in Locally Advanced, Inoperable Squamous Cell Carcinoma of Head and Neck Region

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DOI: 10.36348/sjmps.2024.v10i05.005 | **Received:** 22.03.2024 | **Accepted:** 27.04.2024 | **Published:** 24.05.2024

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Abstract

Background: Head and neck cancer is prevalent in Bangladesh, with a majority of patients presenting with locally advanced, inoperable disease. This study aimed to compare the effectiveness and accessibility of concurrent and sequential (CCRT with RT) chemoradiotherapy in treating this condition, addressing a debate among oncologists. ***Materials and Methods:*** A quasi-experimental study at Rajshahi Medical College Hospital (June 2019 - May 2020) involved 60 inoperable head and neck cancer patients, comparing concurrent chemoradiotherapy with Cisplatin and sequential chemoradiotherapy with Paclitaxel and Cisplatin, monitoring treatment response and toxicities. ***Results:*** The mean age was 56.1 (±9.5) years in Arm-A and 56.9 (±9.4) years in Arm-B. The primary endpoint was loco-regional control and early toxicities. In the final response, 14 weeks after the completion of treatment, the overall loco-regional control rate was 86.67% and 76.67% in Arm-A and Arm-B, respectively. Severe toxicities include grade 3 reaction only and happened 18(58%) vs 13(42%) in Arm-A and Arm-B, respectively. Among severe toxicities, mucositis and skin reaction were higher in the concurrent Arm and anemia and neutropenia were higher in the sequential Arm. However, there was no actual difference in the two treatment modalities (p=>0.05). The overall treatment time was short in concurrent chemoradiotherapy (49 vs 133 days) and lower treatment cost as well, which was statistically significant (p=<0.0001). ***Conclusion:*** concurrent chemoradiotherapy proves cost-effective and accessible, demonstrating outcomes similar to sequential chemoradiotherapy. It stands as a viable treatment choice for locally advanced, inoperable head and neck squamous cell carcinoma.

Keywords: Head and Neck Cancer, Squamous Cell Carcinoma, Treatment Comparison, Sequential Chemoradiotherapy, Treatment Toxicities.

INTRODUCTION

The global cancer burden, with 19.3 million new cases and 10 million deaths in 2020, underscores the pressing healthcare challenges worldwide, exacerbated by factors like population growth, aging, and socio-economic influences [1]. Bangladesh, facing 156,775 new cancer cases, particularly grapples with significant numbers of head and neck cancer (HNC) cases, constituting approximately 20% of total cancer instances [2]. Hospital-based cancer registry data from 2015 to 2017 in Bangladesh revealed that 10.5% of newly diagnosed cases involved HNC, predominantly affecting males (62.2%) and manifesting most commonly in the

lip and oral cavity (54.6%) [3]. With an estimated 1.3 to 1.5 million cancer patients in Bangladesh, 66% aged over 30, the healthcare challenges posed by cancer, especially HNC, are profound [4]. Risk factors such as tobacco use, alcohol consumption, petroleum exposure, and human papillomavirus (HPV) play pivotal roles in HNC incidence, necessitating effective treatment strategies [5-7].

Radiation therapy stands as a crucial modality for HNC treatment, but challenges exist, particularly with factors like smoking during therapy, age, and tumor size influencing outcomes [8-9]. Radiobiological principles guide the delicate balance of killing tumor cells while sparing normal ones during radiation therapy [10]. Two main treatment approaches, concurrent chemoradiotherapy (CCRT) and sequential chemoradiotherapy (SCRT), present distinct advantages and disadvantages. CCRT, with shorter treatment times and radiation enhancement, is favored for local and regional control but comes with increased toxicity [11]. SCRT, while minimizing side effects, extends treatment duration and lacks local synergy [12]. The evolving landscape of HNC treatment emphasizes organ preservation, combining surgery and nonsurgical methods, and recent advancements in chemoradiotherapy. CCRT has become the standard for local and regional control, with ongoing research exploring induction chemotherapy's potential [13]. Despite advancements, challenges persist, warranting effective strategies to address local and distant recurrences and reduce HNC-related mortality [14]. Controversies and debates surround treatment approaches, but the primary goal remains to achieve loco-regional control for enhanced curative efficacy in HNC.

Objectives

General Objective

- To compare the response and early toxicities of treatment with concurrent chemoradiotherapy and sequential chemoradiotherapy in the treatment of locally advanced, inoperable, squamous cell carcinoma of the head and neck region.

