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A Comparative Study to Evaluate Response and Toxicities of Conventional versus Hypofractionated Sequential Chemoradiotherapy in Patients with Inoperable Locally Advanced Non-Small Cell Lung Cancer

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Abstract

Background: Current standard treatment approach for inoperable locally advanced non-small cell lung cancer (NSCLC) is sequential or concurrent conventional chemoradiotherapy. Local tumor control is necessary for the cure of lung cancer. As there is a chance of compromised local control due to accelerated repopulation of tumor cells during conventional radiotherapy, hypofractionated radiotherapy is a strategy to minimize accelerated repopulation that might improve local control. **Objectives:** To evaluate and compare the response and toxicities of conventional and hypofractionated sequential chemoradiotherapy in inoperable locally advanced stage III NSCLC. **Methods:** A Quasi-Experimental study was carried out from January 2021 to December 2021 at the Department of Radiation Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh. Total 66 patients with histologically proven, inoperable locally advanced stage III NSCLC were divided into Arm A and B, 33 patients in each arm. All patients were treated with 4 cycles of chemotherapy (Inj. Paclitaxel and Inj. Carboplatin) on Day 1. After

completion of chemotherapy, patients of Arm A were treated with conventional fractionated radiotherapy, 60 Gy in 30 fractions, 2 Gy per fraction, 5 days in a week over 6 weeks and patients of Arm B were treated with hypofractionated radiotherapy, 55 Gy in 20 fractions, 2.75 Gy per fraction, 5 days in a week over 4 weeks. Then regular assessments of all study patients were done to evaluate treatment responses and toxicities. Data were analyzed and compared by statistical tests. **Results:** The mean age was 56 ± 5.8 years in Arm-A and 56.61 ± 5.8 years in Arm-B. The overall response rate in hypofractionated arm was 78.8% and in conventional arm was 69.7% ($p > 0.05$). Although toxicities (grade 1 and 2) were slightly higher in Arm B ($p > 0.05$). At 6 months, no significant difference in terms of treatment responses and toxicities were found between two groups ($p > 0.05$). **Conclusion:** Hypofractionated sequential chemoradiotherapy is equally effective as conventional fractionated sequential chemoradiotherapy in locally advanced, inoperable NSCLC in terms of treatment response and toxicities.

Keywords

Chemoradiotherapy, Conventional, Hypofractionated, Non-Small Cell Lung Cancer (NSCLC), Response and Toxicities

1. Introduction

The global cancer burden is estimated to have risen to 19.3 million new cases in 2020 [1]. Among all, lung cancer is the 2nd most common in both sexes which is 13% of all malignancies accounting for 2.2 million new cases and leading cause of cancer death worldwide as it accounted for 1.7 million deaths in 2020 [1]. Lung cancer is a malignant lung tumor characterized by uncontrolled cell growth in tissues of lung. It can be divided into two histological groups- non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The major types of NSCLC include adenocarcinoma, squamous cell carcinoma and large cell carcinoma [2]. Non-small cell lung cancer (NSCLC) accounts for 80% - 85% of all lung cancers [2]. Non-small cell lung cancer (NSCLC) represents majority of the lung cancer at diagnosis and most of these are in locally advanced stage, half of which are unresectable [3]. Approximately one third of patients with NSCLC present with stage III tumors which are mostly inoperable due to invasion of local structures, regional lymph node metastases, medical co-morbidities or poor performance status [3]. Significant advancements have been made in lung cancer screening, diagnostic assessment, surgery, radiation therapy, and chemotherapy throughout the last half century. Bimodal combination of chemotherapy and radiation therapy (RT) is the standard of care for patients with inoperable, nonmetastatic, locally advanced NSCLC [4]. At present, concurrent or sequential chemoradiotherapy with a conventionally fractionated dose of 60 - 66 Gy are standard treatments for locally advanced NSCLC [4] [5]. However, the therapeutic effect is disappointing:

the 5-year overall survival (OS) rate is only 13% to 16% [5] [6]. Improving outcomes for these unfavorable patients still remain challenging. Even radiation dose escalation to 74 Gy failed to improve outcome of the patients and increased the toxicity [5]. One of the possible reasons for the failure of high dose radiation to increase outcome was prolong duration of radiation treatment. In NSCLC, cells begin to undergo accelerated repopulation at 3rd to 4th week after the start of radiotherapy and additional daily dose of 0.6 Gy is required to compensate for the loss of local control [7]. Local tumor control is necessary for the cure of lung cancer. As there is a chance of compromised local control due to accelerated repopulation of tumor cells during conventional radiotherapy. Traditional fractionation involves administering 2 Gy doses once daily, five days a week, for a total treatment duration (OTT) of six weeks [8]. It is still necessary to investigate various approaches and radiation schedules in order to maximize the benefits of radiation. In recent years, efforts have been made to intensify radiotherapy regimens by means of hypofractionated radiotherapy in order to improve locoregional control and survival rates [9] [10]. Hypofractionated radiotherapy shortens the total treatment duration and partially offsets the accelerated repopulation effect thereby delivering high-dose radiation to the tumors in a short period of time, improving biological effective dose (BED), strengthening local tumor control ultimately decrease the chance of disease progression [9] [10]. Another important fact is machine occupancy and overall treatment cost both of which can be reduced with hypofractionated radiotherapy. Moreover, patients receiving conventional fractionation regime have to regularly attend the hospital for six weeks and this prolonged treatment time is associated with acute toxicities. If we can reduce the treatment time, it would be more convenient for the patients. The purpose of this study was to compare response and acute toxicities between conventional fractionated and hypofractionated sequential chemoradiotherapy in locally advanced non-small cell lung cancer patients and to help in future treatment decisions.

