Original Article

Neo-adjuvant chemotherapy followed by either continuous hyper-fractionated accelerated radiation therapy week-end less or conventional chemo-radiotherapy in locally advanced NSCLC-A randomised prospective single institute study

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ABSTRACT

Context: Better locoregional control and increased overall survival by continuous hyper fractionated accelerated radiotherapy have been shown in unresectable nonsmall cell lung carcinoma (NSCLC). Dose escalation and neoadjuvant chemotherapy (NACT) along with continuous hyperfractionated accelerated radiotherapy week end-less (CHARTWEL) were also tried for improved survival. In this present study, we compared the results of NACT followed by CHARTWEL against NACT followed by conventional concurrent chemo-radiation therapy.

Aims: The aim of this study is to compare the locoregional control and toxicities in NSCLC Stage IIIA and B in both arms.

Settings and Design: Randomized, prospective single-institutional study with a study population comprising all locally advanced unresectable NSCLC patients enrolled in 2014 at our institute.

Subjects and Methods: All enrolled patients were randomized into two arms-CHARTWEL and concomitant chemo-radiotherapy (CCRT), after three weeks of the fourth cycle of NACT. In CHARTWEL arm 30 patients received two-dimensional radiotherapy (RT) 58.5 Gy/39 fr/2.5 weeks while in CCRT arm 30 received 66 Gy/33 fr/6.5 weeks. Disease response was evaluated at 6 months and toxicity assessment during and after treatment completion. Data were analyzed using tools such as percentage, mean, Chi-square test and *P* value. Chi-square and *P* value was calculated by statistical online software (http://quantpsy.org).

Results: 28% of patients in study arm and 20% in control arm had complete response at 6 months after RT. Locoregional disease control was observed in 44% in study arm and 32% in control arm of patients. There was no statistical difference in grades of toxicities or overall survival (OS)/disease-free survival except persistent esophagitis Grade III seen in two patients of study arm.

Conclusions: Study suggests that CHARTWEL in combination with NACT is an effective strategy to treat patients with locally advanced lung cancer with the advantage of a smaller dose and shorter duration. Although large multivariate studies still needed.

KEY WORDS: Concomitant chemoradiotherapy, continuous hyperfractionated accelerated radiotherapy week end-less, Eastern Cooperative Oncology Group, neo-adjuvant chemotherapy, nonsmall cell lung carcinoma

INTRODUCTION

Nonsmall cell Lung cancer (NSCLC) accounts for approximately 85% of all the Lung cancers. Approximately 40% of patients with NSCLC have locally advanced disease (Stage III) on presentation.[1] Currently, locally advanced inoperable NSCLC is treated by multimodality approaches such as concurrent chemoradiotherapy or sequential chemo-radiotherapy. Recent data indicate that chemotherapy (CT) improve outcome for patients with locoregional disease. Platinum-based therapy used either in

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sequence or concurrently with radiation prolongs survival in the Stage III patients. Eradication of micrometastatic disease appears to be the principal mechanism by which CT improves the survival of patients with locally advanced lung cancer.[2]

The original rationale of administering induction CT is to shrink or downstage a locally advanced disease and thereby facilitates a more effective local treatment with surgery or radiotherapy and to control occult metastasis.[3] The delay incurred in delivering radiotherapy to allow administration of induction CT has been of theoretic concern as it could lead to the proliferation of clonogenic tumor cells in an unresponsive tumor and also increase in chance of metastasis.

The simultaneous use of CT and radiotherapy concomitant chemo-radiotherapy (CCRT) has been intensively investigated. The biological rationale for this type of combination is found in a number of drug-radiation interactions at the cellular level causing a shift of cell-survival curves toward higher cell-killing levels and lower cell-surviving fractions for a given dose of irradiation, this may help prevent the emergence of resistant clones, a decrease in tumor mass and subsequent oxygenation of hypoxic cells, selective toxicity depending on the cell-cycle phase, cytokinetic cooperation, interference in DNA repair, increased apoptosis, and thus better response of tumor to radiation.[4]

Conventional radiation therapy is the standard of care at many radiotherapy centers, but this might not be ideal in every situation. Inherent radioresistance and repopulation of tumor clonogens are the few possible causes of local failure with conventional radiotherapy. The meta-analysis of 1205 patients demonstrated that CCRT contributed better overall survival than sequential treatment with manageable toxicities.[5]

To get a better therapeutic response, various fractionation schedules (hyper fractionation, hypofractionation, accelerated fractionation, continuous hyperfractionated accelerated radiotherapy [CHART]) have been tried. These schedules have shown a promising result in locally advanced NSCLC regarding achieving a better locoregional control (LRC) and overall survival (OS) at the cost of slightly higher but acceptable toxicities, without any deterioration on the quality of life. In the present study, we have compared the results of induction CT followed by CHARTWEL with induction CT followed by chemoradiation in the form of conventional radiation therapy.

