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Original Article

A Comparative Study on Response of Concurrent versus Sequential Chemoradiation in Inoperable Locally Advanced Non-Small Cell Lung Cancer

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ABSTRACT

Introduction: *Nearly one third of non-small cell lung cancer (NSCLC) patients present in locally advanced stage (stage III). Various clinical trials have proved that the combination of chemotherapy and radiotherapy produce better response in inoperable locally advanced NSCLC. But the optimal sequencing and integrating scheme is yet to be established.* ***Objective:*** *To evaluate and compare the response of concurrent (simultaneous chemotherapy and radiotherapy) and sequential (chemotherapy followed by radiotherapy) chemoradiation approach using the same chemotherapeutic agents and radiation dose in locally advanced NSCLC patients.* ***Methods and material****: A Quasi-experimental study was carried out in the Department of Radiotherapy of Rajshahi Medical College Hospital. Sixty six diagnosed patients were enrolled on the basis of eligibility criteria and allocated into two groups by purposive sampling. The concurrent arm was treated with thoracic radiotherapy (60 Gy in 30 fraction) by conventional planning with concomitant Inj. Cisplatin and Inj. Etoposide on day 1-5 and day 29-33 of radiotherapy and the sequential arm was treated with Inj. Cisplatin and Inj. Etoposide on day 1-3, I/V 4 weekly for 3 cycles, if no progression occurred it was followed by radiotherapy with same radiation dose and technique.* ***Results****: In this study the overall response was higher in concurrent arm than sequential arm (78.8% vs 72.7%) but the superiority was not confirmed statistically (p=0.56).* ***Conclusion:*** *Concurrent chemoradiation had slightly higher response, but considering its toxicity profile, it should be the choice of treatment approach in patients with good performance status.*

Keyword: *Non-small cell lung cancer, Chemoradiotherapy*

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INTRODUCTION

Worldwide, lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, representing close to 1 in 5 (18.4%) cancer deaths and the 5-year survival is around 17.8%[1]. There are two main subtypes of lung cancer, small cell lung carcinoma and non-small-cell lung carcinoma (NSCLC), accounting for 15% and 85% of all lung cancer, respectively. NSCLC is further classified into three types mainly: squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma[2]. In Bangladesh, a WHO study estimates that there are 1,96,000 lung cancer cases in 2013, is the leading cause of death from cancer in Bangladesh[3].

One of the reasons of lung cancer being such a highly lethal disease is only a small fraction present in early stage. Majority of patients present in either as metastatic (stage IV) or locally advanced (stage III) disease. Approximately 35% of patients with NSCLC present with locally advanced non-metastatic disease. Although gathered under one umbrella, stage III lung cancer is a broad spectrum heterogeneous stage. Thus an ideal sequencing of modalities of treatment options is hard to determine which is also reflected in 5 year survival of stage III patients ranging from 36% to 13% only[4].

Like most of the cancers, lung cancer is also treated with surgery, chemotherapy and radiotherapy alone or their various combinations. Among all the treatment modalities, although surgery yields the best results but there are some very important factors that determine the operability of a NSCLC patient. If there are evidences of distant metastases, including metastases to the opposite lung or persistent pleural effusion with malignant cells or superior vena cava obstruction or involvement of the supraclavicular or neck lymph nodes or contralateral mediastinal lymph nodes (proved histologically) or recurrent laryngeal nerve or phrenic nerve involvement or invasion of tracheal wall or carina, the tumor is considered as unresectable. Also some other factors such as old age, presence of comorbidities like poor cardiac status or impaired pulmonary function make the patient inoperable[5]. All these features are very common in stage III NSCLC. Also some patient may refuse to go for surgery. Thus chemotherapy and radiotherapy have to play the pivotal role in management of locally advanced NSCLC especially in our context where there is an inadequacy of thoracic surgery facilities.

