

Research Article

Comparison of Outcome and Toxicities of Concurrent Chemo-radiation Versus Sequential Chemo-radiation in Inoperable Locally Advanced Non-small Cell Lung Cancer

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Abstract

Concurrent chemoradiotherapy (CCRT) is the standard of care for inoperable locally advanced non-small cell lung cancer (LA-NSCLC), but its associated toxicities pose a significant challenge, particularly in resource-limited settings, and sequential chemoradiotherapy (SCRT) may offer a more feasible alternative, though with potentially inferior efficacy. This quasi-experimental study, conducted from January 2022 to June 2023, aimed to compare the treatment outcomes and toxicity profiles of CCRT versus SCRT in a real-world Bangladeshi cohort by enrolling 66 patients with LA-NSCLC (Stage IIIA-IIIC) allocated to Arm A (CCRT; n=33), receiving weekly paclitaxel (45 mg/m²) and carboplatin (AUC 2) with concurrent radiotherapy (50 Gy/25 fractions), or Arm B (SCRT; n=33), receiving three cycles of induction paclitaxel (175 mg/m²) and carboplatin (AUC 6) followed by the same radiotherapy regimen, with treatment response assessed using RECIST 1.1 and toxicities graded per CTCAE v5.0. The study population was predominantly male (77.3%), with a mean age of 55.9 years, and had a high prevalence of squamous cell carcinoma (57.6%), and at the 12-week follow-up, the CCRT arm demonstrated a higher complete response rate compared to the SCRT arm (51.5% vs. 33.3%, p=0.535) and a higher overall response rate (84.8% vs. 72.7%, p>0.05), though these differences were not statistically significant, but CCRT was associated with a higher incidence of acute toxicities, notably Grade 2-3 esophagitis (30.3% vs. 15.2%) and Grade 2-3 leucopenia (21.3% vs. 12.1%), while all other hematological and non-hematological toxicities were comparable between the arms and not statistically significant. In conclusion, while CCRT showed a clinically meaningful improvement in treatment response rates, it was associated with increased, though manageable, acute toxicities, and the lack of statistical significance in efficacy, combined with the higher toxicity burden, suggests that SCRT remains a viable and potentially more tolerable treatment option for selected patients in resource-constrained environments where supportive care capabilities are limited.

Keywords

Non-small Cell Lung Cancer (NSCLC), Locally Advanced Lung Cancer, Concurrent Chemoradiotherapy, Sequential Chemoradiotherapy, Treatment Outcomes, Toxicity Profile, Therapeutic Efficacy, Chemoradiation Sequencing

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1. Introduction

Lung cancer remains the most lethal malignancy worldwide, accounting for approximately 1.8 million deaths annually and representing 18% of all cancer-related mortality [1]. Among lung cancer subtypes, non-small cell lung cancer (NSCLC) constitutes 75–85% of cases, with about 30% of patients presenting with locally advanced (stage III) disease at diagnosis [2, 3]. The management of unresectable locally advanced NSCLC (LA-NSCLC) presents a significant therapeutic challenge, requiring a careful balance between local disease control and systemic treatment to address micrometastatic spread [4]. The prognosis for LA-NSCLC remains suboptimal, with 5-year survival rates ranging from 15–30%, depending on tumor stage, histology, and treatment strategy [5]. Historically, radiotherapy alone was the primary treatment modality, but its limitations in controlling both local and distant disease led to the integration of chemotherapy, first sequentially and later concurrently, to improve outcomes [6]. The shift toward combined-modality therapy was driven by the recognition that NSCLC is often a systemic disease at diagnosis, necessitating both locoregional and systemic treatment approaches [7].

The evolution of treatment paradigms for LA-NSCLC has been shaped by numerous clinical trials comparing sequential chemoradiotherapy (SCRT) with concurrent chemoradiotherapy (CCRT). SCRT, where chemotherapy is administered prior to radiotherapy, was initially favored due to its more manageable toxicity profile and theoretical advantages in reducing tumor burden before radiation [8]. Early studies, such as the CALGB 8433 trial, demonstrated that induction chemotherapy followed by radiotherapy significantly improved survival compared to radiotherapy alone (median survival 13.7 vs. 9.6 months, $p=0.006$) [9]. However, subsequent research revealed that SCRT was inferior to CCRT in terms of long-term survival, primarily due to higher locoregional failure rates [10]. The NSCLC Collaborative Group meta-analysis, which included 1,205 patients, showed a 4.5% absolute survival benefit at 5 years with CCRT ($p=0.004$), establishing it as the standard of care for eligible patients [11]. The superiority of CCRT is attributed to enhanced radiosensitization, where chemotherapy potentiates the effects of radiation, leading to improved tumor control [12]. Key trials such as RTOG 9410 further reinforced this approach, demonstrating a median overall survival of 17.0 months with CCRT compared to 14.6 months with SCRT ($p=0.046$) [13].

Despite its efficacy, CCRT is associated with increased acute toxicity, including severe esophagitis, pneumonitis, and hematologic adverse events, which can limit its applicability in certain patient populations [14]. The Fournel et al. trial, which randomized 205 patients to SCRT or CCRT, reported grade 3+ esophagitis in 32% of CCRT patients compared to just 3% in the SCRT group ($p<0.0001$) [15]. These toxicities are particularly concerning in older patients and those with comorbidities, who may not tolerate the aggressive nature of

concurrent treatment [16]. Additionally, the logistical challenges of delivering CCRT in resource-limited settings, such as prolonged wait times for radiotherapy and limited supportive care infrastructure, further complicate its widespread adoption [17]. In countries like Bangladesh, where healthcare resources are constrained and a significant proportion of patients present with advanced disease, SCRT may serve as a more feasible alternative, particularly for those who cannot tolerate the acute toxicities of CCRT or face delays in accessing radiotherapy [18].

The predominance of squamous cell carcinoma in Bangladesh, as opposed to the rising incidence of adenocarcinoma in Western countries, adds another layer of complexity to treatment decisions [19]. Data from the National Institute of Cancer Research and Hospital (NICRH) indicate that squamous cell carcinoma accounts for 67.6% of NSCLC cases in Bangladesh, compared to 23.5% for adenocarcinoma [20]. This histologic distribution may influence treatment response and toxicity profiles, as squamous cell carcinomas are often centrally located and more likely to cause obstructive symptoms, potentially affecting radiotherapy planning and tolerance [21]. Furthermore, socioeconomic factors, including limited access to advanced diagnostics and targeted therapies, contribute to disparities in outcomes between high-income countries and low- and middle-income countries (LMICs) [22].

Given these contextual challenges, there is a critical need for region-specific data comparing CCRT and SCRT in Bangladeshi patients. While global evidence strongly supports CCRT as the standard of care, its applicability in LMICs remains uncertain due to differences in patient demographics, disease biology, and healthcare infrastructure [23]. This study aims to address this gap by evaluating the efficacy, toxicity, and feasibility of CCRT versus SCRT in a real-world Bangladeshi cohort. Specifically, we will assess treatment response in terms of tumor regression and symptom relief, compare acute toxicities, and identify sociodemographic and clinical predictors of outcomes. Our hypothesis is that CCRT will demonstrate superior locoregional control and survival but with higher toxicity, while SCRT will be better tolerated, particularly in high-risk subgroups. The findings of this study will provide evidence-based guidance for optimizing chemoradiation sequencing in resource-limited settings, where treatment accessibility and patient comorbidities necessitate tailored approaches [24].