The Eastern Cooperative Oncology Group (ECOG) 2597 trial compared 64 Gy/32 fractions/6.5 weeks with hyperfractionated accelerated radiation therapy (57.6 Gy/36 fractions/3 weeks) after induction CT in locally advanced Stage III NSCLC and reported a trend of improved survival in the accelerated arm.[6]

A major problem with such accelerated hyper fractionation is that tumoricidal doses delivered in such short overall time are likely to exceed acute tolerance limits. One way around this is to complete the treatments in such a short time that the acute reactions reach their peak only after the radiotherapy has been completed. This was how the CHART regimen was conceived at Mount Vernon Hospital in London.[7] With CHART, treatments 6 h apart are delivered three times a day, 7 days a week. With a dose fraction of 1.5 Gy, a total dose of 54 Gy can be delivered in 36 fractions over 12 successive treatment days including weekends. With this schedule used for the treatment of lung and head and neck cancers, patients can complete treatment without a break because peak acute reactions occur approximately 2 weeks after the start of therapy.

The LRC and increased OS obtained by CHART (1985) were more than that calculated by a meta-analysis of randomized controlled trials of chemo-radiotherapy.[8,9]

To decrease the normal tissue damage, reduce the inconvenience to the patients and the treating physician week-end rest was given in CHART regimen. This is called continuous hyperfractionated accelerated radiotherapy week end-less (CHARTWEL), wherein the 54 Gy at 1.5 Gy/fraction at three fractions/day is delivered over a total of 16 days without treatment on the weekend.[10] Baumann *et al*. (2011) described that the overall survival was not significantly different after CHARTWEL,[11] but the lower total dose was compensated by shorter overall treatment time, confirming a time factor for NSCLC. The higher efficacy of CHARTWEL versus conventional fractionation (CF) in advanced stages and after CT provides a basis for further trials on treatment intensification for locally advanced nonsmall lung cancer.

In recent past some studies of CHARTWEL combined with induction CT has shown that the strategy is feasible and that a possible therapeutic benefit may be obtained by the addition of CT.[12,13] Although neoadjuvant treatment increased acute mucosal reactions and mild-to-moderate pneumonitis seen with CHARTWEL 60 Gy, the clinical management and quality of life of these patients were found to be similar to those treated with radiotherapy alone.

SUBJECTS AND METHODS

Our study population was a randomized prospective consecutive cohort of 60 patients of locally advanced carcinoma of lung Stage IIIA–IIIB (T3–T4 N2, Tany N3) who received care at our institute. The randomization scheme was generated using the website randomization.com (http://www.randomization.com) to eliminate the selection bias. All eligible histologically proven cases of nonsmall cell carcinoma were enrolled from December 2013 to December 2014. The disease was staged as per AJCC 2010.

Eligibility criteria included age 18–75 years, ECOG status 0–2, inoperable locally advanced, histologically proven, Stage IIIA and IIIB NSCLC tumors; bidimensional measurable

disease; no pleural effusion on chest X-ray; no prior history of malignancy or chemo-radiotherapy; and presence of chest symptoms (cough, dyspnea, hemoptysis, chest pain, and dysphagia).

The protocol was approved by the Hospital's Institutional Ethical Committee and all patients were properly informed and consented for treatment study. All patients underwent a baseline evaluation consisting history of symptoms, physical examination, and blood tests including complete blood count (CBC), renal function and liver function tests (LFT); and chest X-ray, CT scan of the chest and upper abdomen, and bronchoscopy. If any symptom of metastatic disease was present further work was done to rule out metastasis.

Treatment plan

All (60) patients in the study were administered sequential chemoradiotherapy. Neoadjuvant (anterior) CT was same for all the patients. In CT, four cycles, each consisting of Inj. Cisplatin 75 mg/m^2 divided into day 1 and day 2 and Inj. Paclitaxel 175 mg/m^2 intravenous on day 1, was administered according to protocol repeated every 3 weeks.

