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Concomitant Chemoradiotherapy (Using Cisplatin And Etoposide) Vs Accelerated Radiotherapy In Inoperable Or Non-Resectable Locally Advanced Non-Small Cell Lung Cancers.

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Abstract
Introduction: *Lung cancer is the most common cancer in the world and the leading cause of cancer deaths. Though the use of combined-modality therapy including radiation and chemotherapy is recommended for locally advanced NSCLC but majority of our patients do not tolerate this treatment. With this study ,we aim to find out whether we can achieve better or comparable local control, tolerability and survival with AFRT (which may be helpful in patients of advanced cases of lung cancer as majority of these patients are not fit for CRT because of borderline or poor general condition and related comorbid conditions) in comparison to that of conventional chemo-radiation.*
Aim and objectives: *We did this study to compare the disease response, loco-regional tumorcontrol,quality of life and toxicity profile in accelerated radiation (six fractions per week) and conventional chemoradiation in locally advanced non-small cell lung cancer.*
Materials and methods: *Total 50 patients were enrolled and randomized into two groups the study(Accelerated Radiation n=25) and control group(Conventional chemoradiation with etoposide – cisplatin n=25). We included previously untreated patients of locally advanced inoperable or non resectable NSCLC. Patients assigned to accelerated radiation arm were given radiation six fractions per week (60Gy/5wks/30#) from Monday to Saturday. Patients assigned to Concomitant chemoradiation arm were given radiation 5 fractions per week (60Gy/6wks/30#)from Monday to Friday along with Injection cisplatin 20 mg/m2 iv days 1-5 & days 29-33 + Injection etoposide 50 mg/m2 iv days 1-5 &days 29-33 .*
Results: *The response in both the treatment arms at 6 weeks follow up was comparable (p=0.569).The grade II hematological toxicity was more in control arm (p=0.000).The quality of life parameter like hair loss and sore throat worsened in control arm.*
Conclusion: *Accelerated RT may prove a good alternate to concurrent CRT in lung cancer patients who are not a suitable candidate for CRT.*
Keywords: *carcinoma non –small cell lung ,chemotherapy , radiotherapy .*
Abbreviations :
RT- Radiotherapy
AFRT- accelerated fractionated radiotherapy
CRT – chemoradiotherapy

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I. Introduction

Lung cancer constitute 13% of cancers worldwide. It is the leading cause of cancer deaths. In India ,it is the most common cancer along with oral cancer (11.3% of total cases)[1] .NSCLC constitute >80% of all lung cancer and 35% of patients presents with locally advanced non metastatic disease[2]. Till mid-1990s, the standard treatment for locally advanced NSCLC patients was thoracic radiotherapy and after that combined radiochemotherapy. The NSCLC Collaborative Group meta-analysis[3] and the meta-analysis of platin-based concomitant chemotherapy in NSCLC[4] demonstrated that adding sequential or concomitant chemotherapy to radical radiotherapy improved survival in locally advancedNSCLC.But, chemotherapy is also with its hazards and safety concerns precludes its administration in elderly patients, those with pre-existing medical problems (with abnormal renal, hepatic or bone-marrow function),with poor performance status & in patients whorefuse chemotherapy or are reluctant to use chemotherapy.In India, many patients are not fit for CRT because of borderline/poor general condition and related comorbid conditions.

