

# A Randomized Prospective Study Comparing Concomitant Chemoradiotherapy Using Paclitaxel-Carboplatin with Concomitant Chemoradiotherapy Using Etoposide-Cisplatin in Inoperable or Nonresectable Locally Advanced Non-small Cell Lung Cancer

## Abstract

**Context:** Several randomized trials have established that the best survival can be achieved in patients with locally advanced non-small cell lung cancer (NSCLC) with concurrent chemoradiation (CRT). In this study, we have compared different chemotherapy regime along with radiation in locally advanced NSCLC. **Aims:** Compare the disease response, toxicity, quality of life (QoL) and overall survival in concomitant CRT using paclitaxel-carboplatin versus cisplatin-etoposide for the radical treatment of NSCLC. **Subjects and Methods:** In this randomized study, 36 patients were enrolled. In study arm, patients were treated with injection cisplatin-etoposide along with external beam radiotherapy (EBRT) to a total dose of 60 Gy, using CO-60 machine. In study arm, patients were treated with injection paclitaxel-carboplatin along with EBRT. QoL was evaluated using QLQ-LC13 questionnaire. **Results:** The median age of patients was 65 years. Complete response was obtained in two patients in control and two patients in the study arm. Partial response was obtained in 11 patients in the control arm and 13 patients in the study arm. The observation was statistically insignificant. When Grade  $\geq$ III toxicities are analyzed, the total number of events in the control arm were three (16.7%) and in the study arm were five (27.8%) which is statistically insignificant. **Statistical Analysis Used:** The data were analyzed using Chi-square and *t*-test, and *P* values were calculated. **Conclusion:** The response rates and disease progression are similar between the two arms. The other endpoints are also similar between the two arms. However, larger studies are needed to establish comparability.

**Keywords:** Concurrent chemoradiotherapy, non-small cell lung cancer, quality of life

## Introduction

Lung cancer is the most common (2.094 million, 11.6% of all new cases) and the deadliest (1.8 million, 18.4% of all cancer-related deaths) form of cancer worldwide.<sup>[1]</sup> Non-small cell lung cancer (NSCLC) represents more than 80% of all lung tumors and approximately 35% of patients with NSCLC present with locally advanced nonmetastatic disease.<sup>[2]</sup> Surgery is the standard mode of treatment of patients with Stage I and II tumors and for selective patients with Stage III tumors. Only about 20% of all patients presenting with lung cancer are suitable candidates for curative surgery. The use of combined-modality therapy, including radiation and chemotherapy, is recommended for locally advanced Stage

III disease. Combination chemoradiotherapy was superior to radiotherapy alone in locally advanced NSCLC. Several studies demonstrated that adding sequential or concomitant chemotherapy to radical radiotherapy improved survival in locally advanced NSCLC.<sup>[3,4]</sup>

Several randomized clinical trials, as well as meta-analyses, have established that the best survival can be achieved in patients with locally advanced NSCLC with concurrent chemoradiation (CCRT) instead of the sequential approach at the cost of increased acute toxicity.<sup>[2,5]</sup> Concurrent chemotherapy and radiation, however, are intended to enhance the locoregional efficacy of this modality. Combined effects of these modalities are based on their

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different toxicity profiles, leading to reduced toxicity: efficacy ratio of the combination.

The treatment of locally advanced (III<sub>A</sub> and III<sub>B</sub>) unresectable NSCLC has rapidly evolved over the last two decades. What has not evolved is the grim prognosis of this set of patients where we might have added a few months to the patients' lives at the expense of significantly higher treatment-related toxicities. Issues regarding the quality of life (QoL) have been found missing in the studies in the radical setting. With the comorbidities of such patients and the aggressive intent which we now employ to treat these patients radically, the QoL is bound to get affected depending on our treatment approach as well as patient-related factors. QoL parameters must be incorporated even in the radical setting as it is the third essential dimension other than the response rates and toxicities. This trial has compared CCRT using paclitaxel-carboplatin and concomitant chemoradiotherapy using cisplatin-etoposide for unresectable locally advanced NSCLC regarding local control, toxicity, overall survival (OS), and QoL in Indian population.