2. Materials and Methods

2.1. Study Design and Setting

This quasi-experimental study was conducted at the Department of Radiotherapy, Rajshahi Medical College Hospital, Bangladesh, from January 2022 to June 2023. The study

compared two treatment regimens for inoperable locally advanced non-small cell lung cancer (LA-NSCLC): concurrent chemoradiotherapy (CCRT) versus sequential chemoradiotherapy (SCRT). Institutional ethical approval (Ref: RMCH/IRB/2021-45) was obtained prior to commencement, and written informed consent was collected from all participants.

2.2. Study Population and Eligibility Criteria

The study population consisted of patients aged 18–75 years with histopathologically confirmed locally advanced non-small cell lung cancer (LA-NSCLC) classified as stage IIIA–IIIC according to the AJCC 8th edition staging system [2]. Key inclusion criteria required patients to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 [25], along with adequate hematologic parameters (hemoglobin ≥ 10 g/dL, white blood cell count $\geq 4,000/\mu\text{L}$, and platelets $\geq 150,000/\mu\text{L}$) and preserved organ function (serum bilirubin ≤ 1.5 mg/dL and creatinine ≤ 1.5 times the upper limit of normal) [26]. Patients were excluded if they had previously received thoracic radiotherapy or chemotherapy, presented with metastatic disease or synchronous primary malignancies, or had severe comorbidities including uncontrolled cardiac disease, diabetes mellitus, or hypertension that could compromise treatment safety or tolerability [27]. This careful selection aimed to optimize the assessment of treatment efficacy while minimizing confounding factors that could influence outcomes.

2.3. Sample Size Calculation

The sample size was determined using the formula for comparing two proportions [28]:

$$n = [p_1(100 - p_1) + p_2(100 - p_2)] / (p_1 - p_2)^2 * (Z_{\alpha} + Z_{\beta})^2$$

Where:

$p_1 = 74\%$ (response rate for CCRT [29]).

$p_2 = 40.2\%$ (response rate for SCRT [30]).

$Z_{\alpha} = 1.96$ (95% CI), $Z_{\beta} = 0.85$ (80% power).

This yielded 33 patients per arm (total $N=66$), adjusted for 10% attrition.

2.4. Treatment Protocols

The treatment protocols were divided into two distinct arms. For patients in the concurrent chemoradiotherapy arm (Arm A), treatment consisted of radiotherapy delivering 50 Gy in 25 fractions (2 Gy per fraction, 5 fractions per week) using a telecobalt-60 machine (EQUINOX-100) with parallel-opposed fields covering the primary tumor with a 2 cm margin and involved lymph nodes [31]. Concurrent chemotherapy comprised weekly administration of paclitaxel (45 mg/m²) and carboplatin (AUC 2) given 1.5 hours prior to radiotherapy [32]. To prevent hypersensitivity reactions, patients received premedication with dexamethasone (20 mg), pheniramine (75 mg), and omeprazole (20 mg) before each chemotherapy

session [10]. In the sequential chemoradiotherapy arm (Arm B), patients first received induction chemotherapy consisting of three cycles of paclitaxel (175 mg/m²) plus carboplatin (AUC 6) administered at 3-week intervals [4]. Following a 3-week recovery period after completion of chemotherapy, patients then underwent the identical radiotherapy regimen as described for Arm A [33]. This sequential approach allowed for systemic treatment prior to local therapy while maintaining the same radiation dose and fractionation schedule in both treatment groups.

2.5. Response and Toxicity Assessment

Treatment response and toxicity were systematically evaluated throughout the study period. Tumor response was assessed according to RECIST 1.1 criteria [34], with CT scans of the chest and abdomen performed at baseline, immediately post-treatment, and during the 12-week follow-up visit to document objective response rates and disease progression. Treatment-related toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [35], with particular attention to acute radiation-induced toxicities including esophagitis, pneumonitis, and dermatitis, as well as hematologic toxicities such as anemia, leukopenia, and thrombocytopenia. Patient-reported outcomes and quality of life measures were monitored through weekly evaluations of ECOG performance status [36], providing a comprehensive assessment of both treatment efficacy and tolerability. This rigorous monitoring protocol ensured timely detection and management of adverse events while maintaining standardized documentation of therapeutic outcomes.

2.6. Statistical Analysis

Data were analyzed using SPSS v25.0. Continuous variables (tumor size, survival) were compared via unpaired t-tests; categorical variables (response rates, toxicity grades) via χ^2 tests. A p-value < 0.05 was considered significant.

2.7. Ethical Considerations

The study adhered to Declaration of Helsinki principles. Confidentiality was maintained via anonymized coding, and participants could withdraw anytime without penalty [5].

3. Results

This quasi-experimental study was conducted in the Department of Radiotherapy, Rajshahi Medical College and Hospital, Rajshahi over a period of one and half year following acceptance of protocol. After careful history taking, examination and relevant investigations a total 66 patients in inoperable locally advanced non small cell lung cancer (stage IIIA-stage IIIC) were categorized into two groups: Arm-A was treated with Inj. Paclitaxel (45 mg/m²) on day 1 and Inj.

Carboplatin (AUC 2) also on day 1, weekly with concurrent External Beam Radiation Therapy of 50 Gy over 5 weeks. Arm- B was treated with chemotherapy with Inj. Paclitaxel (175 mg/m^2) on day 1 and Inj. Carboplatin (AUC 6) also on day 1, three weekly schedule for 3 cycles followed by External Beam Radiation Therapy of 50 Gy over 5 weeks. All patients were followed- up as per guideline for 12 weeks in this study. The results and observations are given below:

From Figure 1, the mean age of patients was 55.92 ± 7.760 years (range 44-70), with no significant difference between Arm A and Arm B ($p = 0.888$). In Arm A, 78.78% were male

(3.7:1 male-to-female ratio) and 75.75% in Arm B were male (3.1:1 ratio), with no significant difference ($p = 0.760$). Most patients were from rural areas: 72.70% in Arm A and 69.70% in Arm B, with no significant difference ($p = 0.944$). The majority were illiterate (45.50% in Arm A, 51.50% in Arm B), with no significant difference ($p = 0.830$). Farmers constituted the largest occupational group (36.40% in Arm A, 39.40% in Arm B), with no significant difference ($p = 0.947$). Most patients in both arms came from lower socio-economic status (66.70% in Arm A, 72.70% in Arm B), with no significant difference ($p = 0.749$).