Specific Objectives:

- To assess and compare the response regarding symptomatic improvement, tumor, and nodal size reduction, stage, site, degree of differentiation, and performance status in two treatment modalities.
- To assess and compare the early toxicities associated with concurrent and sequential chemoradiotherapy.
- To determine the demographic characteristics of the patients.

MATERIALS AND METHODS

Study Design

This quasi-experimental study was conducted at Rajshahi Medical College Hospital's Department of Radiotherapy in Rajshahi, Bangladesh, over one year from June 1, 2019 to May 31, 2020. The study involved a total of 60 patients who had histologically confirmed locally advanced, inoperable squamous cell carcinoma of the head and neck region. These patients were actively receiving treatment at the Department of Radiotherapy during the specified time frame and the study aimed to compare the outcomes of two different treatment modalities, concurrent chemoradiotherapy and sequential chemoradiotherapy.

Inclusion Criteria

- Patients of locally advanced, inoperable, biopsy-proven squamous cell carcinoma of head and neck region with stage III, IVA and IVB disease.

Exclusion Criteria

- ECOG performance status (PS) >2
- Age below 18 and above 70 years to include adult population with more life expectancy.
- Patients with a history of prior chemotherapy or radiotherapy to the head and neck region.
- Initial surgery (excluding diagnostic biopsy) or radiotherapy of the primary site.
- Pregnant or lactating women to avoid any harm to the baby.
- Uncontrolled serious concomitant medical illness, including heart disease, diabetes mellitus, hypertension and renal disease.
- Patient with uncontrolled infection.

Treatment Modalities

1. **Arm-A (Concurrent Chemoradiotherapy):** Patients in this group received concurrent chemoradiotherapy with 30 mg/m² Cisplatin. Cisplatin was administered starting from the first day of radiotherapy and continued weekly until the completion of radiotherapy.
2. **Arm-B (Sequential Chemoradiotherapy):** This group treated patients with sequential chemoradiotherapy. This involved administering Paclitaxel at 175 mg/m² and Cisplatin at 75 mg/m² on Day 1, with three-week intervals for three cycles. After a three-week gap, patients received radiotherapy at 200cGy/fraction, five days a week, for a total of 66Gy delivered in 33 fractions. The radiotherapy was performed using a Telecobalt-60 machine.

Data Collection

Patients were selected from those attending the Department of Radiotherapy in Rajshahi Medical College Hospital, who met selection criteria and

distributed in Arm-A and Arm-B upon the researcher's judgment. Patients were interviewed before enrollment into the study, and the treatment protocol's aim, objective, procedure, risk, and benefits were explained. After selecting the patients, informed written consent was taken in Bangla before they participated in the study. Response and toxicities were evaluated and recorded in a semi-structured data collection form.

Data Analysis

The data was tabulated in separate tables for both Arm-A and Arm-B. It was checked, edited, coded manually, and entered into the computer. Data analysis was done according to the study's objective by using the IBM SPSS (Statistical Package for the Social Sciences) software program for Windows, version 24, available in the institute. The data was analyzed using the study's 't-test for continuous variables and the Chi-square ($\chi 2$) test for categorical variables. The results were presented in text, table, and figures. All reported *p* values were two-sided; $p < 0.05$ was considered statistically significant.

Ethical Consideration

Prior to the commencement of the study, the research protocol was approved by the institutional review board and Ethical committee of Rajshahi Medical College. Permission for the study was also obtained from the Department of Radiotherapy. All the potential participants were informed about the nature of the study. They were explained about the study's aim, objective, procedure, risk, benefit and their right to refuse or accept to participate in easily understandable language. Written informed consent was taken from each patient. It was assured that all patient information would be kept secret and no participant would be gained financially from the study.

RESULTS

In this quasi-experimental study, demographic features were similar in both Arms, with insignificant differences. The mean age was 56.1 (± 9.5) in Arm-A and 56.9 (± 9.4) in Arm-B, and 76.67% were over 50. Males dominated, with a ratio of 3.6:1. Notably, 75% were smokers, maintaining a 3:1 smoker-to-non-smoker ratio.