## Subjects and Methods

This prospective randomized study was conducted at our institute from July 1, 2013 to May 31, 2014 on patients suffering from locally advanced nonmetastatic NSCLC. Signed informed consent was taken from all the patients enrolled in this study. The study included all the eligible previously untreated and unresectable patients of squamous cell or adenocarcinoma of the lung with a histologically confirmed diagnosis and no evidence of distant metastasis. The subsites included were Stage IIIa, Stage IIIb and squamous cell carcinoma and adenocarcinoma. All patients were of the age not more than 75 years and having Karnofsky performance status score >70, with normal hematological, renal function, and liver function status.

### Pretreatment work-up

A complete history and thorough physical examination were done. Baseline investigations such as Chest X-ray (posterioranterior and lateral views) blood – hemogram and biochemistries, computed tomography (CT) chest, bronchoscopy + biopsy (or guided FNAC), sputum for cytology/acid-fast bacillus, pulmonary function tests, ultrasonography abdomen and pelvis, electrocardiogram and echocardiogram, bone scan or CT/magnetic resonance imaging brain, if indicated were done. The patients were staged as per American Joint Committee on Cancer staging manual 2010 [Flow Diagram 1].<sup>[6]</sup>

### Randomization

Before randomization, we stratified patients according to clinical stage and histology. Four blocks were created from the stratification factors: III<sub>A</sub> + squamous cell,

III<sub>A</sub> + AdenoCa, III<sub>B</sub> + squamous cell, and III<sub>B</sub> + AdenoCa. In each block, patients were randomized into two groups – control group (CCRT using cisplatin-etoposide) and study group (CCRT using paclitaxel-carboplatin).

### Control arm

Patients were given external beam radiotherapy (EBRT) to a total dose of 60 Gy in 30 fractions at 2 Gy/fraction along with concurrent chemotherapy of injection cisplatin 20 mg/m<sup>2</sup>/day intravenous (iv) and injection etoposide 50 mg/m<sup>2</sup>/day iv days 1–5 and days 29–33 of starting radiation.

### Study arm

Patients were given EBRT to a total dose of 60 Gy in 30 fractions at 2 Gy/fraction along with concurrent chemotherapy injection paclitaxel 50 mg/m<sup>2</sup> iv and injection carboplatin AUC2 every Monday concomitant with radiation.

## Administration of treatment

### Radiotherapy

EBRT was delivered by teletherapy theratron 780e and Equinox Cobalt-60 machines. The conventional simulator was used for radiation planning. Headrest with the bar was used wherein patient's hands were above the head holding the bar. The initial fields encompassed the gross + nodal disease, plus a margin; in the craniocaudal axis 2–3 cm margin was taken on each side, and in the transverse or anteroposterior axes 1–2 cm margin was taken on each side. Spinal cord was off the fields after 44 Gy. Fields were shrunk after 50 Gy to include only the gross + nodal disease, which was treated till 60 Gy. All the plans and field reductions/modifications were verified using simulator before the actual treatment. Differential beam weightage and oblique beams were also utilized to optimize the radiation delivery better.

### Chemotherapy

Antiemetics such as 5HT<sub>3</sub> receptor antagonists (palonosetron 0.25 mg), high-dose steroids (dexamethasone 8–16 mg), and H<sub>2</sub> receptor antagonists (ranitidine 50 mg) were a part of the premedication, and these were infused 30 min before chemotherapy. In the control arm, injection cisplatin 20 mg/m<sup>2</sup>/day and injection etoposide 50 mg/m<sup>2</sup>/day iv days 1–5 and days 29–33 was completed before the delivery of radiation. In the study arm, injection paclitaxel 50 mg/m<sup>2</sup>, injection carboplatin AUC2 iv every Monday concomitant with radiation was completed before the delivery of radiation therapy.

