Original Article

"A Comparative Study Using Conventional Concomitant Chemoradiotherapy (Using Cisplatin-Based Chemotherapy) with Accelerated (Six Fractions a Week) Chemoradiotherapy in Inoperable or Nonresectable Locally Advanced Non-small Cell Lung Cancers:" A Prospective Randomized Trial

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Abstract

Context: The conventional concomitant chemoradiotherapy (CCRT) is the standard treatment for locally advanced non-small cell lung cancer. Accelerated CCRT results in shortening of overall treatment time which can contribute in controlling accelerated tumor repopulation. The increase in tumor control probability (TCP) can be expected with no or little effect on late normal tissue injury for a given total dose. **Aim:** The aim of this study was to compare the disease response, toxicity profile, quality of life (QoL), and overall survival in accelerated versus conventional CCRT. **Subjects and Methods:** Total 42 patients were randomized into two groups – study group (n = 21): Accelerated CCRT, radiation was given as 6 fractions per week (60 Gy/5 weeks/30#) with injection cisplatin 20 mg/m^2 intravenous (iv) days 1–5 and days 29–33 + injection etoposide 50 mg/m^2 iv days 1–5 and days 29–33 and control group (n = 21): Conventional CCRT, radiation was given as 5 fractions per week (60 Gy/6 weeks/30#) along with the same chemotherapy. External beam radiation therapy was delivered by cobalt-60 machines. **Results:** The overall response rate (complete and partial response) for all patients was 66.6%. In the control group, it was 66.2%, and in the study group, it was 66.6%. Grade ≥II pulmonary, hematological, and esophageal toxicities were seen in 57%, 43%, and 24% in patients of the control group and 53%, 53%, and 33% in the study group, respectively. In QoL analysis, maximum improvement was noted for hemoptysis, arm/shoulder pain, dyspnea, and chest pain in both the groups. **Statistical Analysis Used:** The data were analyzed by Student's t-test and Chi-square test. $P < 0.05$ was taken as statistically significant. **Conclusion:** As response rates and disease progression were similar in both the groups, accelerated chemoradiotherapy can be considered as an alternate therapy, especially in high-volume centers.

Keywords: *Cobalt-60, concomitant chemoradiation, dyspnea, fractions*

Introduction

Lung cancer constitutes 13% of all cancers worldwide. It is the most common cancer in the world and the leading cause of cancer deaths.[1] In India, the incidence in men has increased and it is now the most common cancer along with oral cancers (11.3% of all cancer cases) and causes 13.7% of cancer deaths in Indian men. In Indian women, incidence is 3.1% of all cancers.[1] Till the mid-1990s, the standard treatment was thoracic radiotherapy, later on combined radio-chemotherapy for locally advanced non-small cell lung cancer (NSCLC). The optimal dose of radiotherapy was determined as 60 Gy (Gray) and to be administered as 2 Gy/fractions in 6 weeks.[2] In Asian countries due to the differences in race, availability of radiotherapy machines, and socioeconomic factors, standardization of concomitant chemotherapy schedules and dosage has not become possible. Thus, different strategies and radiotherapy schedules are still required to explore to enhance the effects of radiotherapy. In conventional fractionation, doses of 2 Gy are delivered once each day, 5 days/week, and overall treatment time (OTT) is 6 weeks. In hyperfractionation, smaller doses per fraction are delivered two or three times per day.[3] Radiobiologically,

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in hyperfractionation, OTT will remain unchanged and allows the total tumor dose to be escalated without increasing the late morbidity, thereby improving the therapeutic index. In a recent review of hyperfractionated radiotherapy in human tumors, it was consistently demonstrated to be more effective in terms of responses than conventional radiotherapy.[3] 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 tumor cell repopulation during the treatment course. The Radiation Therapy Oncology Group (RTOG) published a preliminary report of a prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable carcinoma of the lung in 1980.[2] Radiological complete response (CR) rate was 10%–25%, and 2-year survival was only 12%. From this, the exploration of novel radiotherapy schedules has mushroomed in a determined effort to find the optimum scheduling. Accelerated radiotherapy will shorten the OTT and limit accelerated tumor repopulation and will help in increasing tumor control probability for a given dose. Since treatment time is thought to have little or no influence on the response of late-reacting tissue, as it depends on the fraction size, a reduction in OTT would not be expected to affect the incidence and severity of tissue injury.[4,5] The increase of acute radiation reaction is expected as the clonogenic population of normal epithelial cells will reduce drastically in a short term. Randomized control trials by Danish Head and Neck Cancer Study Groups 6 and 7 proclaimed that the shortening of OTT by increasing number of fractions per week is beneficial in patients with head and neck cancers.[6] Studies have shown better locoregional control with comparable toxicity with altered fraction radiotherapy.[7,8] Furthermore, lung tumor has short tumor doubling time similar to head and neck tumors, and accelerated radiotherapy may prove beneficial in lung cancer.