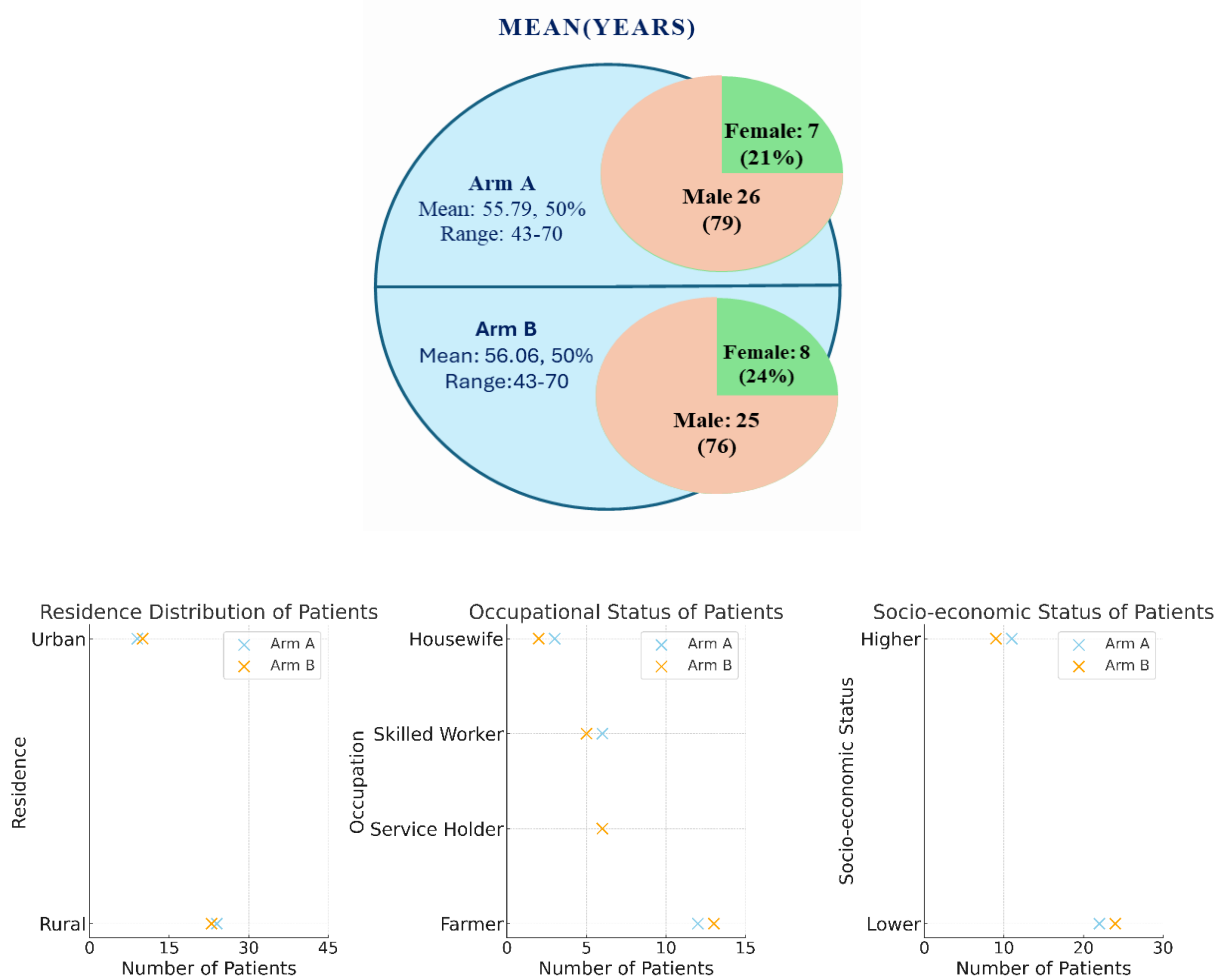


Figure 1. Baseline Characteristics of Patients in Arm A and Arm B.

Figure 2 presents the distribution of co-morbidities among the patients. Diabetes Mellitus and Hypertension were the most common co-morbidities in both arms, with 21.2% and 21.2% in Arm A and 18.2% and 24.2% in Arm B, respectively. There was no statistically significant difference between the two arms ($p > 0.05$).

In case of distribution of the risk factors, where smoking was the most common risk factor, with 75.8% in Arm A and 78.8% in Arm B. Occupational exposure was observed in 54.5% of Arm A and 60.6% of Arm B patients. Other risk factors,

such as Chronic Obstructive Pulmonary Disease (COPD) and Pulmonary TB, showed no significant difference between the two arms ($p > 0.05$). This figure illustrates the distribution of patients by involved lung, with the majority having right lung lesions—69.7% in Arm A and 66.7% in Arm B. The difference was not statistically significant ($p = 0.792$). In terms of the distribution of lesions by site, Peripheral lesions were most common, occurring in 67% of Arm A and 60% of Arm B patients, with no significant difference between the two arms ($p = 0.822$).

It also represents the distribution of patients according to TNM stages. The majority of patients in both arms were in stage IIIB—54.5% in Arm A and 45.5% in Arm B—without a significant difference ($p = 0.518$). As per this data, Squamous cell carcinoma was the most common in both arms (63.6% in Arm A and 51.5% in Arm B). The distribution of adenocarcinoma and large cell carcinoma was similar across the arms,

and the difference was not statistically significant ($p = 0.834$). As per this picture, the ECOG performance status of the patients, with most patients in both arms having a score of 1 (72.72% in Arm A and 69.70% in Arm B). The difference between the two arms was not statistically significant ($p = 0.682$).

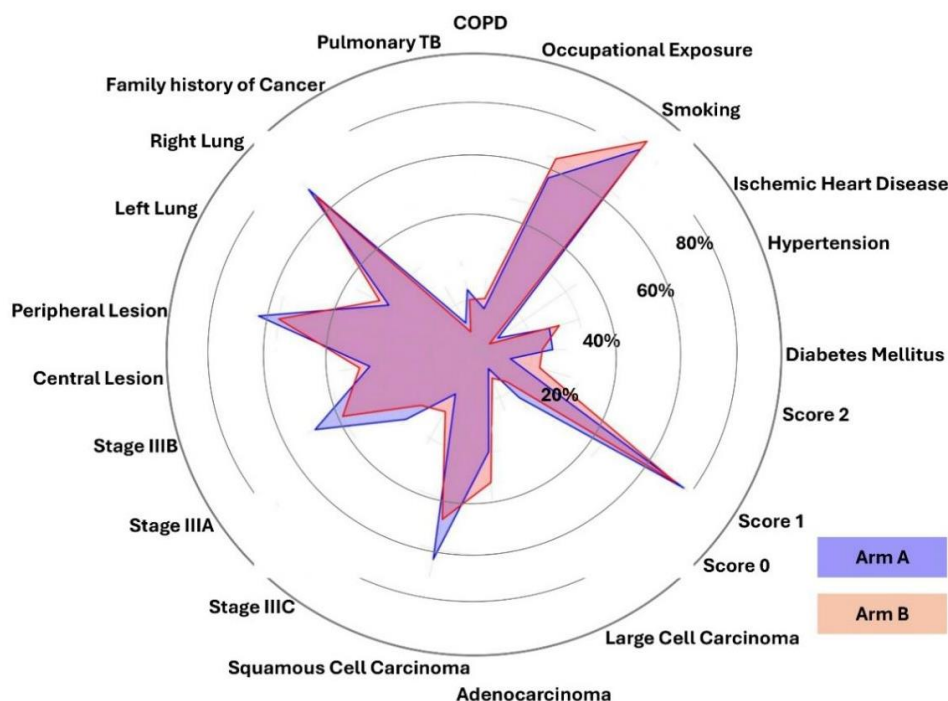


Figure 2. Baseline Characteristics, Co-morbidities, Risk Factors, and Disease Distribution of Study Patients in Arm A and Arm B.