After 3 weeks of 4th cycles of CT, all patients were evaluated for disease status. All patients eligible for radical treatment (metastatic excluded) were randomized into two arms-Arm-A (study) and Arm-B (control). In study arm, patients received a total of 58.5 Gy in 39 fractions (1.5 Gy for each fraction) in 17 days, three fractions a day (6 h apart) (continuous accelerated hyperfractionated radiotherapy weekend less) [Figure 1 and Table 1].

All patients were planned radiotherapy and treated in two phases; in phase I, the volume included the mediastinum and primary tumor with a 2-cm margin. The ipsilateral hilar nodes and para-tracheal nodes were included but the contralateral hilum excluded. The phase II volume included the tumor and known nodal involvement with a 2-cm margin. Radiation doses were prescribed to the intersection point of the beams. The large volume received 45 Gy and the small volume 13.5 Gy in CHARTWEL arm, and in conventional arm, large volume of 44 Gy and 22 Gy in reduced volume was used. Treatment volume included primary tumor site plus mediastinum region. Parallel opposed anteroposterior fields were planned. The dose was prescribed at midline.

Response evaluation

Patients were monitored after every course of CT and before and during RT. In each monitoring, patients were assessed for treatment response, control of symptoms and any treatment-related morbidity by doing CBC, biochemistry profile consisting of renal function test (RFT) and LFT, chest X-ray, and ultrasonography (USG) abdomen. Toxicity hematological, renal, biochemical, skin reactions, and disease response were assessed according the CTCAE 3.0 guidelines.

After 1 months of completion of RT, patients were called for first follow-up visit and were assessed for treatment response regarding disease control (tumor regression) using response evaluation criteria in solid tumors (RECIST) criteria and palliation of symptoms using symptomatic response grading. On 1st, 3rd, and 6th month follow-up visit complete general physical examination, hemogram, RFT, chest X-ray and contrast enhanced computed tomography Thorax were done for treatment response and toxicity evaluation and metastatic work up consisted of USG abdomen and LFT.

Patients were deemed to have attained locoregional control if there was either complete disappearance of all radiological abnormalities or when any residual abnormality observed at 6 months remained stable for a further 6 months or more else they were defined as never being disease free.

The endpoint for treatment outcome was locoregional control and to asses treatment-related toxicities in both the arms. Disease control was assessed using RECIST version 1.1 Criteria, and toxicities were assessed according to CTCAE 3.0 version.

RESULTS

At 6th month follow-up, 7 (28%) patients in study arm and 4 (16%) patients in control arm had complete response (5 for Stage IIIA and 6 for Stage IIIB) ($\chi^2 = 3.273$, $P = 0.0704$). Four (all Stage IIIB) and four patients (1 IIIA and 3 for Stage IIIB) had partial regression in study and control arms, respectively χ^2 (chi square) $= 0$ and $P = 1$. 2 (2 for IIIB) and 4 (0 IIIA and 4 for Stage IIIB) had stable disease in study and control arms, respectively ($\chi^2 = 2.66$, $P = 0.1024$). 12 (all for Stage IIIB) patients in study and 13 in control arm had progressive disease respectively at 6th month follow-up ($\chi^2 = 0.16$, $P = 0.689$) [Table 2].

Stage-wise, there was better regression in Stage IIIA than Stage IIIB; in Stage IIIA, 100% (6 out of 6 patients) responded to treatment whereas in Stage IIIB, regression seen only in 29.54% patients (13 out of 44) in both the arm at third follow-up.

When analyzed at 6th month follow up, 56% patients in study arm and 68% patients in control arm had progressive/stable disease while 44% patients in study arm and 32% patients in control arm had regression of disease.

Toxicities

There was no significant difference in Grade I skin, pneumonitis, and gastrointestinal toxicity (GIT) in either of the arm. There was Grade II esophagitis seen in 10 (40%) and 7 (28%) patients in study and control arm, respectively ($\chi^2 = 2.11$, $P = 0.145$). While Grade III was seen in 4 (16%) and 2 (8%) patients study and control arm, respectively ($\chi^2 = 7.2$, $P = 0.007$). Acute pneumonitis Grade II seen in 6 (24%) and 2 (8%) patients in study and control arm, respectively ($\chi^2 = 8$, $P = 0.0046$) while Grade III was seen in 2 (8%) patients in study and 1 (4%) in