The administration of chemotherapy and radiotherapy within a chemoradiation regimen may be sequential (chemotherapy is followed by radiotherapy) or concurrent (the two modalities are administered at the same time). Both approaches have been investigated extensively. The largest meta-analysis, conducted by the Non-Small CellLung Cancer Collaborative Group, was based on data from 22 randomized trials with total of 3,033 locally advanced patients comparing sequential chemoradiation to radiotherapy only. The overall pooled mortality HR (hazard ratio) was 0.90 ($p<0.006$), demonstrating an absolute survival benefit of 3% at 2 years in favor of sequential chemoradiation[6]. Another large meta-analysis performed to examine the value of concurrent chemotherapy in definitive management of NSCLC included 19 randomized studies with a total of 2,728 patients with NSCLC (stages I through III), who were randomized to receive either concurrent chemoradiotherapy or radiotherapy alone. Concurrent chemotherapy significantly reduced overall risk of death (HR 0.71) and improved overall progression free survival at any site (HR 0.69)[7].

However it is still a controversial topic and various studies are going on to determine which chemoradiotherapy combination approach has the best outcome with least toxicity. A phase III randomized trial comparing concurrent chemoradiotherapy

with mitomycin, vindesine, and cisplatin (MVP) to sequential chemotherapy with same regimen and radiation dose, demonstrated a statistically significant response rate and survival advantage to the concurrent approach (response rate 84% vs 66% and 5-year survival of 15.8% vs. 8.9%)[8]. In another study where sequential and concurrent chemoradiation both with cisplatin and vinorelbin was compared, a statistically significant response rate in favor of concurrent was observed (80% vs 47%; $p<0.001$)[9]. Both of the studies also showed higher toxicity in concurrent arms than sequential. On the contrary, in a similar randomized trial, conducted by Fournel et al.(2005)[10] found higher response in sequential arm than concurrent arm .The response rates were 54% with sequential treatment and 49% with concurrent treatment , although the differences were not statistically significant ($p>0.56$). So the optimal sequencing and integrating scheme of chemoradiation is yet to be confirmed. Moreover, most of the radiotherapy centers in our country are not sophisticated enough, making it more challenging. As Cisplatin based regimens are considered as standard[11] and have so far shown the best response in various trials, the aim of this study was to evaluate and compare the response of concurrent and sequential chemoradiotherapy using the same chemotherapeutic agents (Cisplatin and Etoposide) and radiation dose (60 Gy), in a quest to sort out the more suitable approach in a low set up center.

OBJECTIVE

To compare the response between concurrent and sequential chemoradiotherapy in locally advanced non-small cell lung cancer patients.

METHODS AND MATERIALS

This study was a Quasi-experimental study carried out in Department of Radiotherapy, Rajshahi Medical College Hospital, Rajshahi from November 2018 to October 2019. Patients with histopathologically or cytologically diagnosed locally advanced NSCLC meeting the eligibility criteria, attended in the department during the study period were selected. Sample size was calculated as sixty six (n=66,with 33 in each arm) at 5% level of significance with 95% confidence level. Sampling technique was Non random (purposive sampling). Inclusion criteria was determined as patients with histological or cytological diagnosis of NSCLC in locally advanced stage (stage III according to AJCC TNM staging, 2017), who could not be treated surgically and having good performance status [Eastern Co-operative Oncology Group (ECOG) score ≤ 2]. All patients should have a normal hepatic and renal function evidenced by biochemical tests. Patients with history of prior chemotherapy or radiotherapy to the chest region or any surgery (excluding diagnostic biopsy) of the primary site, or had any serious concomitant medical illness were excluded. A semi-structured data collection form was used as the research instrument. Eligible patients were allocated into 2 arms-

1. Arm-A (concurrent chemoradiotherapy):Definitive thoracic radiotherapy with 60 Gy 30 fraction, 2 Gy per fraction, 5 days a week for 6 weeks concurrent with Inj. Cisplatin 20 mg/m^2/day and Inj. Etoposide 50 mg/m^2/day on Day 1-5 and Day 29-33 of radiotherapy.
2. Arm-B (sequential chemoradiotherapy):Inj. Cisplatin 100mg/m^2 on Day 1 and Inj. Etoposide 100mg/m^2 on Day 1-3, 4 weekly for 3 cycles, if no progression, then 2 weeks rest which was followed by definitive thoracic radiotherapy with 60 Gy 30 fraction, 2 Gy per fraction, 5 days a week for 6 weeks.