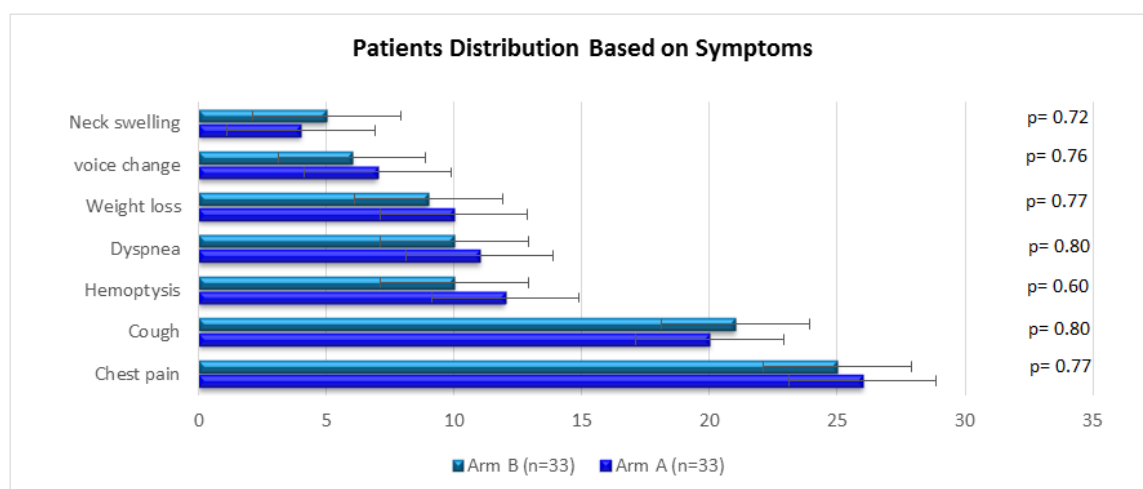


Figure 3. Distribution of the Study Patients According to Presenting Symptoms.

Above Figure 3 shows that most of patients had chest pain (78.8% in Arm-A and 75.8% in Arm-B). Next majority was cough (60.6% in Arm-A and 63.6% in Arm-B). Hemoptysis was 36.4% and 30.3% in Arm-A and Arm-B respectively.

Dyspnea was present 33.3% patients in Arm-A and 30.3% in Arm-B. Weight loss 30.3% in Arm-A and 27.3% in Arm-B. Voice change was present 21.2% in Arm-A and 18.2% in Arm-B. Neck swelling was 12.1% in Arm-A and 15.2% in

Arm-B. The difference was not statistically significant between two arms ($p > 0.05$).

Figure 4 shows that most patients in both arms experienced chest pain before treatment: 78.8% in Arm A and 75.8% in Arm B. This decreased significantly at follow-ups, with only 3% of Arm A and 6.1% of Arm B patients reporting chest pain at the 3rd follow-up. No significant difference was found between the two arms ($p > 0.05$). As per this figure, 60.6% of Arm A and 63.6% of Arm B patients had cough pre-treatment. Follow-up assessments showed a decrease in cough prevalence, with 3% of Arm A and 6.1% of Arm B patients experiencing cough at the 3rd follow-up, with no

significant difference ($p > 0.05$).

This graph indicates that 36.4% of Arm A and 30.3% of Arm B patients had hemoptysis before treatment. The prevalence reduced across follow-ups, with 3% of Arm A and 6.1% of Arm B patients reporting hemoptysis at the 3rd follow-up. Again, no significant difference was observed ($p > 0.05$).

The data depicts that 33.3% of Arm A and 30.3% of Arm B patients had dyspnea before treatment. The prevalence decreased at follow-ups, with 3% of Arm A and 6.1% of Arm B patients reporting dyspnea at the 3rd follow-up. No significant difference was found between the arms ($p > 0.05$).

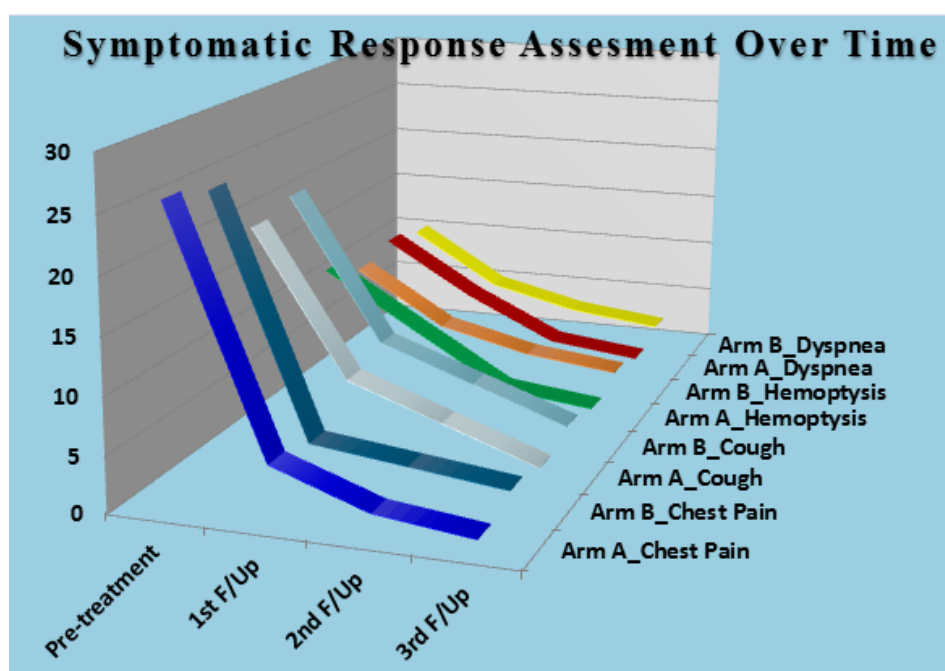


Figure 4. Symptomatic Response Assessment Over Time.

Table 1. Treatment Response Assessment at 4th, 8th, and 12th Week and by TNM Stage and ECOG Performance Status.

Category	Arm A (n=33)	Arm B (n=33)	p-value
Treatment Response at 4th Week			
Complete Response	12 (36.4%)	8 (24.2%)	0.535
Partial Response	16 (48.5%)	18 (54.5%)	
Stable Disease	5 (15.2%)	7 (21.2%)	
Treatment Response at 8th Week			
Complete Response	16 (48.5%)	10 (30.3%)	0.262
Partial Response	12 (36.4%)	14 (42.4%)	
Stable Disease	5 (15.2%)	9 (27.3%)	
Treatment Response at 12th Week			
Complete Response	17 (51.5%)	11 (33.3%)	0.535

Category	Arm A (n=33)	Arm B (n=33)	p-value
Partial Response	11 (33.3%)	13 (39.4%)	0.409
Stable Disease	3 (9.1%)	6 (18.2%)	
Progressive Disease	2 (6.1%)	3 (9.1%)	
Treatment Response by TNM Stage			
Stage IIIA			0.628
Complete Response	7 (70%)	5 (45.5%)	
Partial Response	3 (30.0%)	5 (45.5%)	
Stable Disease	0	1 (9.1%)	
Stage IIIB			0.628
Complete Response	10 (55.6%)	6 (40.0%)	
Partial Response	7 (38.9%)	7 (46.7%)	
Stable Disease	1 (5.6%)	1 (6.7%)	
Progressive Disease	0	1 (6.7%)	
Performance Status (ECOG)			0.261
Score 0			
Complete Response	7 (100%)	5 (83.3%)	
Partial Response	0	1 (16.7%)	
Score 1			0.539
Complete Response	10 (41.7%)	6 (26.1%)	
Partial Response	11 (45.8%)	12 (52.2%)	
Stable Disease	3 (12.5%)	4 (17.4%)	
Progressive Disease	0	1 (4.3%)	

*p value obtained by Chi-square Test (χ^2); Arm A: Concurrent chemoradiation, Arm B: Sequential chemoradiation.

Table 2. Toxicities during chemotherapy in Arm-B (n=33).