2. Materials and Methods

2.1. Study Design

This quasi-experimental study was conducted at the Department of Radiation Oncology, National Institute of Cancer Research & Hospital (NIRCH), Dhaka, Bangladesh from January 2021 to December 2021. This study was approved by the Institutional Review Board (IRB) of the NIRCH, Dhaka, Bangladesh.

2.2. Study Population

A total of 66 adult patients (age > 18 years) with histopathologically or cytologically diagnosed and radiologically proven locally advanced stage III NSCLC, who could not be treated surgically were included following purposive sampling technique.

For determination of sample size following formula was applied:

$$n = \frac{P_1(1-P_1)+P_2(1-P_2)}{(P_1-P_2)^2} \times (Z_\alpha + Z_\beta)^2$$

P_1 = Proportion of patients developed outcome in control arm = 45% [11].

P_2 = Proportion of patients developed outcome in experimental arm = 70.6% [12].

Z_α = Z-value (two tail) at a definite level of significance e.g., 1.96 at 5% level of significance.

Z_β = Z-value (one tail) at a definite power e.g., 0.85 at 80% power.

Conventional fractionated radiotherapy was expected to cause outcome 45% in unresectable locally advanced non-small cell lung cancer patients and 70% in hypofractionated arm. So, we calculated the sample size to examine which treatment is better at 5% level of significance with 95% confidence interval.

Here, P_1 = 45% (0.45), P_2 = 70.6% (0.7), Z_α = 1.96, Z_β = 0.85, n = Sample size

$$n = \frac{(0.45\times0.55)+(0.7\times0.3)}{(0.45-0.70)^2} \times (1.96+0.85)^2 = 58.14 \approx 59$$

With 10% allowance for loss to follow up, final sample size = 59 + 5.9 = 64.9 ≈ 65.

Total of 66 patients included in this study, distributed in two arms (A and B), 33 patients in each arm.

Inclusion criteria were: patients with stage III NSCLC, age between 18 to 70 years with Eastern Co-operative Oncology Group (ECOG) performance status (PS) ≤ 2. Exclusion criteria were: patients having age less than 18 years or above 70 years, patients with histology other than squamous and adenocarcinoma of lung, patients with history of initial surgery (excluding diagnostic biopsy) of the primary site or radiotherapy to chest, patients with features of superior vena caval obstruction, patients having pleural or pericardial effusion, patients having concurrent diseases like- history of pulmonary fibrosis, myocardial infarction within last 12 months, grade II and above heart failure, uncontrolled heart failure, uncontrolled chronic obstructive pulmonary disease, impaired renal function (serum creatinine level > 1.4 mg/dl or calculated creatinine clearance rate < 60 ml/minute when needed) and abnormal liver function.

2.3. Study Procedure

1) Case selection

Initially total 76 patients were enrolled. After eligibility assessment, 10 patients were excluded, and a total number of 66 patients were included in the study according to the selection criteria. After selecting the patient, informed written consent was taken from each patient. Then a complete medical history, relevant clinical examination findings and necessary investigations reports were documented in a case record form. Location and size of the tumor was recorded prior to treatment. All patients were divided into two arms: Arm A for conventional fraction-

ated radiotherapy and Arm B for hypofractionated radiotherapy. Patients for Arm A and Arm B were allocated by using systematic randomization, assigning odd numbers to Arm A and even numbers to Arm B.

2) Pretreatment evaluation

A thorough history had been taken from the patient or attendant to obtain maximum possible information including demographic characteristics, Eastern Co-operative Oncology Group (ECOG) performance status and details of his/her illness. The mode of onset, progression, duration of chief complaints had been noted.

3) Investigations

Laboratory investigations

- Complete blood count (CBC)—TC, DC, ESR, Hb%, Platelet count.
- Renal function tests—Serum creatinine, Creatinine clearance rate (if needed).
- Liver function tests—Serum bilirubin, Serum glutamic pyruvic transaminase (SGPT).

Imaging

- Bronchoscopy
- Computed Tomography (CT) scan of chest with contrast
- CT scan of abdomen
- CT scan/Magnetic Resonance Imaging (MRI) of brain (if indicated)
- ECG, Echocardiogram
- Whole body bone scan (if indicated)

Special investigation: Histopathology by biopsy or fine needle aspiration cytology (FNAC) report of the lesion.

4) Intervention

Medical and supportive care

Patients were managed symptomatically with antibiotics, steroid, analgesics, antiemetic and conservative management was given according to need throughout the treatment period.