Proper hydration was maintained and pre and post chemotherapy medication with antiemetic, steroid, H_1 and H_2 blocker given before and after chemotherapy. Toxicities of radiotherapy were treated promptly and aggressively to prevent any

discontinuation. Radiotherapy was delivered using telecobalt-60 machine. For both groups thoracic radiotherapy were given in two parallel opposed anterior-posterior fields encompassing primary tumor with 2 cm margin and hilar and mediastinal lymph node regions. Supraclavicular region was not treated routinely unless clinically positive lymph node was present. After 44 Gy spinal cord was spared and primary tumor and involved lymph node were given to 60 Gy. Tumor response was evaluated according to the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors, version 1.1, 2008). After completion of treatment patients were carefully supervised to attain first follow-up at 4th week. Subsequent follow up was done every four weeks interval. Follow up examination done with physical, radiological and laboratory tests as needed. The final response was assessed by clinical examination, chest X-ray, CT scan of chest (if needed) and ultrasonography of whole abdomen at twelve weeks after completion of treatment. Data analysis was done according to the objectives of the study by using the IBM SPSS (Statistical Product and Service Solution) software program for windows, version 25.0 available in the institute. The data was analyzed using the unpaired 't' test for continuous variables and the χ^2 test for categorical variables and presented in tables, figures, diagrams. All reported p values are two sided and $p< 0.05$ will be considered statistically significant. Prior to commencement of the study, research protocol was approved by the Institutional review board and the Ethical committee. All patients included in the study were informed about the nature of the study. They were explained about the aim, objectives, procedures, risk and benefits of the procedures and their right to refuse or accept to participate, in easily understandable language. Written informed consent was taken from each patient. It was assured that all information from the patients will be kept secret.

RESULTS

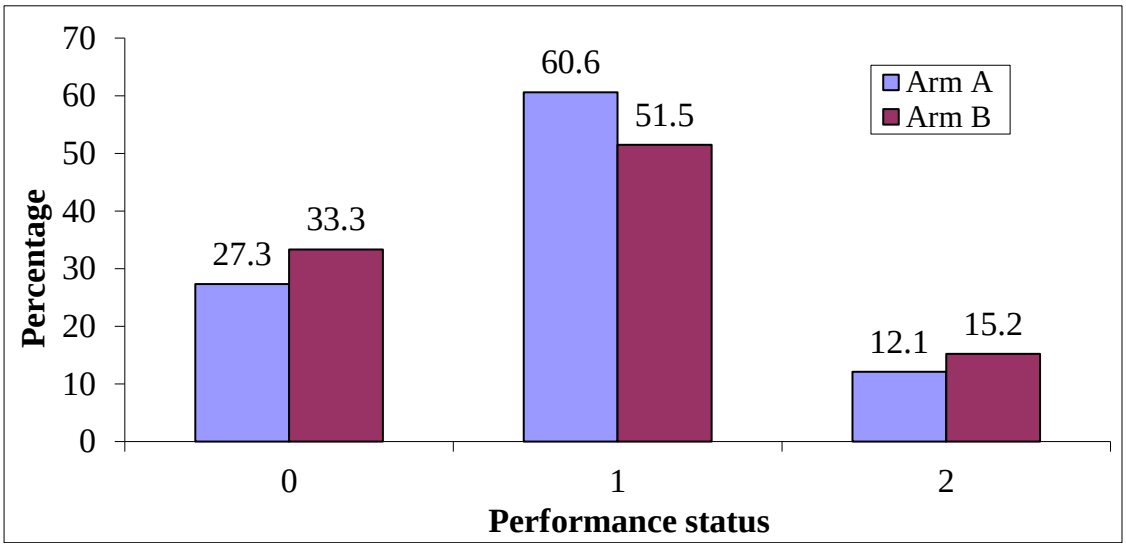

Figure I: Bar diagram shows performance status by ECOG of the study patients

Figure I shows that majority patients had performance score 1 in both groups, which was 20(60.6%) in group Arm A and 17(51.5%) in group Arm B.