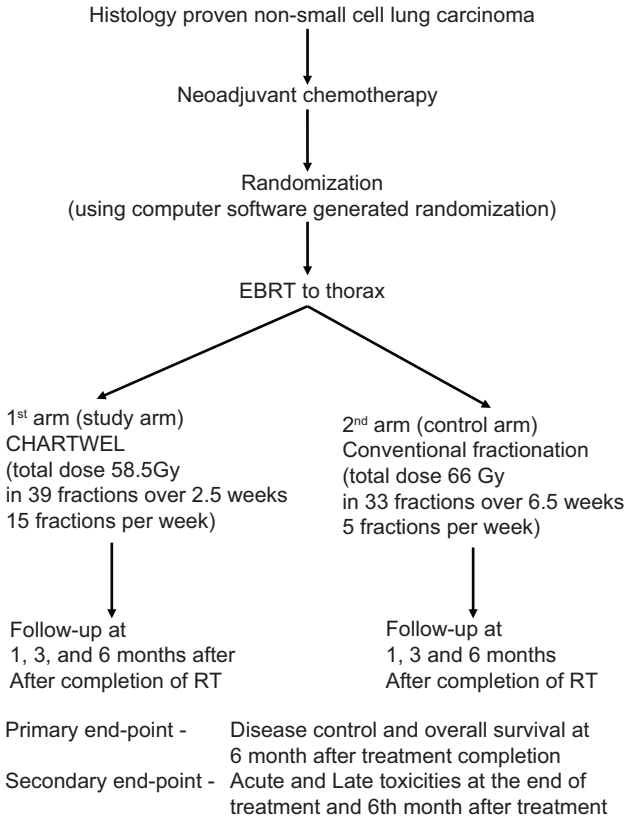

Figure 1: Study design

control arm. There was no Grade IV GIT, pneumonitis and skin toxicity seen in either of the arm. There was no Grade IV acute toxicity in either of the arms [Table 3].

At 6th month follow up, Grade I and II renal toxicities were not significantly different in both the arm. Grade II pneumonitis was common in study arm (24 vs. 8%) ($\chi^2 = 6.4, P = 0.0114$). Grade III pneumonitis was seen only in study arm (8 vs. 4%) ($\chi^2 = 8, P = 0.0046$). Persistence of Grade III esophagitis was seen in 2 (8%) patients in study arm. No Grade IV toxicity was noted in either of arms. None of the patients in both arms showed radiation myelitis [Table 4].

Survival

The median survival for patients in control arm was 12 months (95% confidence interval [CI]: 11.385 to 12.615) and 12 months (95% CI: 8.869 to 15.131) in CHARTWEL arm [K-M plot in Figure 2 and Table 5]. Median disease-free survival was 11 months with 95% CI 8.88–13.11 months in study arm while 8.37–13.62 months in control arm [K-M plot in Figure 3 and Table 6].

DISCUSSION

The patient characteristics in terms of age, sex, socio-economic statuts, habits, and performance status of the patient, stage of the disease and histopathology of the disease are described