Chemotherapy protocol

A total of 66 patients were included in this study and were equally sub-grouped into two Arms, Arm A and Arm B. All received 4 cycles of chemotherapy with Inj. Paclitaxel 175 mg/m^2 in 500 ml normal saline within 3 hours at Day-1 and Inj. Carboplatin (AUC = 6) in 500 ml D/A within 1 hours at Day-1 [13].

Proper hydration was maintained. Patients were monitored for any kind of hypersensitivity reactions. Pre and post - chemotherapy medication with anti-emetics, and other necessary drugs were given before and after chemotherapy.

Also, for Paclitaxel, patients received premedication for prevention of the incidence of hypersensitivity reactions *i.e.*, Dexamethasone 20 mg PO at 12 and 6 hours before and Diphenhydramine 50 mg at 30 minutes before drug administration [13]. Patients were assessed before each cycle by clinical symptoms analysis, physical examination and hematological parameters.

After completion of 4 cycle sequential chemotherapy, all patients underwent evaluation by clinical symptoms analysis, physical examination and with a con-

trast enhanced computed tomography (CECT). The response criteria were based on cross-sectional diameter and tumor response, nodal response, and overall response according to response evaluation criteria in solid tumors (RECIST) response criteria [14].

If there was no progression of disease after 3 weeks of completing 4th cycle of chemotherapy, all patients proceeded for radiotherapy.

Radiotherapy

For both arms

Radiotherapy had been delivered to the patients using

- Method: 3D conformal radiotherapy technique
- Machine: Linear accelerator (LINAC)
- Beam energy: 6 MV

Arm A

Patients of Arm A was treated with conventional fractionated radiotherapy, 60 Gy in 30 fractions, 2 Gy per fraction, 5 days in a week over 6 weeks.

Arm B

Patients of Arm B was treated with hypofractionated radiotherapy, 55 Gy in 20 fractions, 2.75 Gy per fraction, 5 days in a week over 4 weeks.

Dose constraints:

	Arm A	Arm B
Lung-V20 (volume of lung minus PTV receiving > 20 Gy)	<32%	<25% - 30%; Mean lung dose ≤ 15 Gy
Heart-V40 V20	<30% <50%	V33 < 25%
Spinal cord	<45 Gy (Maximum dose (0.1 cc))	≤36 Gy
Esophagus	Mean < 45 Gy	V42 < 32%
Thyroid	Mean < 30 Gy	

5) Patient assessment

Assessment during treatment

During Chemotherapy:

- Hematological tests were done before each cycle of chemotherapy.
- CBC was repeated 7 days after completion of chemotherapy in each cycle.
- Symptomatic response was assessed before each cycle of chemotherapy.
- Patients were assessed after 4 cycles of chemotherapy according to RECIST criteria [12].

During Radiotherapy:

- **Relief of symptoms:** Symptomatic response and evaluation of toxicities were assessed weekly.
- **Toxicity reporting:** To assess toxicity, "The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)" version-5.0 was used

[15].

- If any toxicity developed during treatment, it had been managed appropriately.

Assessment after treatment

- After completion of treatment patients were carefully supervised to attain first follow up at 6th week.
- Subsequent follow ups were done after 12 weeks and 24 weeks.
- During the follow-up, toxicities and tumor response were assessed by clinical examination (general physical examination including regional lymph node examination and chest examination) and relevant investigations like Chest X-ray (P/A view) and CECT chest.
- Treatment response was assessed by RECIST criterion [14].
- Toxicities were assessed by "Common Terminology Criteria for Adverse Events" [15].

2.4. Statistical Analysis of Data

After collection, data were checked and verified. Then, all data were tabulated in a master data sheet. Thereafter, data were entered into computer and coded. Data categorization and summarization were done. Continuous data were expressed as mean ± standard deviation (SD), whereas categorical data were expressed with rate and ratio. Statistical analysis was done according to the study's objective by using Statistical Package for Social Sciences (SPSS) software version 25.0 for windows. The analysis was done using Unpaired t-test for continuous variables and Chi-square test (χ^2)/Fisher's exact tests for categorical variables. All reported p-values were two-sided, and a p value less than 0.05 was taken as statistically significant. The present study was designed to assess and compare the short-term response outcomes of conventional versus hypofractionated radiotherapy in locally advanced non-small cell lung cancer. As such, patient survival data beyond 6 months were not collected, and therefore reliable Kaplan-Meier analyses of progression-free survival (PFS) and overall survival (OS) could not be performed.

3. Results and Observations

Total 66 patients with NSCLC were included in this study, then they were distributed in two arms (A and B), 33 patients in each arm. All patients were enrolled during the time period of 1st January 2021 to 31th December 2021. Data were collected from January 2021 to June 2021 and follow up were done from July 2021 to December 2021.

3.1. Baseline Characteristics

Analyzing the baseline characteristics of the study patients showed that, most of the patients belonged to age group 56 - 65 years. The mean age was 56.03 ± 5.8 years in arm A and that was 56.61 ± 5.8 years in arm B. Minimum age was 45 years in Arm A, it was 44 years in Arm B. Maximum age was 66 years in Arm A, which 65 years in Arm B. The difference was not statistically significant ($p > 0.05$) be-

tween two arms (Table 1).