Table I: Distribution of the study patients according to location of lesion (n=66)

Location of lesion	Arm A (n=33)		Arm B (n=33)		χ^2 value	p value
	n	%	n	%		
Right lung	20	60.6	22	66.7	0.26	0.609^{ns}
Left lung	13	39.4	11	33.3		

ns= not significant
p value reached from chi square test

Table I shows that majority patients had right lung lesion, which was 20(60.6%) in group Arm A and 22(66.7%) in Arm B. The difference was not statistically significant (p>0.05) between two groups.

Table II: Distribution of the study patients according to site of lesion (n=66)

Site of lesion	Arm A (n=33)		Arm B (n=33)		χ^2 value	p value
	n	%	n	%		
Central	12	36.4	14	42.4	0.25	0.614^{ns}
Peripheral	21	63.6	19	57.6		

ns= not significant
p value reached from chi square test

Table II shows that peripheral lesion was found 21(63.6%) in group Arm A and 19(57.6%) in Arm B. The difference was not statistically significant (p>0.05) between two groups.

Table III: Distribution of the study patients according to histological type (n=66)

Histological type	Arm A (n=33)		Arm B (n=33)		χ^2 value	p value
	n	%	n	%		
Squamous cell carcinoma	20	60.6	14	42.4		
Adenocarcinoma	11	33.3	15	45.5	2.34	0.310^{ns}
Large cell carcinoma	2	6.1	4	12.1		

ns= not significant
p value reached from chi square test

Table III shows that squamous cell carcinoma was found 20(60.6%) in group Arm A and 14(42.4%) in Arm B. Adenocarcinoma was found in 11(33.3%) and 15(45.5%) in group Arm A and Arm B respectively. Large cell carcinoma was 23(6.1%) in group Arm A and 4(12.1%) in Arm B. The difference was not statistically significant (p>0.05) between two groups.

Table IV: Distribution of the study patients according to TNM stage (n=66)

TNM stage	Arm A (n=33)		Arm B (n=33)		χ^2 value	p value
	n	%	n	%		
IIIA	15	45.5	14	42.4		
IIIB	12	36.4	14	42.4	0.28	0.870^{ns}
IIIC	6	18.2	5	15.2		

ns= not significant
p value reached from chi square test

Table IV shows that TNM stage IIIA was found 15(45.5%) in group Arm A and 14(42.4%) in Arm B. TNM stage IIIB was 12(36.4%) in group Arm A and 14(42.4%) in Arm B. TNM stage IIIC was 6(18.2%) and 5(15.2%) in group Arm A and Arm B respectively. The difference was not statistically significant (p>0.05) between two groups.

Table V: Distribution of the study patients according to response of primary tumor (n=66)

Reduction of primary tumor	Arm A (n=33)		Arm B (n=33)		χ^2 value	p value
	n	%	n	%		
Complete response	3	9.1	2	6.1		
Partial response	23	69.7	22	66.7	0.62	0.891^{ns}
Stable	4	12.1	6	18.2		
Progressive	3	9.1	3	9.1		

ns= not significant
p value reached from chi square test

Regarding response of primary tumor, it was observed that majority patients had partial response in both groups, which was 23(69.7%) in group Arm A and 22(66.7%) in Arm B. The difference was not statistically significant (p>0.05) between two groups.

Table VI: Distribution of the study patients according to response of lymph node (n=66)

Response of lymph node	Arm A (n=33)		Arm B (n=33)		χ^2 value	p value
	n	%	n	%		
Complete response	6	18.2	4	12.1		
Partial response	21	63.6	23	69.7		
Stable	3	9.1	4	12.1	0.97	0.915^{ns}
Progressive	1	3.0	1	3.0		
No lymphadenapathy	2	6.1	1	3.0		

ns= not significant
p value reached from chi square test

Regarding response of lymph node, it was observed that that majority patients had partial response in both groups, which was 21(63.6%) in group Arm A and 23(69.7%) in Arm B. The difference was not statistically significant (p>0.05) between two groups.