Thus different strategies were needed to enhance the effect of radiation in such condition and one such option is accelerated radiotherapy. In accelerated radiotherapy, treatment is delivered in a shorter overall time,

leaving the fraction size unchanged. The theory behind this is to reduce the amount of tumour cell repopulation during the treatment course. AFRT increases the probability of tumour control for given total dose with no effect on late normal tissue injury.The Radiation Therapy Oncology Group (RTOG) published a preliminary report of a prospective randomised study of various irradiation doses and fractionation schedules in the treatment of inoperable carcinoma of the lung, in 1980.[5] Radiological complete response (CR) rate was 10-25%, and 2-year survival was only 12%.It is interpreted, from a randomized controlled trial that comprised of two sub protocols, Danish Head and Neck Cancer study group-6 & 7, that the shortening of overall treatment time by increasing number of fractions per week is beneficial in patients with head and neck cancers.[6] The 6 fraction regimen has become the standard treatment in Denmark in head and neck cancer patients.By combining hyperfractionation and accelerated radiotherapy, continuous hyperfractionated accelerated radiotherapy or CHART was developed which maximised the potential gain.[7]Thus, it seems plausible to compare AFRT with concomitant chemoradiation.Hence, in this study we compared toxicities and disease response of AFRT with that of concomitant chemo-radiotherapy (CRT), which is the standard treatment for locally advanced NSCLC.

II. Materials and methods :

Prospective randomized study was conducted for a period of one year from July 2015 to June 2016 in the Department of Radiotherapy and Oncology, Regional Cancer Centre ,IGMC Shimla, in patients suffering from locally advanced non metastatic inoperable unresectablenon small cell lung ca.Patients were randomised to receive concomitant CRT arm (n=25) and AFRT arm (n=25).A signed informed consent was taken from all the patients involved in this study. Eligibilty criteria included previously untreated patient ,biopsy proven Squamous Cell Carcinoma, Adenocarcinoma including Bronchioalveolar, Large Cell Carcinoma, Adenosquamous Carcinoma, stage II &III inoperable non metastatic, Karnofsky status >70 and no significant hepatic and renal impairment as judged by biochemical investigations .

PRETREATMENT WORKUP : After detailed history, each patient underwent complete physical examination. The investigations done were Chest X-ray (PA and lateral views), Blood – haemogram& biochemistries, CECT chest (including lower neck and upper abdomen),Bronchoscopy + Biopsy (or guided FNAC if Biopsy was not possible / inconclusive),Sputum for cytology / AFB, Pulmonary Function Tests, USG – abdomen and pelvis, ECG & ECHO, Bone Scan and CT/MRI brain (if indicated), Workup of comorbidities, if any. All patients with potentially resectable disease on imaging studies underwent thoracic surgery evaluation to assess the resectability, before enrolling into the study.

RANDOMIZATION : Patients were randomised according to stage(II_B,III_A,III_B) and histology(squamous, adenocarcinoma &adenosquamous). A total of fifty patients (n=50) were considered for the final analysis. There were 25 patients in the control arm (concomitant chemoradiation using cisplatin-etoposide) and 25 patients in the study arm (accelerated radiation).

STUDY DESIGN :

CONTROL ARM (CRT) :External Beam Radiotherapy to a total dose of 60Gy in 30# starting day 1 of chemotherapy @ 2Gy/# & 5#/week in 40 days, Spinal cord off after 44Gy with Injection cisplatin 20 mg/m^2iv days 1-5 & days 29-33 and Injection etoposide 50 mg/m^2 iv days 1-5 & days 29-33[13-15].Total duration of treatment was 6 weeks.

STUDY ARM(AFRT): External Beam Radiotherapy to a total dose of 60Gy in 30# @ 2Gy/# & 6#/week in 34 days.Spinal cord off after 44Gy.Total treatment duration was 5 weeks.

ASSESSMENT OF DISEASE STATUS , TOXICITY AND QUALITY OF LIFE

CECT chest was done before scheduled commencement of treatment and at 1st follow up 6 weeks post-treatment.During treatment, toxicities were assessed every week using Radiotherapy and Oncology Group (RTOG) acute morbidity scoring criteria and disease response with chest radiographs every 2 weeks.Disease response assessment was done using WHO criteria.Quality of life was evaluated and recorded weekly using European Organisation for Research and Treatment of Cancer (EORTC) QLQ–LC13 questionnaire.