In Arm A, male and female patients were 26 (78.8%) and 7 (21.2%) respectively, and the ratio was 3.7:1. In Arm B, male and female patients were 27 (81.8%) and 6 (18.2%) respectively, and the ratio was 4.5:1. The difference was not statistically

Table 1. Baseline sociodemographic and clinical characteristics of the study population (N = 66).

Characteristics	Arm A (n = 33) n (%)	Arm B (n = 33) n (%)	p-value
Age Group			
<46 years	2 (66.7%)	1 (33.3%)	
46 - 55 years	14 (51.9%)	13 (48.1%)	
56 - 65 years	17 (47.2%)	19 (52.8%)	
>65 years	1 (100.0%)	0 (0.0%)	
Mean Age (±SD)	56.03 ± 5.8	56.61 ± 5.8	0.689[a]
Gender			
Male	26 (78.8%)	27 (81.8%)	0.757[c]
Female	7 (21.2%)	6 (18.2%)	
Risk Factors*			
Smoker	26 (78.8%)	23 (69.7%)	0.398[b]
Occupational exposure	4 (12.1%)	2 (6.1%)	0.672[c]
COPD	3 (9.1%)	4 (12.1%)	1.0[c]
ECOG Performance Status			
Status = 0	6 (18.2%)	7 (21.2%)	
Status = 1	18 (54.5%)	21 (63.6%)	0.484[b]
Status = 2	9 (27.3%)	5 (15.2%)	
Clinical presentations*			
Cough	26 (78.8%)	29 (87.9%)	0.322[b]
Weight loss	23 (69.7%)	22 (66.7%)	0.792[c]
Chest Pain	16 (48.5%)	11 (33.3%)	0.211[b]
SOB/Dyspnea	13 (39.4%)	14 (42.4%)	0.802[b]
Hemoptysis	9 (27.3%)	7 (21.2%)	0.566[b]
Location of lesion			
Right Lung	22 (66.7%)	19 (57.6%)	0.447[b]
Left Lung	11 (33.3%)	14 (42.4%)	

COPD = Chronic obstructive pulmonary disease; SOB = Shortness of breath; p-values obtained from: a = Unpaired t-test, b = Fisher's exact test, c = Chi-square test; *Multiple responses.

significant between the two arms ($p > 0.05$) (Table 1). We evaluate the distribution of study patients according to their exposure to some risk factors. Smoker was quite common in both Arms; 26 (78.8%) in Arm A and 23 (69.7%) in Arm B (Table 1). In this study, most patients had baseline ECOG performance status score 1 in each of the study Arms. ECOG performance status was not significantly different between the study Arms ($p = 0.484$) (Table 1).

Among the study patients, most common presentation in both Arms was cough (78.8% and 87.9%). Weight loss was also common in both groups; 23 (69.7%) patients in Arm A and 22 (66.7%) in Arm B. Chest pain (40.9%) and shortness of breath (40.9%) were equally common presenting features in both Arms. There was no significant difference between the two Arms in context of clinical presentation ($p > 0.05$) (Table 1).

In this study, majority of the study patients had right lung lesion, which was 66.7% in Arm A and 57.6% in Arm B. The difference was not statistically significant between the Arms ($p = 0.447$) (Table 1).

Among the study patients, squamous cell carcinoma was found 18 (54.5%) patients in Arm A and 16 (48.5%) patients in Arm B. Adenocarcinoma was found in 15 (45.5%) patients and 17 (51.5%) patients in Arm A and Arm B respectively. The difference was not statistically significant between the groups ($p > 0.05$) (Table 2). The staging (TNM stage) of the study patients at the time of presentation in both arms was evaluated. In Arm A: 14 (42.4%) patients were Stage III A, 18 (54.5%) patients were Stage III B and 1 (3%) patient was stage IIIC; in Arm B: 16 (48.5%) patients were Stage III A, 17 (51.5%) patients were in Stage IIIB. The distribution of the sample was homogenous in both the Arms (Table 2).

Table 2. Distribution of study participants by histological type and TNM Stage in both Arms (N = 66).

Variable	Arm A (n = 33)	Arm B (n = 33)	p-value
Histological Type			
Squamous cell carcinoma	18 (54.5%)	16 (48.5%)	0.622^{ns}
Adenocarcinoma	15 (45.5%)	17 (51.5%)	
TNM Stage			
Stage IIIA	14 (42.4%)	16 (48.5%)	
Stage IIIB	18 (54.5%)	17 (51.5%)	0.559^{ns}
Stage IIIC	1 (3.0%)	0 (0.0%)	

p-values obtained from Chi-square test, ns = not significant.

3.2. Assessment of Treatment Responses

After completion of 4 cycles of chemotherapy: Patients showing partial responses (PR) were 27 and 29 in Arm A and Arm B respectively; while, stable disease (SD) was observed in 6 and 4 patients in the two arms respectively. The difference was not statistically significant ($p = 0.492$). No complete response (CR)

and progressive disease (PD) were found in both arms (Table 3).

After 6 weeks: In Arm A, 1 (3%) patient showed complete response (CR) whereas in Arm B, CR was observed in 3 (9.1%) patients. At that time, 27 (81.8%) patients in Arm A and 29 (87.9%) patients in Arm B showing partial response (PR); stable disease (SD) was found among 5 (15.2%) patients and 1 (3%) patient in the two Arms respectively. Although Arm B showed better response mathematically, the difference was not statistically significant (p = 0.154) (Table 3).