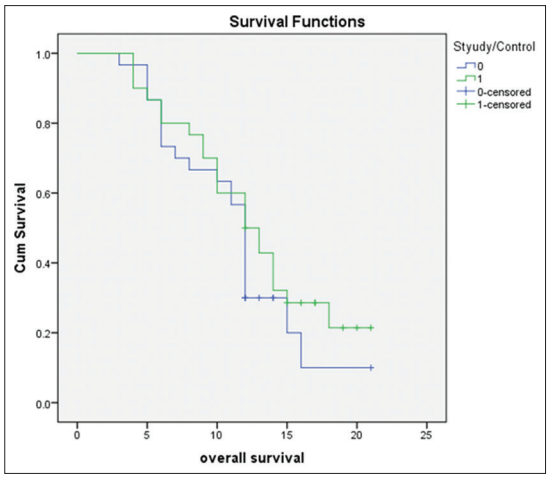

Figure 2: Kaplan meier curve showing overall survival (OS) in months

Table 1: Patients' characteristics

	Number of patients (%)	
	Study arm 30 (100%)	Control arm 30 (100%)
Age (years)		
≤50	6 (20)	12 (40)
51-60	17 (56.7)	6 (20)
61-70	7 (23.3)	12 (40)
Sex		
Male	27 (90)	26 (86.7)
Female	3 (10)	4 (13.3)
Socioeconomic status		
Rural	24 (80)	21 (70)
Urban	6 (20)	9 (30)
Habit		
Smoker	26 (86.7)	27 (90)
Nonsmoker	4 (13.3)	3 (10)
ECOG		
0	9 (30)	6 (20)
1	19 (63.3)	22 (73.3)
2	2 (6.7)	2 (6.7)
T - stage		
2	2 (6.7)	2 (6.7)
3	10 (33.3)	8 (26.7)
4	18 (60)	20 (67.6)
N - stage		
1	1 (3.3)	0 (0)
2	16 (53.3)	21 (70)
3	13 (43.3)	9 (30)
Overall stage		
IIIA	3 (10)	3 (10)
IIIB	27 (90)	27 (90)
Histology		
SCC	19 (63.3)	18 (60)
Adenoca	8 (26.7)	8 (26.70)
Other	3 (10)	4 (13.3)

ECOG=Eastern Cooperative Oncology Group, SCC=Squamous cell carcinoma

Table 2: Treatment response (RECIST criteria)

	Number of patients (%)		*P*
	Study arm 25 (100%)	Control arm 25 (100%)	
Regressive disease	11 (44)	8 (32)	>0.05
Stable disease	2 (8)	4 (16)	0.1024
Progressive disease	12 (48)	13 (52)	0.689

as in Table 1. The meta-analysis of 1205 patients with a 6-year follow-up demonstrated that CCRT contributed absolute benefit on overall survival at 5 years of 4.5% (15.1% vs. 10.5%) over sequential treatment, but at the cost of increased toxicity in the form of Grade III–IV esophagitis from 3% to 18% and myelosuppression depending on CT used.[5]

Although as discussed above, chemoradiotherapy is a better approach than radiotherapy, only desired survival benefit was not achieved, so induction CT before chemo-radiotherapy was also tried in some trials. The cancer and leukemia Group B (CALGB) group compared induction CT followed by CCRT vs. CCRT alone. Median survival in induction arm was 14 months versus 11.4 months in CCRT arm, with one-year survival of 54% and 48%, respectively.[14,15]

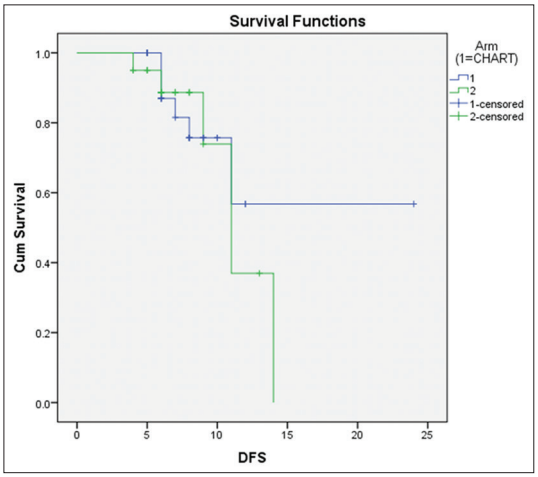

Figure 3: Kaplan Meier Curve showing the Disease Free Survival (DFS Chart)

Saunders *et al*. reported the increasing overall survival benefit with CHART comparing to conventional radiation at the cost of increased toxicity. Median survival was better in CHART arm 15 versus 12 months compared to the conventional arm. 2-year survival was also superior in CHART arm (30% vs. 20%).

In the current study, median survival was similar to that adding induction CT to conventional radiation therapy.

To overcome the normal tissue toxicity without affecting tumor control and physician, patient in-convenience CHART was modified by giving weekend off named CHARTWEL. In CHARTWEL, physical dose can be escalated with maintaining the low dose per fraction of 1.5 Gy. Radiobiological modeling is used to estimate the expected tumor control and normal tissue morbidity after CHARTWEL relative to CHART. Tumor control at 3 years is expected to increase from 19% to 26–33% whereas the incidence of moderate and severe early esophagitis and pneumonitis is expected to increase by about 2%. The incidence of late morbidity, lung fibrosis, and esophageal strictures are expected to increase by 3–4%.