STATISTICAL ANALYSIS

Loco-regional disease response, toxicities and quality of life were the primary end points for analysis. The data obtained from both the arms were analysed using student "t" test and chi-square test.

III. Results

Patients characteristics included in the study are summarised in the table (table 1) tocompare the two treatment arms . When the response rates were assessed at first follow up ,CR was obtained in 3 pateints (12%)in control arm and 1 patient(4%) in study arm(p=0.602). PR was obtained in 12 patients in control (48%)as well as study arm(48%)(p=1.000). Stable disease was observed in 3 patients in control arm (12%) and none of the patient in study arm had stable disease(p=0.234).There were 4 patients(16%) in the control arm and 7(28%) in the study(p=0.440) who were found to have disease progression at 1st follow up. The observations were statistically not significant.

On subset analysis , in the 1st subset [stage IIB + squamous cell carcinoma] (both arms 4 patients each), partial response was seen in 2 patients in the control arm and 3 patients in the study arm; 1 patient had the stable disease in the control arm; 1 patient had progressive disease in both the arms.

In the 2nd subset [stage IIB+ Adenocarcinoma] (2 patients in both arms), partial response in 2 patients in the control arm and 1 patient in the study arm;progressive disease in 1 patient in the study arm .

In the 3rd subset [stage IIIA+ squamous cell carcinoma] (both arms 9 patients each), complete response was observed in 2 patients in control arm and none of the patient in the study arm; partial response in 6 patients in both the arms; 1 patient had stable disease in the control arm, progressive disease was observed in 1patient in the study arm and treatment was incompleted by 2 patient in study arm.

In the 4th subset [stage IIIA+ adenocarcinoma] (both arms 2 patients each) progressive disease was observed in 1 patients in both the arms and treatment was incomplete in 1 patient in both the arms.

In the 5th subset [stage IIIA+ adenosquamous carcinoma] (both arms 2 patients each) progressive disease was observed in 1 patients in both the arms and treatment was incomplete in 1 patient in both the arms.

In the 6th subset [stage IIIB + squamous cell carcinoma] (4 patients in both arms), complete response was observed in 1 patient in both the arms; partial response in 1 patients in both the arm; 1 patient in the control arm had stable disease and 1 patient in both arms had progressive disease.

In the 7th subset [stage IIIB + Adenocarcinoma] (2 patients in both arms), partial response in 1 patients in the study arm; 1 patient in the control arm had stable disease and 1 patient in both arms had incomplete treatment.

TOXICITY POFILE

During treatment, toxicities were assessed every week using RTOG acute morbidity scoring criteria(given in table 2).With regards to pulmonary toxicity, Grade II pulmonary toxicity was observed in 13 patients in control arm and 14 patients in the study arm.Grade III pulmonary toxicity was observed in 4 patients in the control arm and 2 patients in study arm.

With respect to haematologicaltoxicities,Grade II toxicity was observed in 16 patients in the control arm and 3 patients in the study arm (p value =0.000) and it was statistically significant.As far as oesophageal toxicities are concerned, Grade I toxicity was observed in 20 patients in the control arm and 16 patients in the study arm(p=0.208). For grade II toxicity there were 5 patients in the control arm and 7 patients in the study arm(p=0.508).With regards to skin toxicity, Grade I toxicity was seen in 12 patients in the control arm and 9 patients in the study arm(p=0.015). Grade II toxicity was observed in 5 patients in control arm and none of the patient in study arm(p=0.018).

RESULTS: QUALITY OF LIFE

Quality of life was evaluated and recorded weekly using EORTC QLQ–LC13 questionnaire[13].

The commonest symptom at presentation was cough (96%) followed by dyspnea (86%). Maximum improvement was noted for hemoptysis (p=0.236)followed by arm/shoulder pain(p=0.343) followed by dyspnoea(p=0.631) and chest pain(p=0.087). These observations were not statistically significant.The parameters which worsened on treatment were dysphagia(p=0.637) , hair loss (p=0.000), parasthesia(p=0.269) and sore mouth (p=0.000). Hair loss and sore mouth worsening was statistically significant .