After 12 weeks: 3 (9.1%) patients in Arm A and 5 (15.2%) patients in Arm B showed complete response (CR). At this time, most patients in Arm A [21 (63.6%)] and Arm B [23 (69.7%)] maintained partial response (PR); stable disease (SD) was observed among 6 (18.2%) patients and 3 (9.1%) patients in the two Arms respectively. While, 3 (9.1%) patients from Arm A and 2 (6.1%) patients from Arm B showed progressive disease (PD). The difference was not statistically significant (p = 0.617) (Table 3).

Table 3. Treatment responses at different point of time in both Arms (N = 66).

Treatment Responses	Arm A (n = 33)	Arm B (n = 33)	p-value
After 4 cycles of chemotherapy			
Partial Response (PR)	27 (81.8%)	29 (87.9%)	0.492^{ns}
Stable Disease (SD)	6 (18.2%)	4 (12.1%)	
After 6 weeks			
Complete Response (CR)	1 (3.0%)	3 (9.1%)	
Partial Response (PR)	27 (81.8%)	29 (87.9%)	0.154^{ns}
Stable Disease (SD)	5 (15.2%)	1 (3.0%)	
After 12 weeks			
Complete Response (CR)	3 (9.1%)	5 (15.2%)	
Partial Response (PR)	21 (63.6%)	23 (69.7%)	0.61^{nss}
Stable Disease (SD)	6 (18.2%)	3 (9.1%)	
Progressive Disease (PD)	3 (9.1%)	2 (6.1%)	
After 24 weeks			
Complete Response (CR)	3 (9.1%)	5 (15.2%)	
Partial Response (PR)	20 (60.6%)	21 (63.6%)	0.733^{ns}
Stable Disease (SD)	4 (12.1%)	2 (6.1%)	
Progressive Disease (PD)	6 (18.2%)	5 (15.2%)	

p-values obtained from Chi-square test, ns = not significant.

After 24 weeks: In Arm A, 3 (9.1%) patients showed complete response (CR) and in Arm B, CR was observed in 5 (15.2%) patients. Partial response (PR) was found among 20 (60.6%) patients and 21 (63.6%) patients in Arm A and Arm B respectively. Stable disease (SD) was found among 4 (12.1%) patients in Arm A

and 2 (6.1%) patients in Arm B. There were 6 (18.2%) patients having progressive disease (PD) in Arm A and 5 (15.2%) patients had PD in Arm B. At that time, treatment response was not statistically significant between the Arms (p = 0.733) (Table 3).

In this study, according to ECOG performance status (PS); ECOG PS-0 was 13, ECOG PS-1 was 39 and ECOG PS-2 was 14. Complete response and partial response (CR + PR) were seen in 11 patients with ECOG PS-0 and 38 patients with ECOG PS-1; but only partial response (PR) was seen in 1 patient with ECOG PS-2. No treatment response was observed in 2 patients with ECOG PS-0, one (1) patient with ECOG PS-1 and 13 patients with ECOG PS-2. This result reflected that, patients of ECOG PS-0 and patients having ECOG PS-1 were associated with good response rate. The difference was statistically significant (p < 0.001) (Table 4).

In terms of primary tumor response of TNM stages: stage IIIA had significant higher treatment response than other two sub-stages (p = 0.001) (Table 4).

We found that there was significant association between histological type and treatment response of primary tumor (p = 0.015) (Table 4).

It was observed that treatment response was better in non-smoker group but

Table 4. Association between treatment responses of primary tumor with performance status, TNM stage, histological type and smoking status (N = 66).

Variable	Reduction of Primary Tumor		p-value
	Responded (CR + PR) (n = 50)	Not responded (SD + PD) (n = 16)	
Performance status according to ECOG			
0	11 (84.6%)	2 (15.4%)	<0.001[a]
1	38 (97.4%)	1 (2.6%)	
2	1 (7.1%)	13 (92.9%)	
TNM stage			
IIIA	29 (96.7%)	1 (3.3%)	<0.001[a]
IIIB	21 (60.0%)	14 (40.0%)	
IIIC	0 (0.0%)	1 (100.0%)	
Histological Type			
Squamous Cell Carcinoma	30 (88.2%)	4 (11.8%)	0.015[b]
Adenocarcinoma	20 (62.5%)	12 (37.5%)	
Smoking status			
Smoker	35 (71.4%)	14 (28.6%)	0.205[b]
Non-smoker	15 (88.2%)	2 (11.8%)	

p-values obtained from: a = Chi-square test, b = Fisher's exact test.

no significant association between smoking habit and treatment response of primary tumor ($p > 0.05$) (Table 4).

3.3. Toxicities

Most observed toxicity in both Arm A and Arm B (during and after 6 weeks and 12 weeks of completion of radiotherapy) were as follows:

Esophagitis was frequently observed during radiotherapy and after treatment in both arms. In Arm A, 15 patients developed grade 1 esophagitis and 10 patients developed grade 2 esophagitis respectively. In Arm B, 17 patients developed grade 1 esophagitis, 12 patients developed grade 2 esophagitis respectively. This difference was not statistically significant ($p > 0.05$) (Table 5).

