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A Prospective Randomized Trial to Compare Concomitant Conventional Chemoradiotherapy with Accelerated Radiotherapy in Non-resectable Locally Advanced Non-Small Cell Lung Cancer

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ABSTRACT: **Introduction:** Lung cancer is the leading cause of cancer deaths in the world. In India, it constitutes 5.9% of all cancer cases and causes 8.1% of cancer deaths. Over the last 10 years, the combined-modality therapy including radiation and chemotherapy became the standard treatment for locally advanced NSCLC. But chemotherapy has its own side effects and majority of patients with NSCLC are unable to tolerate chemotherapy. So, other forms of treatment need to be evaluated as an alternate to CRT. Hence, we conducted this study to compare the disease response and toxicity with accelerated radiotherapy to CRT.

Aims and objectives: To compare the loco-regional tumor control, toxicity profile and quality of life in accelerated radiation (six fractions per week) versus those in concomitant chemoradiation for radical treatment of locally advanced non metastatic Non-Small Cell Lung Cancer patients.

Material and methods: The patients were enrolled over a period of one year. Total 44 patients were randomized into two arms – the control arm (concomitant chemoradiation n=22) and the study arm (accelerated radiotherapy arm n=22). In CRT arm treatment given was total dose of 60Gy in 30# starting day 1 of chemotherapy @ 2Gy/# & 5#/week in 40 days with Injection cisplatin 20 mg/m2iv days 1-5 & days 29-33 and Injection etoposide 50 mg/m2 iv days 1-5 & days 29-33.In accelerated RT arm treatment given was total dose of 60Gy in 30# @ 2Gy/# & 6#/week in 34 days.

Results: The disease response rate at first follow up was comparable in both the arms (p=0.796). Toxicity profile was also comparable in two arms except significantly higher hematological toxicity in chemo radiotherapy arm (p=0.014). The quality of life improvement was also comparable. However the alopecia and sore mouth were mainly seen in concurrent chemo radiotherapy arm.

Conclusion: Since the outcome of accelerated radiotherapy is comparable to concurrent chemo radiotherapy, the former may be used for frail patients.

KEYWORDS: Lung cancer, Accelerated radiotherapy (ART), Chemoradiation, Quality of life, Toxicities, Fractionation

I. INTRODUCTION

Lung cancer is the most common cancer in the world with 20,93,876 new cases in 2018, constituting 11.6% of all cancer cases. It is the leading cause of cancer deaths with 17,61,007 deaths in 2018 (18.4% of all cancer deaths). In India, the incidence of lung cancer is ranked 4th, constituting 5.9% of all cancer cases. 8.1% of cancer deaths were caused by lung cancer in India in 2018.In Indian males lung cancer is the 2nd most common cancer after lip and oral cancers (8.5% of all cancer cases).[1]In our institute, lung cancer is the single most common malignancy registered in males. In 2013 lung cancer constituted 18.13% of all cancer patients registered at our center. 26.06% of male patients and 10.44% of female patients were diagnosed to have lung cancer.[2]

More than eighty percent of lung cancer is NSCLC and about 35% of these present with

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locally advanced disease.[3]Thoracic radiotherapy was the treatment of choice for patients with unresectable or inoperable stage I-III NSCLC till the results of The NSCLC Collaborative Group meta-analysis[4] and the meta-analysis of platin-based concomitant chemotherapy in NSCLC[5] demonstrated the benefits of adding sequential or concomitant chemotherapy to radical radiotherapy. Hence, the combined-modality therapy including radiation and chemotherapy became the standard treatment for locally advanced stage III disease. But there are also some limitations of chemotherapy use like high toxicities in patients who are elderly, with poor performance status, with preexisting comorbid conditions, abnormal renal or liver function tests etc. and in patients who refuse chemotherapy. In the Asian countries due to differences in race, availability of radiotherapy machines, schedule and socioeconomic factors, standardization of concomitant chemotherapy schedules and dosage has not become possible.

Failure rates and patterns in patients who have unresectable locally advanced disease confined to the thorax indicate an intra-thoracic failure rate of up to 48%, depending on stage, histology and radiation dose delivered.[6] Therefore, methods of improving the radiotherapy technique which might improve local control and survival, need to be pursued.