Table 1: Age distribution of patients in two Arms (N=60)

Age Group (In years)	Arm A		Arm B		df	χ^2	p-value
	n=30	%	n=30	%			
30-39	2	6.67%	1	3.33%	3	0.539	0.915
40-49	5	16.67%	6	20.00%			
50-59	10	33.33%	9	30.00%			
60-69	13	43.33%	14	46.67%			
Mean ± SD	56.1±9.5		56.9±9.4				
Range (min-max)	38-69		30-69				

Arm-A: Concurrent chemo-radiation
Arm-B: Sequential chemo-radiation
Statistically, there is no significant difference between Arm-A and Arm-B.

In the study, most patients were in the age group 60-69 (43.3% in Arm A and 46.7% in Arm B). The lowest number of patients was in 30-39 age group (6.7% in Arm A and 3.3% in Arm B). No patient was in 18-29 age group.

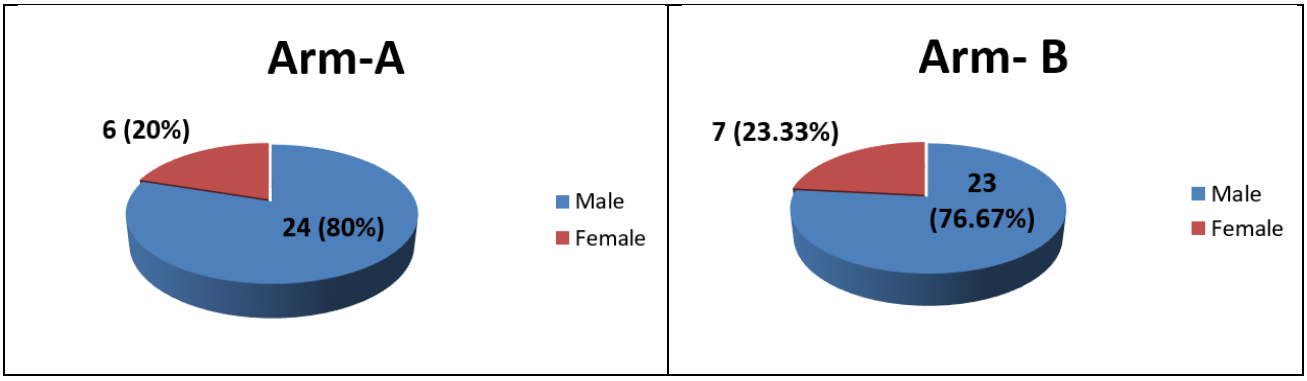

Figure 1: Distribution of sex in two Arms (N= 60)

Out of 60 patients, 47 (78.33%) were male, and the male-female ratio was 3.6:1 in the study group ($P = 0.75$). 80% in Arm-A and 76.67% in Arm-B were male.

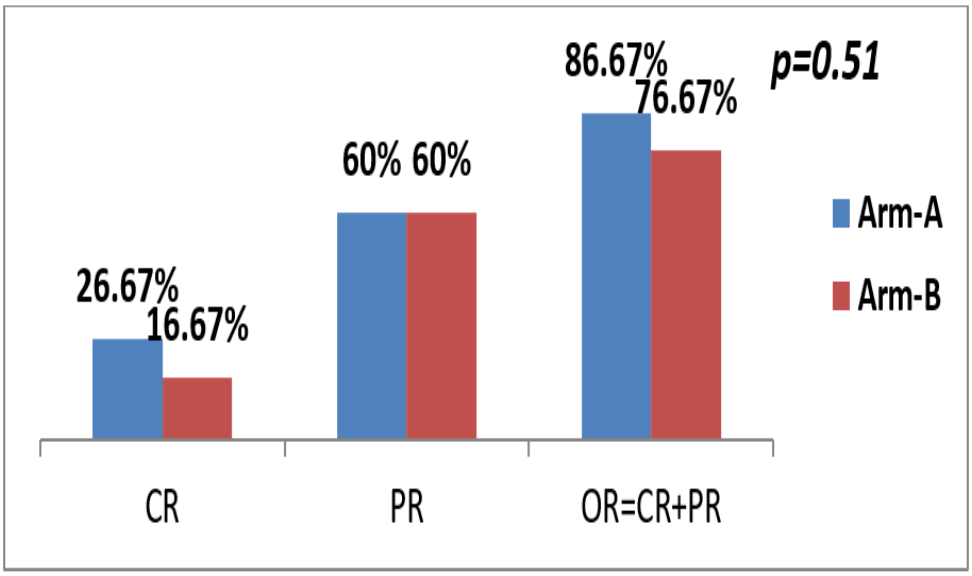

Figure 2: Overall response in two Arms (N=60)

In Arm-A, complete response was 26.67% and partial response was 60%. In Arm-B, the complete response was 16.67% and the partial response 60%. Overall response in Arm-A 86.67% and in Arm-B 76.67%.