Table 5. Distribution of the study patients by toxicities (N = 66).

Variables	Arm A (n = 33)	Arm B (n = 33)	p-value
Esophagitis	**(n = 25)**	**(n = 29)**	
Grade 1	15(45.5%)	17(51.5%)	0.918[a]
Grade 2	10(30.3%)	12(36.4%)	
Pneumonitis	**(n = 18)**	**(n = 23)**	
Grade 1	9(27.3%)	12(36.4%)	0.890[a]
Grade 2	9(27.3%)	11(33.3%)	
Dermatitis	**(n = 8)**	**(n = 10)**	
Grade 1	6(18.1%)	8(24.2%)	1.000[b]
Grade 2	2(6.1%)	2(6.1%)	
Nausea	**(n = 17)**	**(n = 21)**	
Grade 1	15(45.5%)	18(54.5%)	1.000[b]
Grade 2	2(6.1%)	3(9.1%)	
Vomiting	**(n = 20)**	**(n = 24)**	
Grade 1	18(54.2%)	19(57.6)	0.428[b]
Grade 2	2(6.1%)	5(15.2%)	
Anemia	**(n = 19)**	**(n = 22)**	
G1	15(45.5%)	17(51.5%)	1.000[b]
G2	4(12.1%)	5(15.2%)	
Neutropenia	**(n = 14)**	**(n = 11)**	
G1	12(36.4%)	11(33.3%)	0.487[b]
G2	2(6.1%)	0(0.0%)	
Thrombocytopenia	**(n = 33)**	**(n = 33)**	
G1	10(30.3%)	13(39.4%)	0.438[a]

p-values obtained from: a = Chi-square test, b = Fisher's exact test.

Radiation pneumonitis was observed mostly after treatment completion in both arms. In Arm A, 9 patients developed grade 1 and 9 patients developed grade 2 pneumonitis. In Arm B, 12 and 11 patients developed grade 1 and grade 2 pneumonitis respectively. This difference was not statistically significant ($p > 0.05$) (Table 5).

In Arm A, 6 (18.1%) patients and 2 (6.1%) patients developed grade 1 and grade 2 dermatitis respectively. In Arm B, 8 (24.2%) patients and 2 (6.1%) patients developed grade 1 and grade 2 dermatitis respectively. The difference was not statistically significant ($p > 0.05$) (Table 5).

Nausea and vomiting were observed during treatment. But there was no statistically significant difference was found between the groups ($p > 0.05$) (Table 5).

In Arm A, 15 patients and in Arm B, 17 patients had grade 1 anemia. Regarding neutropenia and thrombocytopenia, no significant difference was found between the groups (Table 5).

No patients from either group experienced grade 3 toxicity.

The multivariate logistic regression analysis assessed independent predictors of treatment response. ECOG performance status was not significantly associated with response (OR 0.600, 95% CI: 0.123 - 2.940, $p = 0.529$). Stage IIIA showed a lower odd of response (OR = 0.140, 95% CI: 0.026 - 0.756), but this did not reach statistical significance ($p = 0.221$). Patients treated with hypofractionated sequential chemoradiotherapy had significantly higher odds of response compared to those treated with conventional fractionated chemoradiotherapy (OR = 3.692, 95% CI: 1.027 - 13.268, $p = 0.045$). Smoking status and histology were not included in the multivariate model (Table 6).

Table 6. Multivariate logistic regression to identify predictors of response in patients with inoperable locally advanced NSCLC.

Variables	B	p-value	OR	95% CI	
				Lower	Upper
ECOG status	−0.511	0.529	0.600	0.123	2.940
Stage (IIIA)	1.970	0.221	0.140	0.026	0.756
Hypofractionated Sequential Chemoradiotherapy	1.306	0.045	3.692	1.027	13.268

4. Discussion

Non-small cell lung cancer (NSCLC) represents over 80% of lung cancers and approximately one-third of these NSCLC manifest as non-metastatic locally advanced disease [4]. The standard treatment option for patients with inoperable non-metastatic locally advanced disease is a combination of chemotherapy and radiation therapy (RT) that provide good performance status to these patients [4]. The present study was performed to estimate the effect of hypofractionated radiotherapy compared to conventional RT on responses and acute toxicities after sequential chemotherapy. In this study total 66 patients with inoperable locally ad-

vanced stage III NSCLC were allocated into two arms: Arm A (conventional fractionated radiotherapy) and Arm B (hypofractionated radiotherapy). Most of the patients in this study belonged to the age group 56 to 65 years. The mean age was 56.03 years in arm A and 56.61 years in arm B. Minimum age was 45 years in Arm A, 44 years in Arm B. Maximum age was 66 years in Arm A, 65 years in Arm B. The overall distribution was 80.3% male and 19.7% female; the male to female ratio was 4.07:1. There was no significant difference in mean age and sex among Arm A and Arm B. These findings were consistent with a similar previous study [16].