IV. Discussion

Accelerated radiotherapy was used in the study keeping in mind that it shortens the overall treatment time, thus limiting the extent of accelerated tumourrepopulation[8,11].As lung tumour has short tumour doubling time (similar to head and neck tumours), accelerated radiotherapy may prove beneficial in lung cancer.

On this background, we conducted this study , with the following highlights in the design:

1. Radiation dose is same in both the arms.
2. Fractionation schedule and total treatment time are different in both the arms.
3. Quality of life has been incorporated in this radical setting and analysed in both the arms.

Both the treatment arms were well balanced with respect to histology and stage.

Out of 50 patients enrolled (25 in each arm), complete response was seen in 3 patients (12%) in control arm and 1 patient in study arm (4%) which was not significant statistically.The partial response was seen in 12 (48%)

patients in both the arms.The overall response rate (complete and partial response aggregated) for all patients was 56%. In the control arm it was 60%, and in the study arm it was 52%.The reason for not reaching the statistical significance may be less number of patients. These results were similar to the study by Pierre Fournal et al[9], in which response rate was 49% with concurrent treatment

The second end point of the study was the toxicity profile. There was slightly higher grade II pulmonary toxicity in study arm (56 % vs 52%) but this difference was statistically not significant (p= 0.777). Grade ≥II hematological toxicities were higher in chemo radiotherapy arm (64%) as compare to accelerated radiotherapy arm (12%) which was statistically significant (p=***0.000***). This may directly be attributed to the mylosuppressive effect of chemotherapy given in chemo radiotherapy arm only. The Grade II esophageal toxicities were slightly higher in study arm (28%) as compare to control arm (20%). This may be due to the fact that cumulative dose per week was 12 Gy in accelerated radiotherapy arm and 10 Gy in concurrent chemo radiotherapy arm. Higher cumulative dose per week results into higher acute radiation reaction as seen in DHANCA 6 & 7 accelerated radiotherapy trial in head & neck cancers[6]. Though the difference was not statistically significant (p=0.508). There was no difference in the skin toxicities between two arms .These toxicities were similar to the the study by Pierre Fournel et al[9]. and in the meta-analysis by Dr.Auperin et al[4]. In our study the pulmonary and oesophageal toxicities are comparable in the control and the study arm but the haemetological toxicity is significantly less in the study arm as compared to the control arm.

Quality of life analysis, based on the EORTC QLQ-LC13[13]module, was the third end point of this study. The commonest symptom at presentation was cough (96%) followed by dyspnea (86%). Maximum improvement was noted for (a) hemoptysis (b) arm/shoulder pain (c) dyspnoea (d) Chest pain .These findings support that there was no difference in the two arms as far as quality of life improvement is concerned. The parameters which developed or worsened on treatment were: dysphagia, parasthesia, alopecia and sore mouth.

Our results clearly showed that there is no difference in local control in locally advanced non metastatic inoperable NSCLC between the two arms with similar toxicities profile except hematological toxicities which are mainly seen in concurrent chemo radiotherapy arm.

The quality of life improvement is comparable between concurrent chemo radiotherapy arm and accelerated radiotherapy arm while alopecia is mainly observed in concurrent chemo radiotherapy arm and may be due to systemic effect of chemotherapy. This may be a big psychological factor especially in females where accelerated radiotherapy may be a good option.

Since the outcome is comparable, the accelerated radiotherapy may also be good option in patients who cannot afford chemotherapy, who have deranged renal functions or very old and frail patients who tolerate chemotherapy poorly.

Further the accelerated radiotherapy will increase the turnover on treatment machines thus will reduce the waiting list which is very common in public sector hospitals in developing countries like India. This will also reduce the hospital visits of the patients by almost one week thus saving patient's money as well. However, these findings need to be confirmed on a large prospective randomized trial with longer follow up period.