Table 2: Treatment-related cost in two Arms (N=60)

Trait	**Arm A (n= 30)**		**Arm B (n= 30)**			
	Mean	SD	Mean	SD	t-test	*p-value*
Treatment cost (taka)	12179	845.35	47740	2365.27	77.4	<0.0001

The treatment-related cost was lower in Arm-A rather than Arm-B and the treatment duration was 49 days in concurrent Arm-A rather than 133 days in sequential Arm-B. So, Concurrent chemo-radiation was cost-effective and more accessible to the patients.

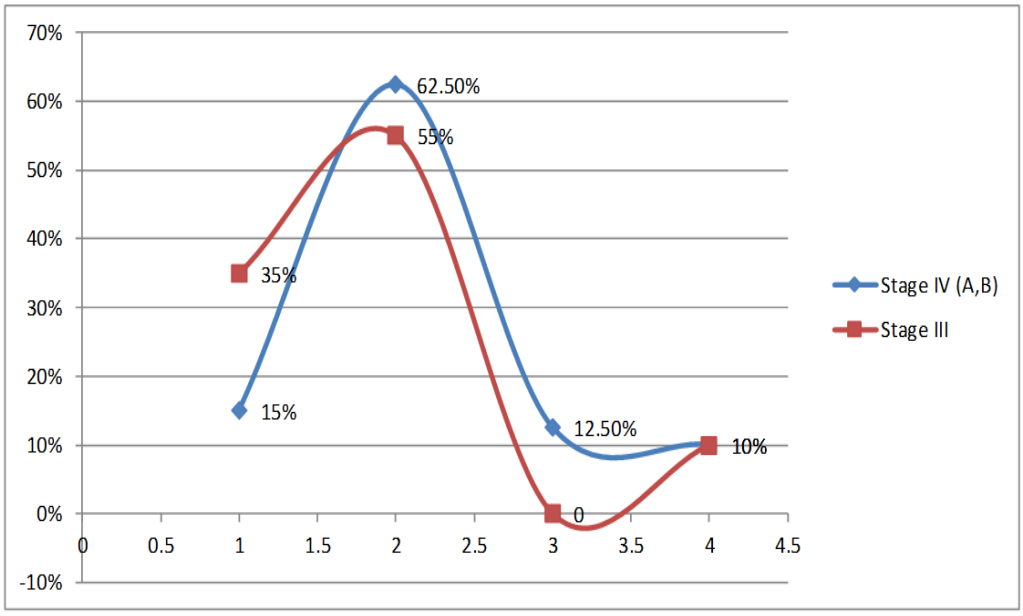

Figure 3: Comparison of response according to stage in two Arms (N= 60)

For stage IV (A, B) the square value 0.848 and *p* value 0.837 and for stage III, the Chi-square value 0.60 and *p*-value 0.740. Statistically no significant difference between Arm-A and Arm-B. For Stage IV (A, B) disease complete response was 15%. Partial response was 62.50%. For Stage III disease complete response was 35% and partial response was 55%. No Progressive disease in stage III and 12.50% in Stage IV (A, B). Stable

disease was 10% in both stages. Overall response in Stage IV (A, B) was 77.5% (37.5% vs 40%) and Overall response in Stage III was 90% (55% vs 35%) in Arm-A and Arm-B respectively.

Table 3: Distribution of the patients according to non-hematological toxicities (N=60)

Toxicity	Arm -A (n=30)		Arm-B (n=30)		*χ2*	*p-value*
	n	%	n	%		
Nausea						
Absent	16	53.33%	12	40%	1.153	0.561
Gr 1	10	33.33%	12	40%		
Gr 2	04	13.33%	06	20%		
Vomiting						
Absent	23	76.67%	20	66.7%	0.742	0.689
Gr 1	05	16.67%	07	23.33%		
Gr 2	02	6.67%	03	10%		
Diarrhea						
Absent	26	86.67%	21	70%	2.531	0.281
Gr 1	03	10%	06	20%		
Gr 2	01	3.33%	03	10%		
Mucositis						
Absent	00	00	00	00	1.517	0.468
Gr 1	04	13.33%	6	20%		
Gr 2	16	53.33%	18	60%		
Gr 3	10	33.33%	6	20%		
Skin reaction						
Absent	00	00	00	00	1.181	0.554
Gr 1	14	46.67%	16	53.33%		
Gr 2	10	33.33%	11	36.67%		
Gr 3	06	20%	03	10%		
Xerostomia						
Absent	00	00	00	00	0.271	0.602
Gr 1	12	40%	14	46.67%		
Gr 2	18	60%	16	53.33%		