Table 3: Acute toxicities

Arm	GIT toxicity (%)	Renal toxicity (%)	Skin (%)	Hematological toxicity (%)	Pneumo (%)
Grade 0					
Study	2 (8)	16 (64)	10 (40)	4 (16)	9 (36)
Control	11 (44)	14 (56)	11 (44)	2 (8)	15 (60)
Grade I					
Study	9 (36)	8 (32)	14 (56)	15 (60)	8 (32)
Control	5 (20)	10 (40)	13 (52)	16 (64)	7 (28)
Grade II					
Study	10 (40)	1 (4)	1 (4)	6 (24)	6 (24)
Control	7 (28)	1 (4)	1 (4)	7 (28)	2 (8)
Grade III					
Study	4 (16)	0	0	0	2 (8)
Control	2 (8)	0	0	0	1 (4)
Grade IV					
Study	0	0	0	0	0
Control	0	0	0	0	0
Total	50	50		50	50

GIT=Gastrointestinal toxicity

Table 4: Late toxicities at 6th month

	Grade															
	1				2				3				4			
	First arm, *n* (%)		Second arm, *n* (%)		First arm, *n* (%)		Second arm, *n* (%)		First arm, *n* (%)		Second arm, *n* (%)		First arm, *n* (%)		Second arm, *n* (%)	
Renal	8	32	9	36.0	0	0	5	20	0	-	0	-	0	-	0	-
Skin	13	52	13	52.0	0	-	1	4	0	-	0	-	0	-	0	-
Esophagitis	3	12	2	8	2	8	1	4	2	8	0	-	0	-	0	-
Pneumonitis	13	52.0	13	52.0	6	24.0	2	8	2	8	1	4	0	-	0	-

Table 5: Means and medians for survival time

Study/ control	Mean[a]				Median			
	Estimate	SE	95% CI		Estimate	SE	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
0	11.367	0.971	9.463	13.270	12.000	0.314	11.385	12.615
1	12.783	1.049	10.727	14.840	12.000	1.598	8.869	15.131
Overall	12.170	0.728	10.743	13.597	12.000	0.345	11.324	12.676

[a]Estimation is limited to the largest survival time if it is censored. 1 - Study arm, 2 - Control arm. SE=Standard error, CI=Confidence interval

Table 6: Means and medians for disease-free survival time

Arm (1=chart)	Mean[a]				Median			
	Estimate	SE	95% CI		Estimate	SE	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
0	17.336	2.519	12.399	22.274	.	.	.	.
1	11.146	0.977	9.231	13.061	11.000	1.078	8.886	13.114
Overall	13.730	2.078	9.657	17.803	11.000	1.341	8.372	13.628

Overall comparisons			
	χ^2	df	Significant
Log rank (mantel-cox)	0.274	1	0.600

[a]Estimation is limited to the largest survival time if it is censored. Test of equality of survival distributions for the different levels of Arm (1=CHARTWEL). SE=Standard error, CI=Confidence interval

In our study, when analyzed at 6th month follow up, 56% patients in study arm and 68% patients in control arm had progressive/stable disease while 44% patients in study arm and 32% patients in control arm had regression of disease. Locoregional control was inferior to the previous study done by Rojas *et al*. which can be explained by the inclusion of earlier stage tumor.

A Rojas *et al*. in a phase II trial CHARTWEL in locally advanced NSCLC found better loco-regional disease control with dose escalation alone 54 to 60 Gy (37 vs. 55%) and neoadjuvant chemotherapy with 60 Gy clinical and radiological remission was 72% at 2 years. There was longer duration of Grade II/III esophagitis and pneumonitis in CHARTWEL 60 with NACT arm compared CHARTWEL alone. Grade III/IV esophagitis and pneumonitis were 20–23% more in NACT arm than the RT only arm.

CHARTWEL has proved to be equally effective as conventional fractionation regarding locoregional control and symptom relief. Acute and longer duration esophagitis and pneumonitis were significantly higher in the CHARTWEL arm as compared to conventional arm; however, there was no interruption in the radiotherapy schedule due to toxicities. It was similar to the previous studies.

The added advantage of CHARTWEL is that, treatment is completed in a shorter time, confirming a time factor for NSCLC with better local tumor control. In busy radiotherapy departments where there is a heavy burden on the machines, NACT followed by CHARTWEL is a feasible option with shorter duration of stay in the hospital.

Small sample size, short follow-up, and single-center study were the limitations of our study. We propose larger multicentric studies with longer follow-up to ascertain the benefits and toxicities of CHARTWEL with NACT in locally advanced NSCLC patients.

CONCLUSION

Study suggests that CHARTWEL in combination with NACT is an effective strategy to treat patients with locally advanced lung cancer with the advantage of a smaller dose and shorter duration. Although large multivariate studies still needed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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