### Assessment

Chest CT scan with contrast enhancement was done before treatment and at first follow-up 6 weeks posttreatment. During treatment, toxicities were assessed every week using radiotherapy and oncology group acute morbidity

scoring criteria.<sup>[7]</sup> Disease response was considered to be complete if there was complete regression of disease, partial, if there was more than 50% regression in the lesion in maximal diameter, stable if lesion regressed <50% in maximal diameter and progressive if lesion increased by 25% or appearance of new lesion or secondary metastatic disease. QoL was evaluated and recorded weekly using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-LC13 questionnaire.<sup>[8]</sup>

### Follow-up

First follow-up was done at 6 weeks. Subsequent follow-up was twice a month for the 1<sup>st</sup> year, followed by once in 4 months for 2 years and once in 6 months after that. Patients with residual disease at first follow-up were considered for salvage surgery if resectable adjuvant chemotherapy was offered to patients with unresectable disease or medically inoperable patients.

### Statistical analysis

The recorded scores of acute radiation reactions experienced by patients in both the arms were analyzed and compared. The locoregional disease status and QoL of the patients in both the arms at the end of radiotherapy and subsequent follow-up were analyzed and compared. The data were analyzed using Chi-square and *t*-test, and *P* values were calculated. Statistical analysis was done with the Statistical Program for Social Sciences (SPSS v23, IBM Corp, USA) was used for analyzing.

### Results

A total of 36 patients of locally advanced NSCLC were included in the analysis. In all, 18 patients were in the control arm and 18 patients in the study arm. Most of the patients in this study were male. The median age at presentation was 57 years ranging from 45 to 65 years. The most common histology in the study was squamous cell carcinoma. Patients were well balanced between the two groups in terms of stage and histology, as shown in Table 1.

### Locoregional control and survival

At first follow-up after completion of treatment, two patients (11.1%) in both the arms had a complete response (CR). Partial response (PR) was obtained in 11 patients (61.1%) in the control arm and 13 patients (72.2%) in the study arm (*P* = 0.480). There were two patients (11.1%) in the control arm and one (5.6%) in the study who were found to have disease progression at 1<sup>st</sup> follow-up [Table 2]. One year progression-free survival was 78% in study arm as compared to 83% in control arm [Figure 1]. The difference was not statistically significant (*P* = 0.674). There was no difference in OS between the two arms (*P* = 0.898) [Figure 2].

Subset analysis by stage and histology showed a similar response in both the arms [Table 3].

**Table 1: Patients characteristics**

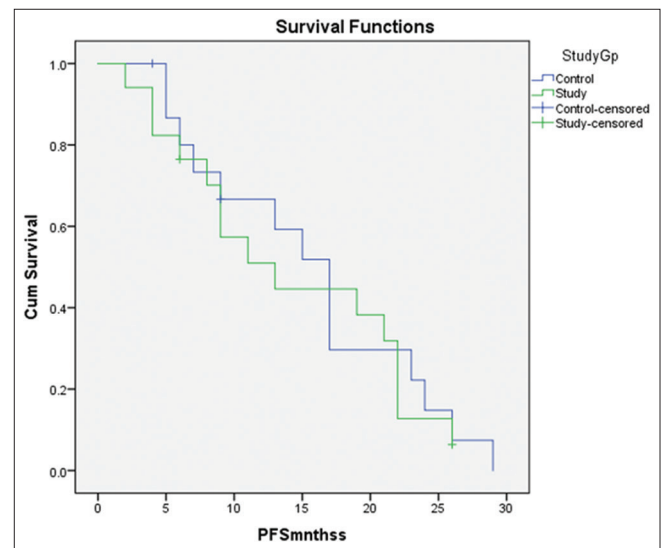
	n (%)	
	Control arm	Study arm
Gender		
Male	16 (88.8)	17 (94.4)
Female	2 (11.1)	1 (5.5)
Age (median)	57	59
Smokers	18	18
Histology		
SCC	13	13
Adenocarcinoma	5	5
Stage		
IIIA	10	9
IIIB	8	9
Karnofsky performance status	>80	>80