V. **Conclusion**

Since the outcome of accelerated radiotherapy is comparable to concurrent chemo radiotherapy, the former may be used for patients who cannot afford chemotherapy, or patients with deranged renal functions or very old and frail patients. These findings need to be confirmed on a large prospective randomized trial with longer follow up period.

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Table1: Patients characteristics

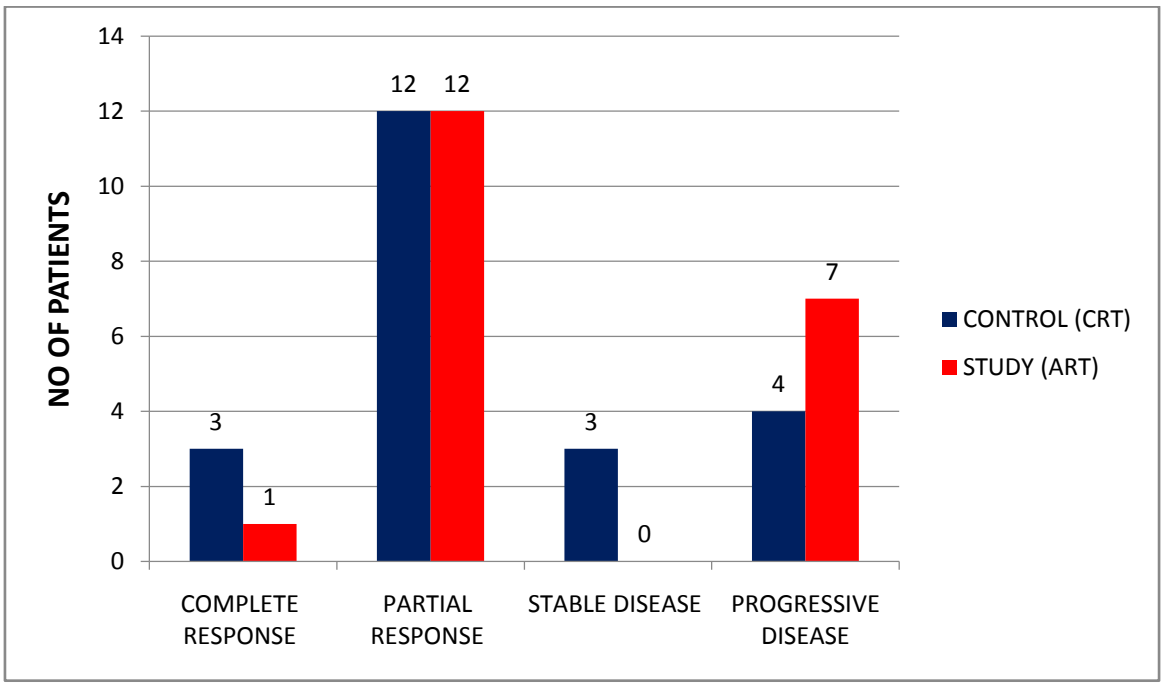
Patients characteristic	Control		Study	
	Frequency	Percentage	Frequency	Percentage
Age in years 45-50 51-55 56-60 61-65 66-70				
	2	8	1	4
	3	12	1	4
	4	16	4	16
	13	52	12	48
	3	12	7	28
Sex Male Female				
	22	88	21	84
	3	12	4	16
Smoker vs non-smoker				
Smoker	25	100	24	96
Non-smoker	0	0	1	4
KPS 70 80 90				
	1	4	5	20
	12	48	11	44
	12	48	9	36
Histology Squamous Adenocarcinoma Adenosquamous				
	17	68	17	68
	6	24	6	24
	2	8	2	8
Stage IIB IIIA IIIB				
	6	24	6	24
	13	52	13	52
	6	24	6	24