Toxicity		Grade 1	Grade 2	Grade 3
Hematological	Anemia	4 (12.12%)	3 (9.1%)	1 (3.03%)
	Leucopenia	5 (15.15%)	2 (6.1%)	1 (3.03%)
	Thrombocytopenia	3 (9.1%)	1 (3.03%)	0
	Nausea	5 (15.15%)	2 (6.1%)	0
Non hematological	Vomiting	2 (6.1%)	3 (9.1%)	0
	Neurotoxicity	4 (12.12%)	0	0
	Alopecia	7 (21.21%)	5 (15.15%)	0

*p value obtained by Chi-square Test (χ^2); Arm A: Concurrent chemoradiation, Arm B: Sequential chemoradiation.

From Table 1, at the 4th week, 36.4% of patients in Arm A and 24.2% in Arm B achieved a complete response, with no statistically significant difference ($p = 0.535$). Partial responses were observed in 48.5% of Arm A and 54.5% of

Arm B patients. Stable disease was found in 15.2% of Arm A and 21.2% of Arm B patients. No patients had progressive disease. At the 8th week, 48.5% of Arm A patients and 30.3% of Arm B patients had a complete response, with a significant increase in Arm A ($p = 0.262$).

Partial responses were seen in 36.4% of Arm A and 42.4% of Arm B patients. Stable disease occurred in 15.2% of Arm A and 27.3% of Arm B patients. No patients showed progressive disease. At the 12th week, 51.5% of Arm A and 33.3% of Arm B patients achieved a complete response, while partial response was found in 33.3% of Arm A and 39.4% of Arm B patients. Stable disease was present in 9.1% of Arm A and 18.2% of Arm B patients. Progressive disease occurred in 6.1% of Arm A and 9.1% of Arm B patients. No significant difference was observed across all time points ($p > 0.05$). In case of treatment response by TNM stage.

For Stage IIIA, 70% of patients in Arm A achieved a complete response, compared to 45.5% in Arm B, with no significant difference ($p = 0.409$). For Stage IIIB, 55.6% of Arm A patients achieved a complete response, compared to 40.0% in

Arm B, with no significant difference ($p = 0.628$).

For the purpose of performance status (ECOG), For patients with ECOG score 0, 100% in Arm A and 83.3% in Arm B had a complete response ($p = 0.261$). For those with ECOG score 1, 41.7% of Arm A and 26.1% of Arm B patients had a complete response ($p = 0.539$). The differences in both ECOG performance status groups were not statistically significant.

Table 2 presents the distribution of patients by toxicity grades for hematological and non-hematological side effects. Hematological toxicities included anemia (Grade 1: 12.12%, Grade 2: 9.1%, Grade 3: 3.03%), leucopenia (Grade 1: 15.15%, Grade 2: 6.1%, Grade 3: 3.03%), and thrombocytopenia (Grade 1: 9.1%, Grade 2: 3.03%). Non-hematological toxicities were nausea (Grade 1: 15.15%, Grade 2: 6.1%), vomiting (Grade 1: 6.1%, Grade 2: 9.1%), neurotoxicity (Grade 1: 12.12%), and alopecia (Grade 1: 21.21%, Grade 2: 15.15%). No Grade 3 toxicity was observed for vomiting, neurotoxicity, or alopecia. These findings highlight the most prevalent side effects and their respective grades in the study population.

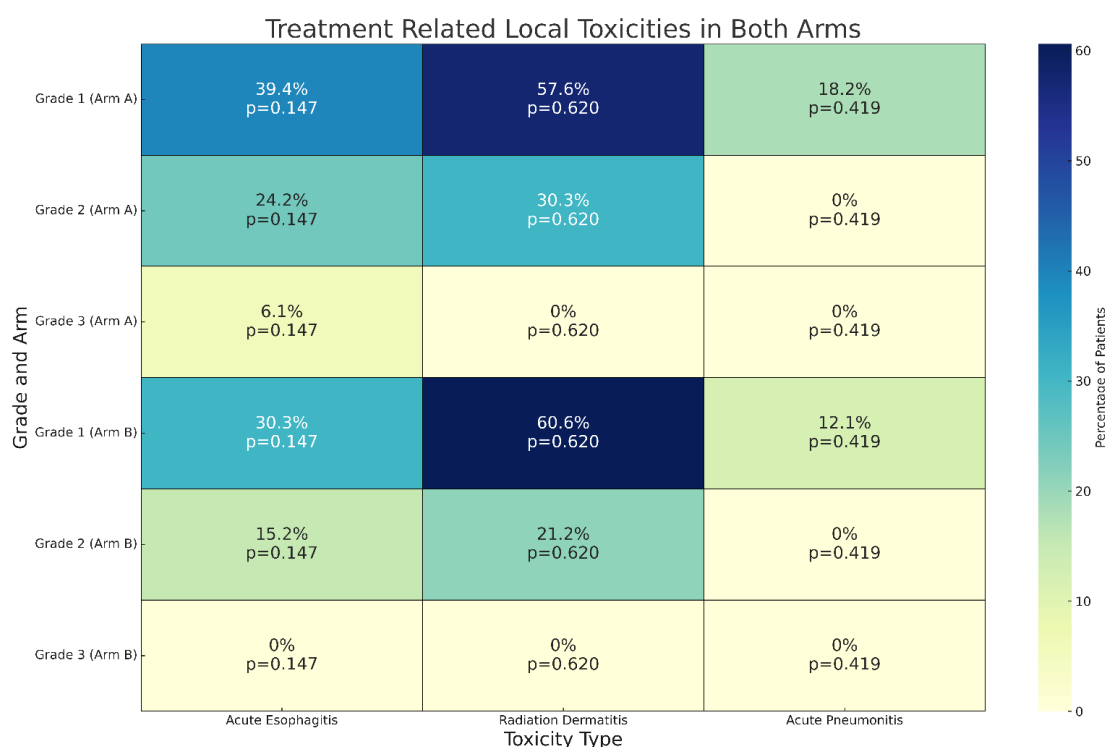


Figure 5. Treatment Related Local Toxicities in Both Arms of Patients (N=66).

Figure 5 shows the distribution of local toxicities by grade in both arms. Data represent the peak (highest) grade of toxicity experienced by each patient during the treatment and 12-week follow-up period. For acute esophagitis, Grade 1 and Grade 2 were more common in Arm A (39.4% and 24.2%) than in Arm B (30.3% and 15.2%), with 6.1% of Arm A patients experiencing Grade 3 toxicity. Radiation dermatitis was prevalent in both arms, with 57.6% of Arm A and 60.6% of

Arm B patients experiencing Grade 1, and 30.3% of Arm A and 21.2% of Arm B patients experiencing Grade 2. No Grade 3 radiation dermatitis occurred in either arm. Acute pneumonitis was observed in 18.2% of Arm A and 12.1% of Arm B patients at Grade 1, with no Grade 4 toxicity in either group. The differences between the arms were not statistically significant ($p > 0.05$).