Established environmental risk factors for lung cancer include smoking cigarettes and other tobacco products and exposure to secondhand tobacco smoke. Cigarette smoking is the predominant cause of lung cancer and the leading worldwide cause of cancer death. Current study also reflected this issue. In this study, among 66 lung cancer patients, 49 patients were found to be smoker which makes almost 74.2% of the study population indicating that smoking indeed can be considered as the prime factor behind lung cancer. This finding is also supported by a related study where 82.8% of patients who presented with locally advanced stage lung cancer were smokers [17].

Most of the patients who were included in the study had ECOG performance status of 0-1. Fewer patients were attributed to ECOG 2. ECOG > 2 were not included in this study owing to their decreased capacity to tolerate the treatment. This observation correlates with the finding of a previous study, where around 78% of patients had an ECOG score of 0 - 1 and 17% had ECOG performance status-2 [18]. After completion of the treatment 6 patients in Arm A and 5 patients in Arm B had ECOG score 3. However, the difference was not statistically significant.

Adenocarcinomas are known to be the most common histological variety of non-small cell lung cancer. However, in our overall observation, adenocarcinoma and squamous cell carcinoma had almost equal proportions; 32 (48.5%) adenocarcinoma and 34 (51.5%) squamous cell carcinoma. Arm A and Arm B had 15 (45.5%) and 17 (51.5%) patients with adenocarcinoma respectively. These findings correlated to the study by Westover KD *et al.*, where squamous cell carcinomas were in similar proportions to adenocarcinoma; 43% and 43% respectively [19].

Stage III NSCLC patients were included in this study; Stage III is divided into IIIA, IIIB, and IIIC according to the new AJCC stage categorization in 8th edition. In Arm A there were 14 (42.4%) patients with stage IIIA, 18 (54.5%) with stage IIIB, and 1(3%) with stage IIIC. Similarly, in Arm B, there were 16(48.5%), 17 (51.5%) patients with stage IIIA and IIIB respectively. Overall, highest number of patients presented with stage IIIB-35 (53%). The difference between the two arms was not statistically significant ($p = 0.805$). This observation was similar to a study conducted by Maguire J *et al.* on-stage III NSCLC, where 43% patients had stage IIIA and 57% patients had stage IIIB disease [20]. Usually, patients with NSCLC

develop symptoms very late in the course of disease and also the symptoms are similar to those of other common illnesses like smoking induced chronic cough. In addition to that, most patients are of older age group and have multiple co-morbidities. These could be the reasons leading to higher proportions of patients presenting in later stages. Another important factor is lack of awareness.

In this study, the overall common presentation in both the groups was cough followed by weight loss and chest pain, shortness of breath, hemoptysis. There was no significant difference between the two groups regarding presenting complaints. Our finding was similar to the observation of Corner J *et al.*, where cough, breathlessness, and chest pain were the most common presentations [21].

The main end-point of current study was clinical response and acute toxicities. On follow up, subjective response was evaluated through history and by analyzing the overall wellbeing of the patients. Based on the findings of CECT chest, objective response was evaluated. After completion of 4 cycles of sequential chemotherapy, response was evaluated in both arms: In Arm A, 27 (81.8%) patients showed partial response (PR) and 29 (87.9%) patients showed partial response (PR) in Arm B. Stable disease (SD) was observed among 6 (18.2%) patients in Arm A and 4 (12.1%) patients in Arm B. No complete response (CR) was found. Then patients of Arm A received 60 Gy radiotherapy in 30 fractions and Arm B patients were treated with 55 Gy radiotherapy in 20 fractions, 21 days after completion of chemotherapy. Six weeks following completion of radiation treatment, 1st follow up was done: we observed that in Arm A, 1 patient had complete response, 27 patients had partial response, and 5 patients had stable disease. Whereas, in Arm B, 3 patients showed complete response, 29 patients showed partial response and 1 patient showed stable disease. Overall, 4 patients showed complete response, 56 showed partial response and 6 patients showed stable disease. None showed progressive disease. Although, arm B showed arithmetically better response compared to Arm A, but that was not statistically significant ($p > 0.05$).

After 12 weeks of treatment completion, 2nd follow up was conducted: at that time, complete response was observed in 3 (9.1%) patients and 5 (15.2%) patients in Arm A and Arm B respectively. Likewise, 21 (63.6%) patients in Arm A and 23 (69.7%) patients in Arm B showed partial response. Stable disease was found in 6 (18.2%) patients in Arm A and 3 (9.1%) patients in Arm B. However, 3 (9.1%) patients in Arm A and 2 (6.1%) in Arm B developed progressive disease. Here, 2 patients in Arm A and 2 patients in Arm B, previously thought to have partial response in 1st follow up, showed complete response later in 2nd follow up; reason for this being, the imaging findings were probably due to post-radiation inflammatory changes which were misinterpreted as residual tumor. A patient with progressive disease had loco-regional progression while rest 3 had distant metastases and one (from Arm B) had disease spread to the bone (vertebral metastases).