In recent years non-standard fractionation schedules have been studied in clinical trials for different disease sites. One of these schedules is accelerated radiotherapy. In accelerated radiotherapy, the overall treatment time is reduced, while the fraction size remains unchanged. Thus, shortening overall treatment time should limit the extent of accelerated tumor repopulation and therefore one may expect an increase in the probability of tumor control for given total dose but with increase in the acute radiation reaction. Since treatment time is thought to have little or no influence on the response of late reacting normal tissue, a reduction in overall treatment time would not be expected to affect the incidence and severity of late normal tissue injury (provided the size of dose per fraction is not increased and the interfraction interval is sufficient for repair to be completed).[7] Accelerated radiotherapy proved beneficial in patients with head and neck cancers in Danish Head and Neck Cancer study group-6 & 7 randomized controlled trial.[8] The 6 fraction regimen has become the standard treatment in Denmark in head and neck cancer patients.

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. By doing so we aimed 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 concomitant chemoradiation. In addition we explored the relevance of this approach of accelerated fractionation for enhancing the effects of radiotherapy in NSCLC and whether it needs further attention or not.

II. MATERIALS AND METHODS

This randomized prospective study was conducted in the department of Radiotherapy and Oncology in our institute in patients suffering from locally advanced non metastatic Non-Small Cell Lung Cancer over a period of one year. A signed informed consent was taken from all the patients involved in this study. Cases included in this study were histologically proven unresectable or inoperable Squamous/Adenocarcinoma including Bronchioalveolar/Large Cell Carcinoma/Adenosquamous Carcinoma patients with Karnofsky performance status $\geq$ 70 and no history of prior thoracic surgery for cancer, thoracic radiotherapy or prior chemotherapy within 5 years.

Pre-treatment workup: After detailed history, each patient underwent complete physical examination. The investigations included: Chest X-ray (PA and lateral views), Blood examinations – 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: Randomization was carried out by stratification; there were 2 stratification factors: Clinical stage (II_A,II_B,III_A and III_B) and Histology (squamous cell carcinoma, adenocarcinoma, adenosquamous).A total of forty four patients (n=44) were considered for the final analysis. There were 22 patients in the control arm (concomitant chemoradiation using cisplatin-etoposide) and 22 patients in the study arm (accelerated radiation).

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Study Design:

Control Arm/ concomitant chemoradiotherapy (using etoposide-cisplatin):Radiation given as External Beam Radiotherapy by TeletherapyTheratron 780E and Equinox Cobalt 60 machines to a total dose of 60Gy in 30# starting day 1 of chemotherapy @ 2Gy/# & 5#/week in 40 days. Spinal cord off after 44Gy. Chemotherapy given as 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. Total treatment duration was6 weeks.

Study arm/ accelerated radiotherapy: Radiation given as External Beam Radiotherapy by TeletherapyTheratron 780E and Equinox Cobalt 60 machines 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 commencement of treatment and at 1st follow up 6 weeks post-treatment.Disease response assessment was done using WHO criteria as: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). During treatment, toxicities were assessed every week using Radiotherapy and Oncology Group (RTOG) acute morbidity scoring criteria.Quality of life was evaluated and recorded weekly using European Organisation for Research and Treatment of Cancer (EORTC) QLQ–LC13 questionnaire.

Statistical analysis: The primary end points were Loco-regional disease response, toxicities and quality of life. The data obtained from both the arms were analysed using student "t" test and chi-square test. p value of <0.05 was taken as significant.

III. RESULTS

Forty four patients of locally advanced non metastatic non-small cell lung cancer were included in the analysis. Both the arms had equal number of patients. The distribution of patients in both the arms was homogenous in regard of stage, histology and other prognosticators like age, smoking history and performance status. The characteristics are summarized in Table1.