SCC: Squamous cell carcinoma

**Table 2: Response rate**

	Frequency, n (%)		<i>P</i>
	Control arm (n=18)	Study arm (n=18)	
CR	2 (11.1)	2 (11.1)	1.000
PR	11 (61.1)	13 (72.2)	0.480
SD	1 (5.6)	1 (5.6)	1.000
PD	2 (11.1)	1 (5.6)	1.000

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease



**Figure 1: Progression-free survival**

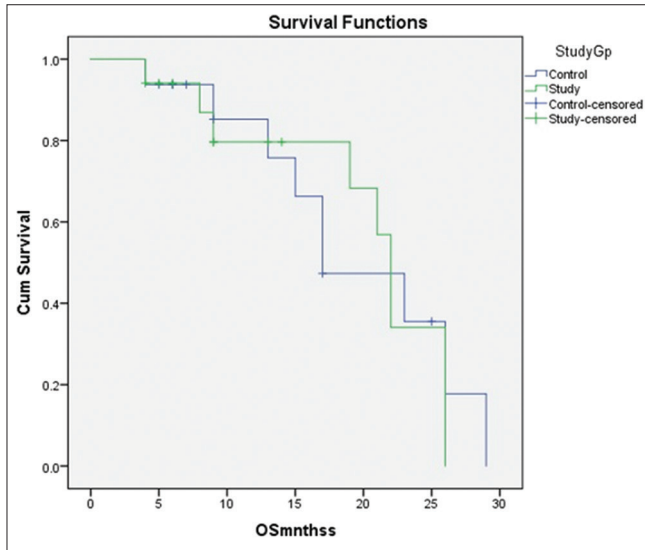
### Toxicities

With regards to pulmonary toxicity, Grade II pulmonary toxicity was observed in eight patients (44.4%) in control arm and seven patients (38.9%) in the study arm, and none of the patients had Grade III/IV toxicities. The values are statistically insignificant (*P* = 0.674). Grade II hematological toxicity was observed in 13 patients (72.2%) in the control arm and nine patients (50%) in the study

**Table 3: Subset analysis**

Subset	Control arm					Study arm				
	CR	PR	SD	PD	Deaths	CR	PR	SD	PD	Deaths
III <sub>A</sub> + adenocarcinoma	0	1	1	0	0	0	2	0	0	0
III <sub>A</sub> + SCC	2	5	0	1	0	0	6	1	0	0
III <sub>B</sub> + adenocarcinoma	0	1	0	1	1	0	2	0	1	0
III <sub>B</sub> + SCC	0	4	0	0	1	2	3	0	0	1

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, SCC: Squamous cell carcinoma