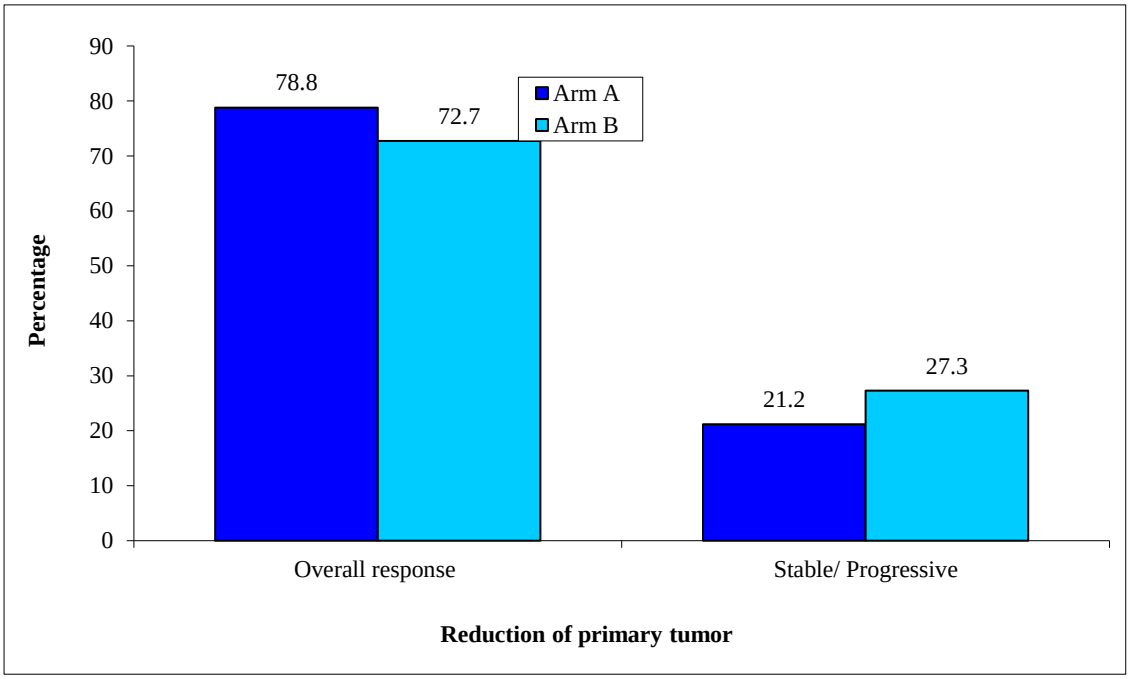

Figure II: Bar diagram shows response of primary tumor of the study patients

Majority patients had overall response in both groups, which was 26(78.8%) in group Arm A and 24(72.7%) in Arm B. The difference was not statistically significant (p>0.05) between two groups.

Table VII: Association between response of primary tumor with performance status (n=66)

Performance status	Reduction of primary tumor								χ^2 value	p value
	Complete response (n=5)		Partial response (n=45)		Stable (n=10)		Progressive (n=6)			
	n	%	n	%	n	%	n	%		
0	4	80.0	10	22.2	4	40.0	2	33.3		
1	1	20.0	28	62.2	6	60.0	2	33.3	11.29	0.080^{ns}
2	0	0.0	7	15.6	0	0.0	2	33.3		

ns= not significant
p value reached from chi square test

Four (80.0%) patients were found performance status score 1 in complete response, 10(22.2%) in partial response, 4(40.0%) in stable and 2(33.3%) in progressive of primary tumor. The difference was not statistically significant (p>0.05) among four groups.

Table VIII: Association between response of primary tumor with TNM stage (n=66)

TNM stage	Reduction of primary tumor								χ^2 value	p value
	Complete response (n=5)		Partial response (n=45)		Stable (n=10)		Progressive (n=6)			
	n	%	n	%	n	%	n	%		
IIIA	4	80.0	23	51.1	2	20.0	0	0.0		
IIIB	1	20.0	20	44.4	3	30.0	2	33.3	27.52	0.001[s]
IIIC	0	0.0	2	4.4	5	50.0	4	66.7		

s= significant
p value reached from chi square test

Table VIII shows that TNM stage IIIA was significantly higher in complete response and partial response than other two sub-stages.