	Control arm		**Study arm**	
	Frequency	%	Frequency	%
Mean Age (overall = 61.57 years)	59.86 years (range: 49-70 years)		61.37 years (range: 52-70 years)	
AGE(inyears)				
45-50	3	13.63 %	0	-
51-55	4	18.18 %	5	22.72 %
56-60	3	13.63 %	3	13.63 %
61-65	7	31.81 %	5	22.73 %
66-70	5	22.73 %	9	40.91 %
SEX				
Male	22	100%	14	63.63 %
Female	0	-	8	36.36 %
SMOKERS/ NON- SMOKERS				
Smokers	21	95.45 %	21	95.45 %
Non-smokers	1	4.54%	1	4.54%
KPS				
70	8	36.36 %	5	22.73 %
80	9	40.91 %	11	50.00 %
90	5	22.73 %	6	27.27 %
HISTOLOGY				
SCC	13	59.09%	13	59.09% %
Adeno.	5	22.73%	5	22.73%
Adenosq.	4	18.18%	4	18.18%
STAGE				
IIa	2	9.09%	2	9.09%
IIb	3	13.64 %	3	13.64 %
IIIa	13	59.09 %	13	59.09 %
IIIb	4	18.18 %	4	18.18 %

Table 1: Patients characteristics

On 1st follow-up, Complete response was seen in 3 patients in each control and study arms (13.64%, p=1.000). Partial response was seen in 4 patients and 5 patients in the control arm and the

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study arm respectively (18.18% vs 22.73%, p=0.739). Stable disease was observed in 2 patients in each arm (9.09%, p=1.000). Progressive disease was seen in 9 patients and 8 patients in the control arm and the study arm respectively (40.90% vs 36.36%, p=0.809). The observations were statistically insignificant (Figure1).

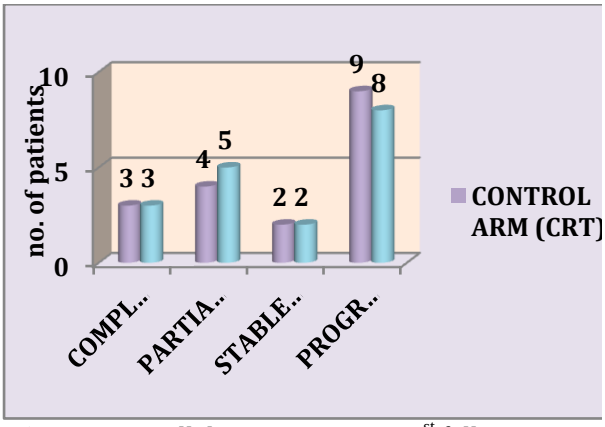

Figure1: Overall disease response at 1st follow up

On subset analysis, the 1st subset analysis [stage IIA + squamous cell carcinoma] (total 2 patients in each arm), showed complete response in1patient both the arms (p=1.000); partial response in 1 patient in the study arm and none in control arm (p=0.317); none of the patients had stable disease; 1 patient had progressive disease in control arm (p=0.317).

The 2nd subset analysis [stage II_B+ squamous cell carcinoma] (total 3 patients in each arm), showed complete response in 1 patient in the study arm and none in the control arm(p=0.317); partial response in 1 patient in the control and none in study(p=0.317); stable disease in 1 in control arm and none in study arm(p=0.317); progressive disease in 1 in both arms(p=1.000) and 1 patient in study arm had incomplete treatment(p=0.317).

The 3rd subset analysis [stage III_A+ squamous cell carcinoma] (total 5 patients in each arm), showed complete response in none of the patients; partial response in 1 patient in the control arm and 2 patients in the study arm(p=0.563); none had stable disease, progressive disease was observed in 3 patients in the control arm and 2 patients in the study arm(p=0.654) and treatment was stopped in between in 1 patient in both the arms(p=1.000).

The 4th subset analysis [stage III_B + squamous cell carcinoma] (total 3 patients in each arm), showed complete response in 1 patient in the study arm and none in the control arm (p=0.317); partial response in 2 patients in the control arm and none in study arm (p=0.157); 1 patient in the study arm had stable disease (p=0.317) and 1 patient in both arms had progressive disease (p=1.000).

In 5th and 6th subset [stage IIA and IIB adenocarcinoma], no patients were enrolled.

The 7th subset analysis [stage IIIA adenocarcinoma] (total 5 patients in each arm), showed complete response in 1 patient in the control arm and none in the study arm(p=0.317), partial response in 1 patient in the study arm and none in control arm(p=0.317), stable disease in 1 patient in both the arms(p=1.000), progressive disease in 2 patients in both the arms(p=1.000) and 1 patient in both arms had incomplete treatment(p=1.000).