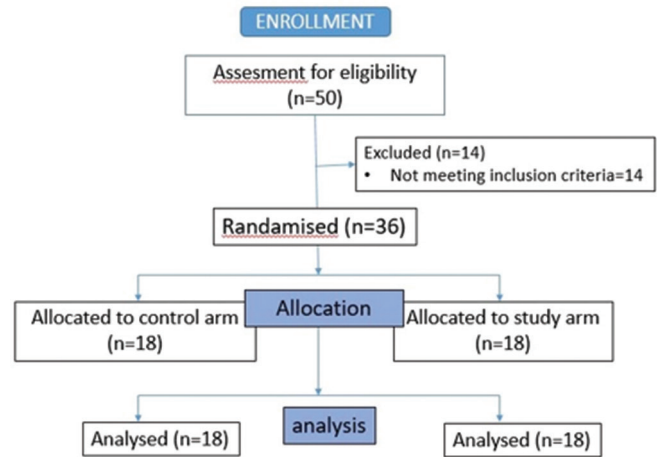


**Figure 2: Overall survival**

arm ( $P = 0.124$ ). Grade III hematological toxicity was seen in one patient (5.6%) in the control arm and five patients (27.8%) in the study arm, and the result was statistically insignificant ( $P = 0.177$ ). Grade II esophageal toxicity was seen in four patients (22.2%) in the control arm and four patients (22.2%) in the study arm, and none of them had Grade III/IV toxicities. With regards to skin toxicity, Grade II toxicity was observed in two patients in control arm, none in the study arm and Grade III toxicity was observed in one patient in control arms and none in the study arm [Table 4]. When Grade >III toxicities are analyzed. The total number of events of Grade >III toxicities in the control arm was three and in the study arm was five, which is statistically insignificant [Table 5].

**Quality of life**

The parameters which improved on treatment were: (a) hemoptysis: all seven out of seven patients in the control arm and all five out of five patients in the study arm improved; (b) arm/shoulder pain: five out of five patients (100%) in the control arm and six out of six patients (100%) in the study arm improved; (c) dyspnea: 15 out of 16 patients (93.75%) in the control arm and 18 out of 18 patients (100%) in the study arm improved. Chest pain improved in 10 out of 13 patients (76.9%) in the control arm and 11 out of 14 patients (78.5%) in the study arm. Minimum improvement was noted for



**Flow Diagram 1: Consort flowdiagram**

cough: Ten out of fourteen patients (71%) in the control arm and 12 out of 16 patients (75%) in the study arm improved. These observations are, however, not statistically significant. The parameters which developed or worsened on treatment were: dysphagia, paresthesia, alopecia, and sore mouth. Dysphagia developed/worsened in 16 out of 16 patients (100%) in the control arm and 14 out of 17 patients (82.3%) in the study arm. Paresthesia developed in five out of 16 patients (31.3%) in the control arm and seven out of 17 patients (41%) in the study arm. Hair loss was noted in 100% of patients in the control arm, and eight out of 17 patients (47%) in the study arm and the observation is statistically significant [Table 6].

**Discussion**

The treatment for Stage III<sub>A</sub> and III<sub>B</sub>, unresectable NSCLC has evolved from radical radiotherapy in the early nineties to sequential chemoradiation (CRT) till 2004 and now, concomitant CRT over the last 10 years. Now, the standard of care for Stage III<sub>A</sub> and III<sub>B</sub>, unresectable NSCLC is definitive CCRT using platinum-based chemotherapy. This has been confirmed in the meta-analysis by Aupérin *et al.*, and the Cochrane meta-analysis, both were published in 2010.<sup>[2,5]</sup> Regarding chemotherapy in concomitant setting for advanced lung cancer, a previous meta-analysis demonstrated that a cisplatin-based regimen is superior to a carboplatin-based regimen regarding OS. During the last decade, the usefulness of several new agents, such as paclitaxel,



**Table 4: Toxicity**

	Grade	Frequency, <i>n</i> (%)		<i>P</i>
		Control arm ( <i>n</i> =18)	Study arm ( <i>n</i> =18)	
Pulmonary	0	0 (0.0)	1 (5.6)	0.674
	1	10 (55.6)	10 (55.6)	
	2	8 (44.4)	7 (38.9)	
	3	0 (0.0)	0	
	4	0 (0.0)	0	
Hematologic	0	0 (0.0)	0 (0.0)	0.124
	1	3 (16.7)	4 (22.2)	
	2	13 (72.2)	9 (50)	
	3	1 (5.6)	5 (27.8)	
	4	1 (33.3)	0	
Esophagus	0	0	4 (22.2)	0.104
	1	14 (77.8)	10 (55.6)	
	2	4 (22.2)	4 (22.2)	
	3	0	0	
	4	0	0	
Skin	0	2 (11.1)	2 (11.1)	0.314
	1	13 (72.2)	16 (88.9)	
	2	2 (11.1)	0	
	3	1 (5.6)	0	
	4	0	0	
Cardiac	0	18 (100)	18 (100)	1.000
	1	0	0	
	2	0	0	
	3	0	0	
	4	0	0	