Mucositis, skin reaction and xerostomia were common radiation-induced toxicities. From the beginning of treatment, patients were asked to avoid using toothbrushes, smoking, pans, betel nuts, spicy and hard foods. A soft, semisolid and liquid high-calorie, protein-rich diet was advised. Mucositis was treated with mouthwash, antifungal and frequent gurgling with salt mixed with lukewarm water from the very 1st day of radiotherapy. Cocktail preparation with topical lidocaine, antacid and phenargan was advised to reduce the local effect. Evomucy spray was also helpful for the rapid relief of painful oral ulcers and dry mouth. Mucaine gel 20 minutes before a meal was useful in some cases. The pain was managed according to the WHO analgesic ladder. Total parenteral nutrition was given for patients unable to maintain adequate nutrition enterally with significant weight loss (>10%).

In xerostomia, frequent rinsing with water, vitamin C, sugar-free gum, lozenges and use of petroleum jelly over lips frequently and bedside humidifier during sleeping hours was advised. Sialogogue (Pilocarpine) was added to stimulate saliva secretion as required. Tablet Xylimelt sublingual administration was also effective for dry mouth. Fluorinated dentifrice was used to control dental caries. Antibiotics and antifungals were added for any suspected infection.

All patients were advised to take general skin care. Patients were encouraged to wash irradiated skin daily, pat dry with soft tissue and avoid friction, rubbing, or scratching. Besides tight-fitting collars, chemical skin products, perfumed soap, extreme heat or cold and wet shavings were advised to avoid. For dry desquamation emollient, gentian violet and topical steroid (1% hydrocortisone) were applied. Moist desquamation was managed with regular dressing and systemic antibiotics. 21 patients had to hold RT for an average of 5.48 ± 1.39 days and treatment gap correction was done according to institutional protocol using the BED (Biological Equivalent Dose) formula. Nausea and vomiting were treated with high emetogenic protocol and diarrhea was treated according to local protocol.

Table 4: Distribution of the patients according to hematological toxicities (N=60)

Toxicity	Arm -A(n=30)		Arm-B (n=30)		$\chi 2$	*p-value*
	n	%	n	%		
Anemia						
Absent	23	76.67%	20	66.67%	0.853	0.836
Gr 1	04	13.33%	05	16.67%		
Gr 2	02	6.67%	03	10%		
Gr 3	01	3.33%	02	6.67%		
Thrombocytopenia						
Absent	26	86.67%	23	76.67%	1.017	0.601
Gr 1	03	10%	05	16.67%		
Gr 2	01	3.33%	02	6.67%		
Neutropenia						
Absent	25	83.33%	21	70%	1.547	0.671
Gr 1	02	6.67%	04	13.33%		
Gr 2	02	6.67%	03	10%		
Gr 3	01	3.33%	02	6.67%		

Anemia was corrected by blood transfusion. Thrombocytopenia was managed by oral Papaya leaf extract and Eltrombopag. Neutropenia was corrected by cytotoxic dose reduction, Granulocyte colony-stimulating factor, antibiotic, antifungal, maintaining fluid and electrolyte balance and supportive management as required. A total 31 events of serious toxicities occurred in 58% in Arm-A and 42% in Arm-B. Toxicities were not significant ($p>0.05$) in any Arm. All the toxicities in both Arms were manageable and no life-threatening event occurred.

DISCUSSION

The most commonly involved cancer sites in this study were the oral cavity (36.67%) and larynx (30%). Other less commonly involved sites included the oropharynx (20%) and hypopharynx (13.33%). These findings correlate with the data from [1, 4, 15] on the estimated head and neck cancer incidence in Bangladesh. Most patients presented with symptoms such as painless masses or difficulty in swallowing. Other common presentations included hoarseness of voice, cough, dyspnea, stridor, pain and oral ulcers. This pattern of presentation is consistent with the findings described by [7], who noted that most head and neck cancer patients present with difficulty in swallowing and neck lumps.