In 8th [stage IIIB adenocarcinoma], 9th and 10th subsets [stage IIA and IIB Adenosquamous carcinoma], no patients were enrolled.

The 11th subset analysis [stage IIIA Adenosquamous carcinoma] (total 3 patients in each arm), showed complete response in 1 patient in the control arm and none in the study arm (p=0.317), none of the patients showed partial response or stable disease, progressive disease in 1 patient in the control arm and 2 patients in the study arm (p=0.563) and 1 patient in both arms had incomplete treatment (p=1.000).

In 12th subset [stage IIIB adenosquamous carcinoma] (1 patient in each arm), the patient in the study arm showed partial response (p=0.317) while the patient in the control arm had incomplete treatment (p=0.317).

Toxicity Profile: The toxicity profile of the patients is shown in Table2.

	Control arm (n=22)		**Study arm (n=22)**		**P value**
	Frequency	%	Frequency	%	
Pulmonary toxicity					
Grade 0	3	13.64 %	2	9.09 %	0.654
Grade I	13	59.09 %	12	54.54 %	0.841
Grade II	5	22.73 %	8	36.36 %	0.405
Grade III	1	4.54 %	0	0.00 %	0.317
Grade IV	0	0.00 %	0	0.00 %	-
Hematological toxicity					

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Grade 0	0	0.00 %	3	13.64 %	0.083
Grade I	4	18.18 %	13	59.09 %	0.025
Grade II	13	59.09 %	6	27.28 %	0.108
Grade III	4	18.18 %	0	0.00 %	0.045
Grade IV	1	4.54 %	0	0.00 %	0.317
Esophageal toxicity					
Grade 0	7	31.82 %	2	9.09 %	0.095
Grade I	12	54.54 %	16	72.73 %	0.447
Grade II	3	13.64 %	4	18.18 %	0.706
Grade III	0	0.00 %	0	0.00 %	-
Grade IV	0	0.00 %	0	0.00 %	-
Skin toxicity					
Grade 0	16	72.73 %	13	59.09 %	0.646
Grade I	5	22.73 %	8	36.36 %	0.373
Grade II	1	4.54 %	1	4.54 %	1.000
Grade III	0	0.00 %	0	0.00 %	-
Grade IV	0	0.00 %	0	0.00 %	-

Table 2: Toxicities seen in both the arms

Pulmonary toxicity: Grade I pulmonary toxicity was observed in 13 patients in the control arm and 12 patients in the study arm (p=0.841). Grade II pulmonary toxicity was observed in 5 patients in the control arm and 8 patients in the study arm (p=0.405). Grade III pulmonary toxicity was observed in 1 patient in the control arm (p=0.317). The values are statistically insignificant.

Haematological toxicities: Grade I toxicity was observed in 4 patients in the control arm and 13 patients in the study arm (p=0.025). Grade II toxicity was observed in 13 patients inthe control arm and 6 patients in the study arm (p=0.108). Grade III toxicity was observed in 4 patients in the control arm with statistically significant difference (p=0.045). Grade IV toxicity was observed in only 1 patient in the control arm.

Oesophageal toxicities: Grade I toxicity was observed in 12 patients in the control arm and 16 patients in the study arm (p=0.447). For grade II toxicity there were 3 patients in the control arm and 4 patients in the study arm (p=0.706). There were no grade III / IV oesophageal toxicities in any of the arms.

Cardiac toxicities: none of the patients had acute cardiac toxicity.

Skin toxicity: Grade I toxicity was seen in 5 patients in the control arm and 8 patients in the study arm (p=0.373).Grade II toxicity was observed in 1 patient in both arms (p=1.000) and Grade III/IV toxicity was not observed in any of the patients.

When grade≥III toxicities were analysed. The total number of events of grade III/IV toxicities in the control arm were 6 and in the study arm was 0.