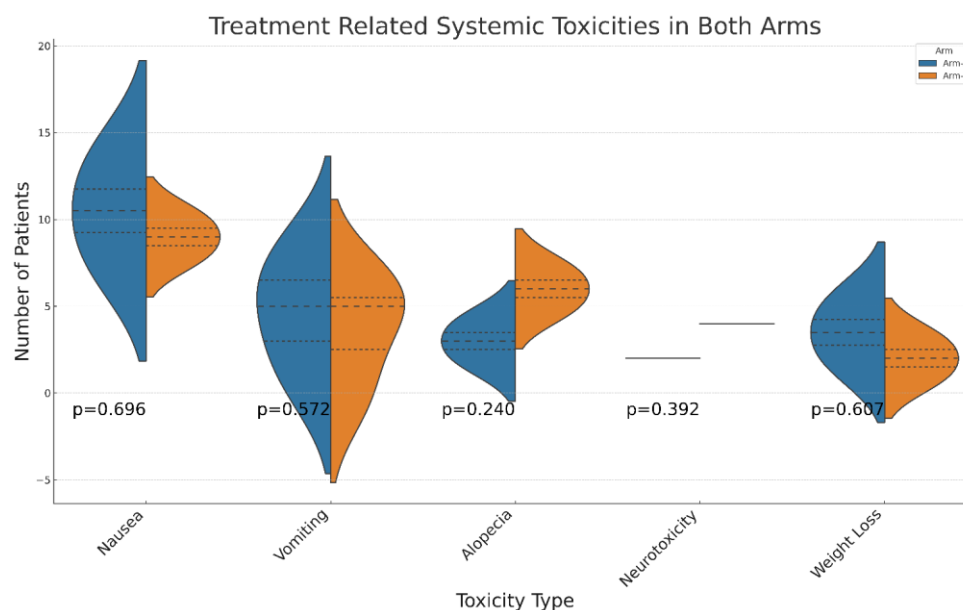


Figure 6. Treatment Related Systemic Toxicities in Both Arms of Patients (N=66).

This figure compares the systemic toxicity profiles of two treatment groups, Arm-A and Arm-B, each comprising 33 patients, for a total of 66 participants. Data represents the peak (highest) grade of toxicity experienced by each patient during the treatment and 12-week follow-up period. The data shows the incidence and severity of five specific adverse events: nausea, vomiting, alopecia, neurotoxicity, and weight loss. For each event, patients are categorized by severity grade (Grade 1 being mild, Grade 2 moderate, and Grade 3 severe), and the results are accompanied by a p-value to assess the statistical significance of differences between the arms. Nausea was the most common toxicity, affecting 34.8% of all patients, with a slightly higher incidence of mild (Grade 1) nausea in Arm-A (39.4%) compared to Arm-B (30.3%), while moderate (Grade 2) nausea occurred equally in both arms (24.2% each). Vomiting was reported across three grades, with Arm-A showing more mild cases and the single instance of severe (Grade 3) vomiting, but the overall difference be-

tween arms was not significant. Alopecia was numerically more frequent in Arm-B for both mild and moderate grades, whereas weight loss was more common in Arm-A across both severity levels. Neurotoxicity, reported only as mild, was also more frequent in Arm-B. Crucially, the p-values for all toxicities—0.696 for nausea, 0.572 for vomiting, 0.240 for alopecia, 0.392 for neurotoxicity, and 0.607 for weight loss—are all greater than the conventional significance threshold of 0.05. This indicates that none of the observed numerical differences in toxicity rates between Arm-A and Arm-B are statistically significant; they are likely attributable to chance rather than a true effect of the treatments. The most prevalent adverse events overall were nausea and vomiting, with most toxicities being mild to moderate in severity. The study's relatively small sample size may limit the ability to detect smaller, yet clinically relevant, differences between the two treatment arms.

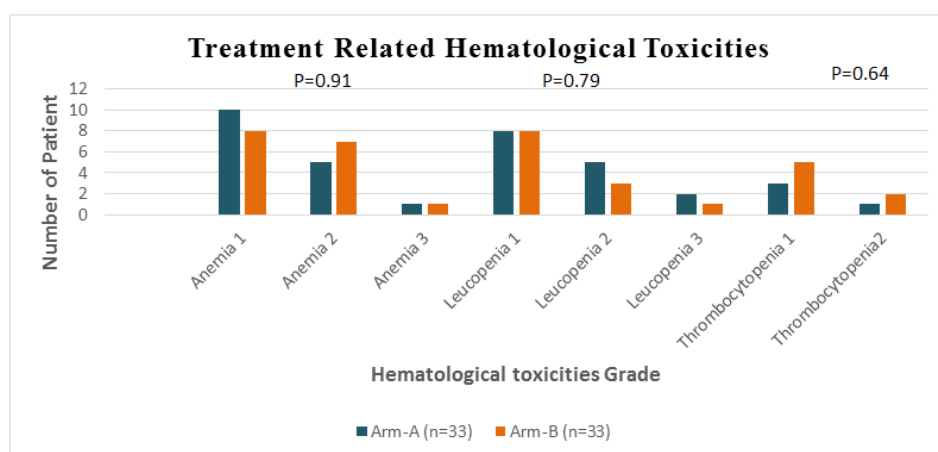


Figure 7. Treatment Related Hematological Toxicities in Both Arms of Patients (N=66).

Figure 7 summarizes the distribution of hematological toxicities in patients receiving concurrent chemoradiation (Arm A) and sequential chemoradiation (Arm B). Data represents the peak (highest) grade of toxicity experienced by each patient during the treatment and 12-week follow-up period. Anemia was observed in both arms, with Grade 1 occurring in 30.3% of Arm A and 24.2% of Arm B patients, and Grade 2 in 15.2% of Arm A and 21.2% of Arm B patients. Grade 3 anemia was observed in 3.0% of patients in both arms. Leucopenia was seen in 24.2% of patients in both arms at Grade 1. Grade 2 leucopenia occurred in 15.2% of Arm A and 9.1% of Arm B patients, while Grade 3 was reported in 6.1% of Arm A and 3.0% of Arm B patients. For thrombocytopenia, 9.4% of Arm A and 15.2% of Arm B patients experienced Grade 1, and 3.0% of Arm A and 6.1% of Arm B patients had Grade 2. No Grade 3 thrombocytopenia was observed in either arm. The differences in hematological toxicity between the two arms were not statistically significant, with p-values greater than 0.05 for all comparisons.

4. Discussion

This study aimed to compare the efficacy, toxicity, and feasibility of concurrent chemoradiotherapy (CCRT) and sequential chemoradiotherapy (SCRT) in patients with inoperable locally advanced non-small cell lung cancer (LA-NSCLC). The findings showed that CCRT had a higher overall response rate (84.8%) compared to SCRT (72.7%). However, this difference was not statistically significant ($p > 0.05$), which is consistent with similar studies that have shown variable results regarding the superiority of CCRT over SCRT [37].

The toxicity profile in this study is in line with what has been observed in other research. CCRT was associated with a higher incidence of acute esophagitis and radiation dermatitis, which mirrors the findings of previous studies. For example, Furuse. et. al and Spencer. et. al, reported that CCRT frequently resulted in increased acute toxicity compared to SCRT, which could be attributed to the synergistic effect of radiation and chemotherapy, enhancing the toxicity in tissues. In this study, Grade 2 acute esophagitis was more common in Arm A (24.2%) than in Arm B (15.2%), and 6.1% of Arm A patients developed Grade 3 esophagitis. This is consistent with the findings of Furuse. et. al, where the concurrent treatment approach was linked to higher rates of severe esophagitis.

In terms of hematological toxicities, including anemia and leucopenia, these were more frequent in the CCRT arm, particularly Grade 2 anemia (15.2%) and Grade 2 leucopenia (15.2%) in Arm A. This is consistent with findings by Furuse. et. al, who reported a higher incidence of hematological toxicities in patients treated with concurrent chemoradiotherapy. Moreover, this study observed that Grade 3 anemia was noted in both arms but was slightly more prevalent in Arm A (3.0%), which concurs with previous research suggesting that hema-

tological side effects are exacerbated in concurrent chemoradiotherapy due to the intensified combination of radiation and chemotherapy [38].