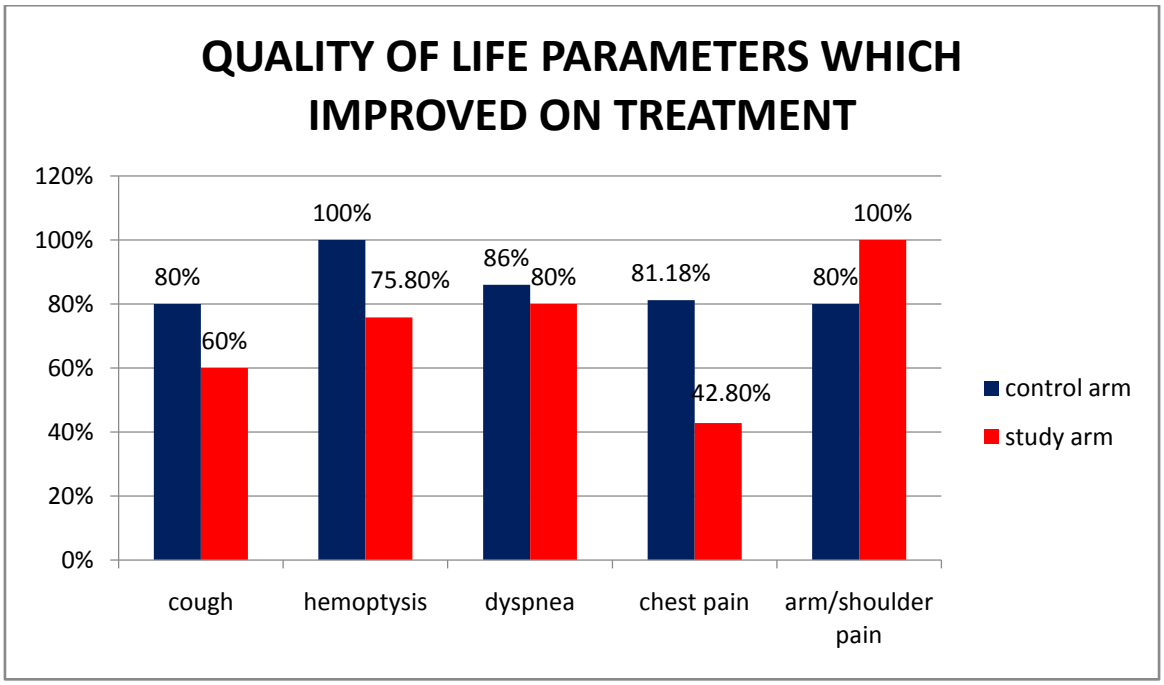
TOXICITY TABLE

TOXICITY	**CONTROL ARM**		**STUDY ARM**	
	FREQUENCY	**PERCENTAGE**	**FREQUENCY**	**PERCENTAGE**
PULMONARY TOXICITY				
GRADE 0 GRADE 1 GRADE 2 GRADE 3 GRADE 4	0	0	0	0
	8	32	9	36
	13	52	14	56
	4	16	2	8
	0	0	0	0
HEMATOLOGICAL TOXICITY				
GRADE 0	4	16	21	84

GRADE 1 GRADE 2 GRADE 3 GRADE 4	5	20	1	4
	16	64	12	48
	0	0	0	0
	0	0	0	0
ESOPHAGEAL TOXICITY				
GRADE 0 GRADE 1 GRADE 2 GRADE 3 GRADE 4	0	0	2	8
	20	80	16	64
	5	20	7	28
	0	0	0	0
	0	0	0	0
SKIN TOXICITY				
GRADE 0 GRADE 1 GRADE 2 GRADE 3 GRADE 4	8	32	21	84
	12	48	4	16
	5	20	0	0
	0	0	0	0
	0	0	0	0

Overall disease response at 1st follow up





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