Quality of life: The commonest symptom at presentation was dyspnea (41 out of 44 patients [93.18%] had some grade ofdyspnea) followed by cough (39 out of 44 patients [88.64%] had cough). Maximum improvement was noted for (a) hemoptysis: all 8 out of 8 patients in the control arm and all 6 out of 6 patients in the study arm improved; (b) arm/shoulder pain: 6 out of 6 patients (100%) in the control arm and 7 out of 7 patients (100%) in the study arm improved; (c) dyspnea: 19 out of 20 patients (95.00%) in the control arm and 19 out of 21 patients (90.48%) in the study arm improved. Chest pain improved in 13 out of 15 patients (86.67%) in the control arm and 10 out of 12 patients (83.33%) in the study arm (Figure2).

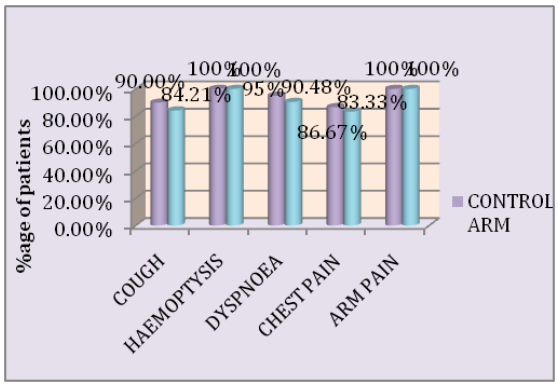

Figure2: Quality of life parameters which improved with treatment

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These observations are, however, not statistically significant. The parameters which developed or worsened on treatment were: dysphagia, paraesthesia, alopecia and sore mouth. Dysphagia developed/worsened in 18 out of 22 patients (81.82%) in the control arm and 20 out of 22 patients (90.91%) in the study arm. Paraesthesia developed in 8 out of 22 patients (36.36%) in the control arm and 4 out of 22 patients (18.18%) in the study arm. Hair loss was noted in 100% patients in control arm and none of the patients in the study arm and the observation is statistically significant. Sore mouth was noted in 15 out of 22 patients (68.18%) in the control arm and none of the patients in the study arm and the observation is statistically significant (Figure3).

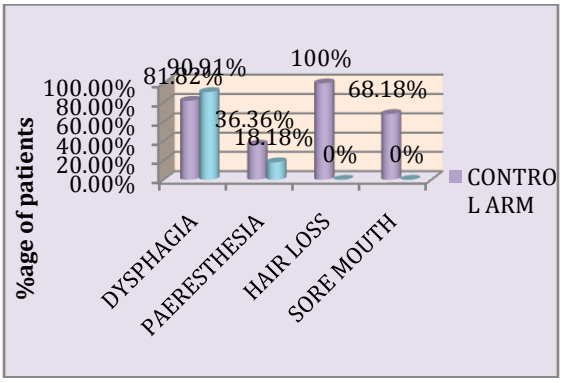

Figure3: Quality of life parameters which worsened with treatment

IV. DISCUSSION

The treatment for locally advanced unresectable or inoperable non-small cell lung cancer has evolved from radical radiotherapy in the early nineties to sequential chemoradiation till 2004 and now, concomitant platinum based chemoradiation over the last 10 years.[9,10]

But chemotherapy has its own toxicities. Majority of our patients with lung cancer do not tolerate the concurrent chemoradiotherapy due to borderline or poor general condition and comorbid conditions. So, other forms of treatment need to be evaluated as an alternate to CRT in lung cancer.

One of the options to be explored is accelerated radiotherapy. The place of more intensive fractionation schedules has been evaluated in a number of other situations. The most promising is in head and neck cancers (as seen in randomized controlled trial that comprised of two sub protocols Danish Head and Neck Cancer study group-6 & 7).[8] There is equivocal evidence at present in oesophageal carcinoma,[11,12] bladder transitional cell carcinoma, prostate cancer and malignant gliomas.

Accelerated radiotherapy shortens the overall treatment time, limiting the extent of accelerated tumor repopulation. Hence, increase the probability of tumor control for a given total dose with no or little effect on late normal tissue injury. As lung tumor has short tumor doubling time (similar to head and neck tumors), accelerated radiotherapy may prove beneficial in lung cancer.

On this background, we conducted a randomized prospective study comparing concomitant chemoradiotherapy using cisplatin-etoposide and accelerated radiotherapy in locally advanced unresectable or inoperable NSCLC, with same total radiation dose in both the arms.