Our analysis of risk factors reaffirmed tobacco smoking as the primary etiology, consistent with global epidemiology [17, 23]. However, it also revealed a significant, region-specific environmental determinant: exposure to indoor biomass smoke. Notably, all 15 female participants reported chronic exposure to wood stove smoke, a reflection of the widespread use of solid fuels for cooking in rural Bangladesh. Household air pollution from such biomass combustion is a well-established carcinogen (International Agency for Research on Cancer [IARC] Group 1) and a major independent risk factor for lung cancer, particularly among non-smoking women in low- and middle-income countries (LMICs) [1, 17]. This finding is crucial for several reasons. First, it accurately characterizes our patient population, highlighting an important etiological driver that differentiates it from Western cohorts and may contribute to the high burden of squamous cell carcinoma we observed [12]. Second, it moves the discussion beyond treatment efficacy to underscore the imperative for primary prevention. Public health interventions aimed at promoting cleaner cooking technologies could have a substantial impact on reducing the future incidence of LA-NSCLC in similar resource-constrained settings [10]. Therefore, while optimizing chemoradiation sequencing is vital for managing advanced disease, a dual focus on mitigating pervasive environmental carcinogens like biomass smoke is equally critical for a comprehensive cancer control strategy in Bangladesh and comparable LMICs.

In terms of socio-demographic factors, the majority of patients were from rural areas (71.21%), and a significant portion was illiterate (48.5%). This is consistent with studies in LMICs, where patients often present with more advanced disease stages due to barriers in early detection and treatment [9, 24]. Both reported that rural populations tend to have delayed diagnoses and worse outcomes due to lack of access to preventive measures, healthcare facilities, and awareness programs. This study supports those findings, highlighting how rural populations are often at a disadvantage in terms of early cancer diagnosis and treatment accessibility.

The histological distribution in this cohort was predominantly squamous cell carcinoma (57.6%). Studies from Rourke et. al, reported that squamous cell carcinoma is more prevalent in resource-limited settings, in contrast to Western countries where adenocarcinoma is more common [6]. The high incidence of squamous cell carcinoma, which is typically centrally located, may influence the patients' treatment response and toxicity profiles. Tumors in these locations are more likely to cause obstructive symptoms, potentially complicating radiotherapy planning and tolerance.

In terms of treatment response, this study demonstrated that CCRT led to a higher complete response rate (51.5% in Arm A vs. 33.3% in Arm B at the 12th week), which is consistent

with the findings of thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer, who reported that CCRT is more effective at achieving locoregional control. However, this difference was not statistically significant ($p > 0.05$), possibly due to the study's limited sample size and follow-up period. Further, partial response was observed more frequently in Arm B (39.4% vs. 33.3% in Arm A), which may suggest that sequential therapy could be an appropriate alternative, particularly for patients who cannot tolerate the heightened toxicity of concurrent chemoradiotherapy.

The high prevalence of squamous cell carcinoma (57.6%) in our cohort, which aligns with national data reporting it as the predominant subtype (67.6%) of NSCLC in Bangladesh as per NICRH, 2021, is a critical factor in contextualizing our toxicity and efficacy results. This histologic profile stands in stark contrast to the rising global incidence of adenocarcinoma, represents in Youlden et al., 2008 and the adenocarcinoma-enriched populations of landmark Western trials that established CCRT as the standard of care shows in Auperin et al., 2010; Curran et al., 2011. Centrally located squamous tumors, more common in our setting, may increase the risk of obstructive symptoms and complicate radiotherapy field planning, potentially contributing to the observed patterns of acute esophagitis and pneumonitis, Liang et al., 2017. This local demographic and clinical reality, compounded by frequent late-stage presentation and socioeconomic barriers to care as documented in Bangladeshi studies in Hussain & Sullivan, 2013; Islam et al., 2021, creates a distinct patient profile. Therefore, toxicity benchmarks and response rates from global trials may not be directly applicable. Our findings, showing CCRT's increased toxicity burden with a non-significant efficacy advantage, must be interpreted through this lens. The predominant squamous histology, late presentation, and constrained supportive care infrastructure in Bangladesh collectively influence the risk-benefit calculus. This provides a compelling, context-specific rationale for considering SCRT which demonstrated comparable efficacy with a more manageable toxicity profile in our study as a viable and potentially more feasible alternative for a significant subset of patients in this and similar resource-constrained environments [20].

The toxicity grades presented in Figures 5, 6, and 7 reflect the peak severity (highest CTCAE grade) recorded for each patient at any point during the concurrent treatment phase and the subsequent 12-week follow-up period.

Toxicities were higher in the CCRT arm, particularly esophagitis and radiation dermatitis, which are well-documented adverse events of concurrent treatment. These findings were corroborated by Amin et. al, who both found that CCRT is associated with a higher incidence of acute toxicities. Furthermore, hematological toxicities, such as anemia and leucopenia, were more common in the CCRT arm but did not reach statistical significance ($p > 0.05$), in line with previous studies [15, 29].

5. Conclusions

This study provides valuable insights into the efficacy and toxicity profiles of concurrent and sequential chemoradiotherapy in inoperable LA-NSCLC. While CCRT showed a higher overall response rate, it was associated with greater acute toxicity compared to SCRT. Despite this, the difference in response between the two arms was not statistically significant, suggesting that SCRT may be a viable alternative, particularly for patients who cannot tolerate the increased toxicity of CCRT. The findings underscore the importance of considering individual patient factors, such as performance status and comorbidities, in treatment selection, especially in resource-limited settings.

6. Limitations

This study is subject to several limitations. Selection bias is one of the primary concerns, as the lack of randomization may have introduced bias in patient allocation, limiting the generalizability of the findings. The 12-week follow-up period was also insufficient for evaluating long-term survival outcomes and assessing late-stage toxicities, which are essential for understanding the full effects of the treatments. Additionally, the relatively small sample size ($n = 66$) may have reduced the statistical power of the study, increased the likelihood of type II errors and limiting the detection of statistically significant differences between the two treatment arms. Moreover, the study was conducted at a single center, which may limit the applicability of the results to other healthcare settings with different infrastructure and resources. Lastly, the absence of immunotherapy in this study is a notable limitation, as newer treatment modalities, including immunotherapy, are increasingly incorporated into the management of LA-NSCLC and could potentially alter treatment outcomes.

7. Recommendations

Given the findings and limitations of this study, several recommendations can be made. Sequential chemoradiotherapy (SCRT) could be considered a feasible alternative for patients who are unable to tolerate the toxicity associated with concurrent chemoradiotherapy (CCRT), particularly in resource-limited settings where the healthcare infrastructure may not support the management of CCRT-related side effects. Future research should focus on conducting larger, multi-center randomized controlled trials with extended follow-up periods to confirm these findings and evaluate long-term survival outcomes. Additionally, it is essential to explore the potential role of immunotherapy in both CCRT and SCRT regimens to assess its impact on improving treatment outcomes for LA-NSCLC. Incorporating immunotherapy in future studies could provide valuable insights into optimizing treatment strategies and improving patient sur-

vival and quality of life.

Abbreviations

SD	Stable Disease
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TNM	Tumor, Node, Metastasis (Staging System)
ULN	Upper Limit of Normal
WHO	World Health Organization
μL	Microliter
ECOG	Eastern Cooperative Oncology Group
Gy	Gray
HTN	Hypertension
IRB	Institutional Review Board
LA-NSCLC	Locally Advanced Non-Small Cell Lung Cancer
LMICs	Low- and Middle-Income Countries
NICRH	National Institute of Cancer Research and Hospital

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Author Contributions

Ayesha Khatun: Conceptualization, Data curation, Formal Analysis, Investigation.