In terms of cancer staging, 40 (66.67%) patients were classified as stage IV (A, B), with 18 (45%) in Arm-A and 22 (55%) in Arm-B. Additionally, 20 (33.33%) patients were categorized as stage III, with 12 (60%) in Arm-A and 8 (40%) in Arm-B. Lymph node involvement was observed in 80% of patients at the presentation time. Furthermore, most patients had moderately differentiated tumors (43.33%). Regarding performance status, most patients had a performance status of 1 (46.67%). These findings are more or less similar to those of the study conducted by [17]. In their study, 46% of patients were in performance status 1 and approximately 87% were in stage IV (A, B) disease, with the majority having lymph node involvement at the time of presentation.

In this study, symptomatic improvement was achieved in 80% of patients in Arm-A and 66.67% in Arm-B, although this difference was not statistically significant ($p=0.242$). In terms of overall response, Arm-A demonstrated a rate of 86.67%, with a complete response in 26.67% of cases and a partial response in 60%. In Arm-B, the overall response was 76.67%, with a complete response in 16.67% of cases and a partial response in 60%. These results align with concurrent chemoradiotherapy exhibited a better overall response than sequential chemoradiotherapy (83.3% vs. 94.4%). Notably, the highest overall response rate was observed in cases of laryngeal carcinoma, with 88% responding well [17]. The overall treatment time was significantly shorter in Arm-A (49 days) compared to Arm-B (133 days), leading to fewer hospital admissions. Treatment compliance and cost-effectiveness favored concurrent chemoradiotherapy.

Hematologic toxicities were more pronounced in sequential Arm-B due to high-dose chemotherapy. In Arm-B, two patients developed Grade 3 neutropenia and two had Grade 3 anemia. In Arm-A, one patient developed Grade 3 neutropenia and one developed Grade 3 anemia. A similar study found toxicities that required hospital admission [18]. Both concurrent and sequential chemoradiotherapy approaches resulted in the observation of CT and RT-related toxicities. RT-related toxicities were more common in concurrent Arm-A, with oral mucositis, xerostomia and skin reactions observed in all patients during this period. Severe mucositis was noted in 33.3% of Arm-A and 20% in Arm-B and serious skin reactions were observed in 20% of Arm-A and 10% of Arm-B. Grade 2 xerostomia was also observed in 60% of patients in Arm-A and 53.3% in Arm-B. These findings align with found similar toxicities in concurrent and sequential arms [19,20].

A total of 21 patients had to hold radiotherapy due to toxicity management, with an average break duration of 5.5 (±1.4) days. Gap correction was performed according to the institutional protocol using the BED formula. A similar study, toxicity-related breaks in radiotherapy were observed in 17.6% of patients [21-23]. A total of 31 events of serious toxicities occurred in the study, with 18 (58%) in Arm-A and 13 (42%) in Arm-B. Other less common and less severe toxicities included thrombocytopenia, nausea, vomiting, diarrhea, neurotoxicity, nephrotoxicity, weight loss and hypersensitivity. All toxicities were manageable within the study's clinical setting. The study doesn't establish superiority but emphasizes better compliance and cost-effectiveness with concurrent chemoradiotherapy for locally advanced head and neck cancer, highlighting the importance of tailored treatment decisions and contributing significantly to understanding treatment in Bangladesh.

CONCLUSION

This study aimed to compare the effectiveness of concurrent and sequential chemoradiotherapy between the two approaches that were mainly used. There is no difference in effectivity and toxicity between these two treatment modalities. Since the treatment duration and cost are lower in concurrent than sequential chemoradiotherapy, concurrent chemoradiotherapy can be a choice of treatment for patients with locally advanced inoperable squamous cell carcinoma of the head and neck region.

Recommendations

Based on the findings of the study, there are some recommendations:

- Concurrent chemoradiotherapy could be practiced as a more compliant and cost-effective approach to patients with similar efficacy.
- The study should continue to determine the treatment's overall survival and late toxicity.

Acknowledgment

I deeply thank Dr. Ashim Kumar Ghosh, my dedicated guide, for his unwavering support throughout this thesis. I am thankful to Prof. Dr. Md. Abdul Bari, Prof. Dr. Sarwar Alam, and Dr. Rawshan Ara Khatun for their valuable contributions and guidance. Thanks to my family, especially my beloved wife, Khaleda Ifaet, for their unwavering support. I also appreciate the cooperation of my colleagues, research assistant and the staffs at the Department of Radiotherapy, Rajshahi Medical College Hospital.

Funding: No funding sources

Conflict of Interest: None declared

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