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

We did not find any difference in complete response between the two arms at first follow up after 6 weeks (13.64% vs 13.64%). Similarly the partial response was seen in 4 (18.18%) patients in the control arm and 5 (22.73%) patients in the study arm which was not significant statistically. The overall response rate (combined complete and partial response) for all patients was 34.09%. It was 31.81% in the control arm and 36.36% in the study arm. These differences were, however, not statistically significant.

Our data suggest that the complete response in stage II disease was slightly better in accelerated RT arm (40%) as compare to chemo radiotherapy arm (20%) though the difference was not significant statistically (p=0.564). In stage III disease, the complete response was better in chemo radiotherapy arm (11.76%) as compare to accelerated arm (5.88%). Since the sample size was small so this difference did not reach statistical significance (p=0.564) in this sub group as well. We cannot draw any firm conclusion from the above findings but we may generate a hypothesis based on our data that accelerated radiotherapy may be superior for stage II NSCLC and concurrent chemo radiotherapy may be more effective for more advance stage III disease. The possible reason may be that in stage III disease, the tumor bulk is big and more than one modality (RT and CT) is required to take care of large number of clonogenic cells. This needs to be tested on a larger prospective randomized trial. Further, on subset analysis of twelve subsets created by using different variable, we did not find any difference in disease response between the two groups.

In the study by Pierre Fournal, et al, [13] the response rate was 49% with concurrent treatment (all assessable patients) and 32% (intent to treat analysis). In the study by C. Pottgen, et al[14] the

locoregional control rate of 21% was obtained in chemotherapy/radiotherapy protocol. The response rates obtained in our study is similar to the response rates in the studies discussed above and the response rate in the study arm is comparable to the control arm.

The second end point of this study was the toxicity profile. There was slightly higher grade II and III pulmonary toxicity in study arm (27.27 % vs 36.36%) but this difference was not statistically significant (p= 0.592). Grade ≥II hematological toxicities were higher in chemo radiotherapy arm (81.81%) as compare to accelerated radiotherapy arm (27.28%) which was statistically significant (p=***0.014***). This may directly be attributed to the myelosuppressive effect of chemotherapy given in chemo radiotherapy arm only. The Grade I and II esophageal toxicities were slightly higher in study arm (90.91%) as compare to control arm (68.18%). 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. Though the difference in acute esophageal toxicities was not statistically significant (p=0.398). No cardiac toxicity was observed in any patient in both the arm and may be due to short median follow up as cardiac toxicities are usually observed after many years. There was no difference in the skin toxicities between two arms and only Grade I & II skin toxicities were observed. Treatment interruption was observed in 4 patients in each arm.

Quality of life analysis, based on the EORTC QLQ-LC13[15]module, was the third end point of this study. The commonest symptom at presentation was dyspnea (93.18%), followed by cough (88.64%). Maximum improvement was noted for (a) hemoptysis: 100% in both arms; (b) arm/shoulder pain: 100% in both arms; (c) dyspnea: 95.00% in the control arm and 90.48% in the study arm. Chest pain improved in 86.67% of the patients in the control arm and 83.33% in the control arm. Cough improved in 90.00% in the control arm and 84.21% in the study arm. The parameters which developed or worsened on treatment were: dysphagia, paresthesia, alopecia and sore mouth. Dysphagia developed/worsened in 81.82% patients in the control arm and 90.91% in the study arm. Paresthesia developed in 36.36% patients in the control arm and 18.18% in the study arm. Hair loss was noted in 100% patients in control arm and 0% in the study arm and the observation is statistically highly significant (p=0.000). Sore mouth was noted 68.18% patients in the control arm and 0% in the study arm and the observation is also statistically highly significant (p=0.000). These findings reflects that quality of life worsened in concurrent chemo radiotherapy arm on two parameter i.e. 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 chemoradiotherapy 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. However, these findings need to be confirmed on a large prospective randomized trial with longer follow up period.

V. CONCLUSION

Local control, toxicity profile and quality of life index were comparable in the two arms. The accelerated radiotherapy may be used for patients who are not good candidates for chemotherapy, like patients with deranged renal functions or very old and frail patients. However the above findings need to be tested on a larger trial with a longer follow up period.

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