TableI X: Association between response of primary tumor with histological type (n=66)

Histological type	Reduction of primary tumor								χ^2 value	p value
	Complete response (n=5)		Partial response (n=45)		Stable (n=10)		Progressive (n=6)			
	n	%	n	%	n	%	n	%		
Squamous cell carcinoma	4	80.0	23	51.1	5	50.0	2	33.3		
Adenocarcinoma	1	20.0	17	37.8	4	40.0	4	66.7	4.03	0.673[ns]
Large cell carcinoma	0	0.0	5	11.1	1	10.0	0	0.0		

ns= not significant
p value reached from chi square test

Table IX shows that there was no significant association between histological type and response of primary tumor (p=0.673).

DISCUSSION:

Despite non-random allocation of patients into study arms demographic features were homogenous in both arms and difference were insignificant (p>0.2) in this study. Central lesion was defined as tumor (epicenter) arising within the sagittal plane passing through the medial two third of hemithorax in chest image (X-ray or CT scan) at level of maximum thoracic diameter in accordance with NCCN (National Comprehensive Cancer Network) guideline[12]. Central lesions are difficult to treat. Excessive toxicity has been reported in organs at risk like spinal cord, esophagus, contralateral lung and heart, when treating central tumors with high dose radiotherapy[13]. Although incidence of central tumor is more than peripheral (Sharma et al., 2002)[14], but in this study more (about two third) peripheral tumors were taken intentionally. Peripheral lesions found in 21(63.6%) in Arm A and 19(57.6%) in Arm B. The difference was not statistically significant (p>0.05) between two groups.

Among the histologic types, squamous cell carcinoma was the eminent one (34 in 66; 51.5%). Similar results shown in various studies like Fournel et al. (2005)[10] and Zatloukal et al. (2004[)][9], where squamous cell carcinoma was 58% and 45%

respectively. Although in arm-B adenocarcinoma was slightly more than squamous cell carcinoma (45.4% versus 42.5%). This could be reasoned by the effect of purposive sampling.

Regarding the response in both groups, it was found that 26(78.8%) in concurrent arm and 24(72.7%) in sequential arm had overall response, but only 3 (9.1%) in arm-A and 2 (6.1%) in arm-B had complete response. Rest of patients, that is 7(21.2%) in concurrent arm and 9(27.3%) in sequential arm had either stable or progressive disease. The difference was not statistically significant (p=0.56) between two groups. Similar result shown in Fournel et al. (2005)[10], where response rate of concurrent arm was 49% and sequential arm was 54% with an insignificant difference (p=0.56). But a comprehensively higher response rate for the concurrent arm (84.0%) than the sequential arm (66%) was found (p =0.0002) in Furuse et al. (1999)[8]. In a recent phase III RCT concurrent arm response rate (70%) was also significantly higher than sequential arm (61%) $p<0.05$[15]. In these 3 trials mentioned, very large sample size (200 to 600 plus) were used in comparison to my study. This could have been the distinctive point to the fact that despite having a better response in the concurrent arm in this study the superiority was not proven statistically.

This response was further analyzed to see association with performance status of the patients, histologic type and TNM staging of the tumor. Although 80% of the complete response were seen in performance status ECOG score '0' and 'squamous cell carcinoma' histology separately, a statistical association could not be reached with χ^2 test. However TNM stage IIIA clearly had a better response than other two (IIIB and IIIC), p=0.001. It should be mentioned here that the staging evaluation in this study was image based only and despite having indications, no patient had invasive mediastinal staging. Thus this finding would be defied by many authors, as such described by Chiang et al. (2019)[16] - "Several studies have shown that despite the existence of clinical guidelines for many years recommending careful mediastinal staging with biopsy confirmation, the large majority of patients are staged using chemotherapy alone which is notoriously inaccurate and such limited clinical stage evaluation is associated with dramatically worse clinical outcomes".

CONCLUSION

Combination of chemotherapy and radical radiotherapy with curative intent stands the best possible approach in treating the locally advanced inoperable lung cancer patients. The aim of this study was to compare the response and toxicity of concurrent and sequential chemoradiation, two mostly used approaches. Although the overall response was higher in concurrent arm than sequential arm (78.8% vs 72.7%) but the superiority was not confirmed statistically (p=0.56). Concurrent chemoradiation has slightly higher response, but considering its toxicity profile, it should be the choice of treatment approach in patients with good performance status. Further study involving multiple centers with a larger sample size should be carried out to confirm its superiority.

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