On 3rd or final follow up, after 24 weeks of treatment completion, it was found that, 3 (9.1%) patients in Arm A and 5 (15.2%) patients in Arm B maintained complete response. Twenty (60.6%) patients in Arm A and 21 (63.6%) patients in

Arm B showed partial response. Four (12.1%) patients in Arm A and 2 (6.1%) patients in Arm B had stable disease. Arm A had 6 (18.2%) patients and Arm B had 5 (15.2%) patients with progressive disease. Overall, 69.7% patients in Arm A and 78.8% patients in Arm B showed response. Although, the overall response was found to be better mathematically in Arm B but it was not statistically significant ($p > 0.05$). In a retrospective study it was documented that overall, 71.4% response rate in conventional fractionation arm (Arm A) and 88.2% response rate in hypofractionated radiotherapy arm (Arm B) [10]. Reason behind their increased response may be the use of more advanced techniques. Tsao MN *et al.* concluded that hypofractionated radiotherapy can achieve similar local control outcomes as conventional fractionated radiotherapy in carefully selected patients [22].

Responses were also analyzed on the basis of ECOG performance status, smoking habit and histological variety. Out of total 52 patients with ECOG PS of 0-1, 49 of them showed Response (CR + PR), while from 14 patients with ECOG PS-2, 1 of them showed partial response. More patients with ECOG PS-2 developed stable disease or progression. Study result reflected that good locoregional control was achieved by patients having ECOG PS (0-1). Machtay M *et al.* evaluated the association between locoregional control and ECOG PS; in line with our outcome, their analysis revealed that ECOG PS (0-1) was associated with better locoregional control [23].

Regarding stage, in stage IIIA 29 patients showed response (CR + PR) and in stage IIIB, total 21 patients showed response (CR + PR) and one patient from stage IIIC went to progressive disease group. This reflected that response rate was better in stage IIIA than stage IIIB and IIIC and that was statistically significant ($p = 0.001$). Pemberton LS *et al.* also observed in his study that early stage was a significant predictor of overall survival [18]. While considering histological variety, 32 patients had adenocarcinoma and 34 patients had squamous cell carcinoma. There was better overall response in squamous cell carcinoma compared to adenocarcinoma ($p = 0.015$). This finding was supported by Liu-Jarin X, who found that squamous carcinoma was associated with a significantly higher probability of treatment response than adenocarcinomas [24]. Reasons behind poor local control in adenocarcinoma as preferred chemotherapy protocol in adenocarcinoma is cisplatin and pemetrexed which was not selected to maintain uniformity in both arms.

Out of total 49 smokers and 17 non-smokers, overall response (CR + PR) was better in non-smokers. But no significant association between them.

All patients were assessed every weekly for any toxicities during radiotherapy period. Different types of toxicities *i.e.*, both hematological and non-hematological were observed during the therapy and on subsequent follow ups. In current study, main observed toxicities were esophagitis and radiation pneumonitis. Esophagitis was slightly higher in Arm B but the observed difference was not statistically significant ($p = 0.647$). Most of the toxicities were grade 1. Most of the toxicities were relieved spontaneously and few patients needed conservative man-

agement. Nutritional status and hydration of these patients were carefully maintained. It was reported that, hypofractionated radiotherapy significantly reduced the risk of esophagitis; which reflected those acute toxicities were less in hypofractionated radiotherapy [25] [26].

Radiation pneumonitis was quite common mostly grade 1 and 2, but was observed after the completion of treatment in both arms. No patient developed ≥ grade 3 pneumonitis. Difference between two arms was not statistically significant ($p > 0.05$). Similar to our observation Zhu ZF *et al.* showed 26.5% grade 1, 26.5% grade 2 radiation pneumonitis in his study while using hypofractionated radiotherapy [26]. Meta-analysis done by Liu J *et al.* extracted data from six trials with 1211 patients where the results suggested that hypofractionated radiotherapy led to significant relative decreases of 11% and 2% in esophagitis and pneumonitis, respectively, compared to conventional radiotherapy though in this study pneumonitis is slightly increased in hypofractionated arm (Arm B) most probably due to no use of motion management except in some cases where deep inspiration breath hold techniques were applied [25].

Regarding skin toxicities very few patients developed grade 1 or grade 2 dermatitis. The difference was not statistically significant ($p = 0.908$). Study conducted by Osti MF *et al.* showed 7% Grade 1 & no grade 2 and 3 dermatitis [27]. Three-dimensional conformal radiotherapy using high megavoltage energy could be the reason for a low percentage of patients developing skin toxicities. Although statistically not significant, nausea and vomiting were found slightly more common in Arm B. They were managed with counselling, antiemetic as well as nutritional supports and hydration. Hematological toxicities were less commonly observed in both arms and there was no significant difference between the two arms. Said BI *et al.* Concluded acute toxicities of hypofractionated radiotherapy were broadly comparable to conventional fractionation when modern techniques and planning constraints were used [28].

5. Conclusion

This study reflected that hypofractionated sequential chemoradiotherapy is equally effective as conventional fractionated sequential chemoradiotherapy in the management of inoperable locally advanced non-small cell lung cancer as there is no significant difference in treatment response and acute toxicities.

Limitations of the Study

The current study had certain limitations. It was a single center study and conducted on small number of samples without randomization. Pulmonary function tests were not done in all cases. Image fusion and motion management were not done in all cases. Late toxicities were not evaluated due to time constrains.

Recommendations

Further studies involving multiple centers with large sample size may be helpful

to explore effectiveness of hypofractionated sequential chemoradiotherapy with long term toxicities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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