**Table 5: Toxicity profile: ≥ Grade III toxicities**

	Frequency, <i>n</i> (%)		<i>P</i>
	Control arm ( <i>n</i> =18)	Study arm ( <i>n</i> =18)	
Pulmonary	0 (0.0)	0 (0.0)	-
Hematologic	2 (11.1)	5 (27.8)	0.402
Esophagus	0 (0.0)	0 (0.0)	-
Skin	1 (5.6)	0 (0.0)	1.000
Cardiac	0 (0.0)	0 (0.0)	-
Total	3 (100.0)	5 (166.7)	0.691

**Table 6: Quality of life**

QoL: Parameters which improved on treatment			
	Control (%)	Study (%)	<i>P</i>
Cough	10/14 (71.4)	12/16 (75)	0.842
Hemoptysis	7/7 (100)	5/5 (100)	-
Dyspnea	15/16 (93.8)	18/18 (100)	0.716
Chest pain	10/13 (76.9)	11/14 (78.5)	0.931
Arm/shoulder pain	5/5 (100)	6/6 (100)	-
Parameters which developed/worsened on treatment			
Dysphagia	16/16 (100)	14/17 (82.4)	0.305
Paresthesia	5/16 (31.3)	7/17 (41.2)	0.486
Hair loss	16/16 (100)	8/17 (47.1)	0.0004*
Sore mouth	8/16 (50)	5/17 (29.4)	0.099

QoL: Quality of life. \*As *P* value is significant in case of hair loss, which shows better quality of life with respect to hair loss. but need a larger study to confirm the result

gemcitabine, vinorelbine, and docetaxel, has been studied, usually administered in combination with the platinum compounds. In a recent prospective study (456 patients) by Yamamoto *et al.* published in 2010, the author concluded that the third-generation carboplatin regimen (particularly carboplatin plus paclitaxel) was at least comparable with the better toxicity profile to the second-generation cisplatin regimen, which is the conventionally used therapeutic regimen, regarding the survival prolonging effect when applied in combination with concurrent thoracic radiotherapy.<sup>[9]</sup> On this background, we conducted a randomized prospective study comparing CCRT using paclitaxel-carboplatin and CCRT using cisplatin-etoposide in Stage III (unresectable) NSCLC, with the following highlights in the design:

1. Chemotherapy drugs are different in both the arms (paclitaxel-carboplatin in the study arm and cisplatin-etoposide in control arm)
2. Radiation dose and fractionation scheme are same in both the arms
3. QoL has been incorporated in this radical setting and analyzed in both the arms.

Both the treatment arms were well balanced with respect to different prognosticators such as histology, stage, age, males: females, smokers: never smokers, and performance status. The hemoglobin level of all the patients maintained above 10 g% during the entire treatment.

The overall response rate (CR and PR aggregated) for all patients was 84.8% in our study. In the control arm, it was 81.3%, and in the study arm, it was 88.2%. Progressive disease at 1<sup>st</sup> follow-up was observed in 11.1% in the control arm and 5.6% in the study arm. The results were, however, not statistically significant. In a study by Yamamoto *et al.*, the overall response rate was 66.4% in cisplatin arm and 63% in paclitaxel-carboplatin arm and progress disease of 13% in cisplatin arm and 13.9% in paclitaxel arm.<sup>[9]</sup> In a study by Lau *et al.* the overall response rate in the paclitaxel-carboplatin arm was 71%, which was achieved in the induction phase.<sup>[10]</sup> In a study by Choy *et al.* the overall response rate was 75.7%.<sup>[11]</sup> The response rates obtained in our study are superior to the response rates in the studies we have discussed and this is probably because of the number of patients in our study are less compare to other studies. However, the trends in the response rates in both the arms are in harmony with the similar studies published with CCRT using paclitaxel-carboplatin showing noninferiority to the cisplatin-based regimen as described in the previous paragraph.