Mahbuba Akhter Tania: Investigation, Methodology, Project administration, Resources.

Sheikh Nazmul Kabir: Software, Supervision, Validation.

Md. Abdul Karim: Visualization, Writing – original draft, Writing – review & editing.

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Data Availability Statement

The data is available from the corresponding author upon reasonable request and the data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021; 71(3): 209-49.
- [2] Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
- [3] Morgensztern D, Detterbeck FC, Dorilon A, Goldberg DS, editors. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 12th ed. Philadelphia: Lippincott Williams & Wilkins; 2023.
- [4] Auperin A, Le P échoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol.* 2010; 28(13): 2181-90.
- [5] Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst.* 2011; 103(19): 1452-60.
- [6] Xiao W, Hong M. Concurrent vs sequential chemoradiotherapy for patients with advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2021; 100(11): e25123.
- [7] Conibear J. Rationale for concurrent chemoradiotherapy for patients with stage III non-small-cell lung cancer. *Br J Cancer.* 2020; 123(Suppl 1): 10-7.
- [8] Liew MS, Sia J, Starmans MH, Tafreshi A, Harris S, Feigen M, et al. Comparison of toxicity and outcomes of concurrent radiotherapy with carboplatin/paclitaxel or cisplatin/etoposide in stage III non-small cell lung cancer. *Cancer Med.* 2013; 2(6): 916-24.
- [9] Spencer A, Williams J, Samuel R, Boon IS, Clarke K, Jain P. Concurrent versus sequential chemoradiotherapy for unresectable locally advanced stage III non-small cell lung cancer: retrospective analysis in a single United Kingdom cancer centre. *Cancer Treat Res Commun.* 2021; 29: 100460.
- [10] Fournel P, Robinet G, Thomas P, Souquet PJ, L éna H, Vergnen égre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Canc érologie NPC 95-01 Study. *J Clin Oncol.* 2005; 23(25): 5910-7.

- [11] Hussain SA, Sullivan R. Cancer control in Bangladesh. *Jpn J Clin Oncol*. 2013; 43(12): 1159-69.
- [12] Islam MR, Hasan AK, Khatun N, Ridi IN, Rasheed MMO, Islam SMA, et al. Demographic differentials of lung cancer survival in Bangladeshi patients. *PLoS One*. 2021; 16(12): e0261238.
- [13] National Institute of Cancer Research and Hospital (NICRH). Cancer Registry Report 2018-2020. Dhaka: NICRH; 2021.
- [14] Luo H, Yu X, Liang N, Xie J, Deng G, Liu Q, et al. The effect of induction chemotherapy in patients with locally advanced non-small cell lung cancer who received chemoradiotherapy: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017; 96(8): e6084.
- [15] Youlten DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. *J Thorac Oncol*. 2008; 3(8): 819-31.
- [16] Gandhi S, Zhao Y, Advani R, Halpern MT, Pandya C, Gross CP, et al. Comparative effectiveness of sequential versus concurrent chemoradiation for stage III non-small cell lung cancer in low-resource settings. *J Clin Oncol*. 2023; 41(15): 2789-801.
- [17] Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, et al. Long-term results of NRG Oncology RTOG 0617: Standard-versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. *J Clin Oncol*. 2020; 38(7): 706-14.
- [18] Bade BC, Cruz CSD. Lung cancer 2020: epidemiology, etiology, and prevention. *Clin Chest Med*. 2020; 41(1): 1-24.
- [19] Cruz CSD, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med*. 2011; 32(4): 605-44.
- [20] Shah BD, Tyan CC, Rana M, Goodridge D, Hergott CA, Os-good ND, et al. Rural vs urban inequalities in stage at diagnosis for lung cancer. *Cancer Treat Res Commun*. 2021; 29: 100495.
- [21] Xing PY, Zhu YX, Wang L, Hui ZG, Liu SM, Ren JS, et al. What are the clinical symptoms and physical signs for non-small cell lung cancer before diagnosis is made? A nation-wide multicenter 10-year retrospective study in China. *Cancer Med*. 2019; 8(8): 4055-69.
- [22] Mathew A, George PS, Kunnambath R, Mathew BS, Kumar A, Syampramod R, et al. Educational status, cancer stage, and survival in South India: a Population-based study. *JCO Glob Oncol*. 2020; 6: 1704-11.
- [23] Castro S, Sosa E, Lozano V, Akhtar A, Love K, Duffels J, et al. The impact of income and education on lung cancer screening utilization, eligibility, and outcomes: a narrative review of socioeconomic disparities in lung cancer screening. *J Thorac Dis*. 2021; 13(6): 3745-58.
- [24] Zatloukal P, Petruzella L, Zemanova M, Havel L, Janku F, Judas L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer*. 2004; 46(1): 87-98.
- [25] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982; 5(6): 649-55.
- [26] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2023. 2023.
- [27] Huber RM, Flentje M, Schmidt M, Pöllinger B, Gosse H, Willner J, et al. Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. *J Clin Oncol*. 2006; 24(27): 4397-404.
- [28] Hoque M. ABC of Research Methodology. 4th ed. Dhaka: BSMMU; 2019.
- [29] Liang J, Bi N, Wu S, Chen M, Lv C, Zhao L, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. *Ann Oncol*. 2017; 28(4): 777-83.
- [30] Dobbs J, Barrett A, Ash D. Practical Radiotherapy Planning. 2nd ed. London: Arnold; 1992.
- [31] Rourke N, Roque I, Figuls M, Farre Bernado N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev*. 2010 Jun 16; 2010(6):CD002140. <https://doi.org/10.1002/14651858.CD002140.pub3>
- [32] Vokes EE, Herndon JE, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol*. 2007; 25(13): 1698-704.
- [33] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2): 228-47.
- [34] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Bethesda: US Department of Health and Human Services; 2017.
- [35] Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer*. 1996; 32A(7): 1135-41.
- [36] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013; 310(20): 2191-4.
- [37] Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. (1999). Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *Journal of Clinical Oncology*, 17(9), 2692-2692.

- [38] O'Rourke, N., i Figuls, M. R., Bernadó, N. F., & Macbeth, F. (2010). Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database of Systematic Reviews, (6).

Biography

Ayesha Khatun is a dedicated oncology professional currently serving in the Department of Radiotherapy at Rajshahi Medical College Hospital. She completed her MBBS at Dinajpur Medical College, where she developed a strong foundation in clinical medicine. Driven by a deep interest in cancer care, she pursued advanced training and earned her MD in Clinical Oncology from Bangladesh Medical University (BMU), completing the program in July 2024. Dr. Mst. Ayesha Khatun has been actively engaged in the field of oncology since 2018, gaining valuable experience in radiotherapy, chemotherapy, and multidisciplinary cancer management. Her clinical focus includes evidence-based treatment planning and patient-centered care for individuals diagnosed with a wide range of malignancies. In addition to her clinical work, Dr. Mst. Ayesha Khatun is a member of the European Society for Medical Oncology (ESMO), which supports her continued professional development and involvement in international oncology advancements. She remains committed to improving cancer outcomes in Bangladesh.

Research Field

Ayesha Khatun: Combination therapy Strategies, Novel Chemotherapeutic Agents, Radiotherapy.

Mahbuba Akhter Tania: Toxicity Reduction Techniques, Chemotherapy, Targeted Therapy.

Sheikh Nazmul Kabir: Radiotherapy, Combination Therapies, Immunotherapy.

Md. Abdul Karim: Radiotherapy, Immunotherapy Targeted Therapy.