When Grade >III toxicities are analyzed. The total number of events of Grade >III toxicities in the control arm were 3 and in the study arm were 5 (*P* =0.691), which is statistically insignificant. The number of interruptions, due to toxicities, was 3 in the control arm and 5 in the study arm (*P* = 0.691). This observation is also statistically insignificant. In a study

by Yamamoto *et al.* Grade >III hematological toxicity was observed in 93.8% in cisplatin arm and 23.1% in the paclitaxel-carboplatin arm, Grade >III esophageal toxicity was observed in 4.1% in cisplatin arm and 7.5% in paclitaxel arm.<sup>[9]</sup> In a study by Albain *et al.* Grade >III hematological toxicity was observed in 32% of patients and Grade >III esophageal toxicity was observed in 20% of patients in the cisplatin arm.<sup>[12]</sup> In a study by Chandra *P et al.* Grade > III pulmonary toxicity was observed in 16% of the patients, Grade > III hematological toxicity was observed in 26% of patients in and Grade > III esophageal toxicity was observed in 28% of patients in the paclitaxel-carboplatin arm.<sup>[12]</sup> When these toxicity-related data are compared with our study, they are similar except for hematologic toxicity and esophageal toxicity. The documented acute esophageal toxicity of Grade > III has been 17.75% (7.5%–28%) for CCRT using paclitaxel-carboplatin and 12% (range 4.1%–20%) for the cisplatin-based regimen. Whereas in our study, there was no Grade III/IV esophageal toxicity in any of the arms. This may, again, be due to higher doses of radiation used in the study by Yamamoto *et al.* Albain *et al.* and Belani *et al.*<sup>[9,12,13]</sup>

QOL analysis, based on the EORTC QLQ-LC13 module, was the next endpoint of this study. The most common symptom at presentation was dyspnea, followed by cough. Maximum improvement was noted for hemoptysis, arm/shoulder pain, and dyspnea. Minimum improvement was noted for cough. The parameters which developed or worsened on treatment were: dysphagia, paresthesia, alopecia, and sore mouth. Hair loss was noted in 100% of patients in control arm, and 47% in the study arm and the observation is statistically significant. Both, the improvement and worsening/appearance of symptoms, show equal QoL in both control and study arm except for alopecia which is worsened in control arm with significant *P* value.

The response rates, disease progression and the OS, are similar between study and the control arm. The other two endpoints namely the toxicity profile and QoL are also similar between the two arms except for the hair loss which is better in the CCRT using the paclitaxel-carboplatin arm with significant *P* value. Since we are not only treating the disease but treating the patient as a whole, apart from the response rates due consideration must be given to toxicities as well as QoL.

## Conclusion

This study has attempted to address the topic of different chemotherapeutic agents in combination with radiotherapy for the definitive treatment of Stage III<sub>A</sub> and III<sub>B</sub> (unresectable) NSCLC. The properly balanced treatment arms with respect to different prognosticators and the same radiation dose/schedule with different chemotherapy drugs reduce the role of confounding factors to a minimum. The

response rates and disease progression are similar between the study and the control arm. The other endpoints namely the toxicity profile, OS and QoL are also similar between the two arms except for the hair loss which is better in the concurrent CRT using the paclitaxel-carboplatin arm with significant *P* value.

Since we are not only treating the disease but treating the patient as a whole, apart from the response rates due consideration must be given to toxicities as well as the QoL which are bound to suffer from the aggressive intent which we now employ to treat these patients radically.

However, larger study with longer follow-up is needed to establish the comparability of these two regimens. It is recommended that treatment options should be individualized.

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## Conflicts of interest

There are no conflicts of interest.

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