Subjects and Methods

This randomized prospective study had included patients of locally advanced nonmetastatic NSCLC. The inclusion criteria were as follows: histologically proven squamous cell carcinoma, adenocarcinoma, large cell carcinoma and adenosquamous carcinoma, Stage IIIA, IIIB (unresectable or inoperable) staged by the American Joint Committee on Cancer 2010, and patients with Karnofsky performance status (KPS) >70. The exclusion criteria were as follows: age >65 years and <18 years, histology other than squamous cell, adenocarcinoma, large cell or adenosquamous, patients who have had prior thoracic surgery for cancer, thoracic radiotherapy or prior chemotherapy within 5 years, deranged kidney function test and liver function test, and KPS <70. The study was carried out only after the protocol was approved by the institution's ethics review board.

Pretreatment workup

It includes complete physical examination including chest X-ray, bronchoscopy, and contrast-enhanced computed tomography (CECT) for clinical staging. Baseline pulmonary function tests, complete hemogram, and blood biochemistry were done. Ultrasound abdomen and pelvis, bone scan, and computed tomography (CT)/magnetic resonance imaging brain were done when indicated.

Randomization

Before randomization, we stratified patients according to clinical stage and histology. Four blocks were created from the stratification factors: IIIA + SCC, IIIA + adenocarcinoma, IIIB + SCC, and IIIB + adenocarcinoma. In each block, patients were randomized into two groups – control group (conventional chemoradiotherapy) and study group (accelerated chemoradiotherapy).

Control group

Study design for control group (concomitant chemoradiotherapy): External beam radiation therapy (EBRT) to a total dose of 60 Gy in 30# (fractions) starting day 1 of chemotherapy at 2 Gy/# and 5#/week. Spinal cord off was done after 44 Gy. Chemotherapy**:** injection cisplatin 20 mg/m^2 and injection etoposide 50 mg/m^2 intravenous with #1–#5 and #21–#25.

Study group

For study group **(**accelerated chemoradiotherapy): EBRT to a total dose of 60 Gy in 30# starting day 1 of radiotherapy at 2 Gy/# and 6#/week. Spinal cord off was done after 44 Gy along with the same chemotherapy of the same dose and schedule in the control arm. EBRT was given by teletherapy Theratron 780E and equinox cobalt-60 machines. The dose–volume constraints for the surrounding normal structures were respected. CECT thorax was done before scheduled commencement of treatment and at 1st follow-up posttreatment.

Assessment

During treatment, toxicities were assessed every week with chest radiographs every 2 weeks. Response assessment was done by the Response Evaluation Criteria in Solid Tumors (1.1). Toxicities were monitored and the Eastern Cooperative Oncology Group toxicity criteria were utilized to assess and document hematological toxicities and Radiotherapy Oncology group (RTOG) acute morbidity criteria to assess toxicities from radiotherapy. Quality of life (QoL) was evaluated using the European Organization for Research and Treatment of Cancer QLQ–LC13 questionnaire.[9] The first follow-up was done at 6 weeks post-treatment during which chest CT for local control, pulmonary function test, and QoL evaluation were done. Subsequent follow-ups were done every 2 months during which patients assessed for subacute or late toxicities.

Statistical analysis

The recorded scores of acute radiation reaction experienced by patients 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. The *P* values were calculated. Statistical analysis was done with the Statistical Program for Social Sciences (SPSS) (SPSS v23, IBM Corp, USA) which was used for analyzing.

Results

Patient accrual was started from July 2016, and patients were enrolled till June 2017. Last follow-up was taken in January 2019. Patients with minimum follow-up of 6 months were included in this study. Forty-two patients of locally advanced non-metastatic NSCLC were included in the analysis. Twenty-one patients were randomized into control group and 21 in study group.

Patient characteristics

The baseline profile of the patients like: age, gender, smoking status, stage, histology and KPS were comparable in both groups [Table 1].

Locoregional control and survival

The overall response rate (CR + partial response) was 66.2% in the control group (13/21) and 66.6% in the study group (14/21). As far as stable disease is concerned, it was observed in 3 patients (14.2%) in the control group and three patients (19%) in the study group. There were four patients (19%) in the control arm and 4 (19%) in the study group who were found to have disease progression at 1st follow-up. The response rates are shown in Table 2. The two-year progression-free survival rate was 61% in control group as compared to 66.6% in study group [Figure 1]. The difference was not statistically significant ($P = 0.778$). There was no difference in overall survival between the two arms ($P = 0.730$) [Figure 2]. Subset analysis by stage and histology was similar [Table 3].

Toxicity profile

During treatment, pulmonary, hematological, esophageal, cardiac, and skin acute toxicities were assessed every week [Table 4]. ≥ Grade III toxicities in both the groups were comparable.

Quality of life

QoL was evaluated and recorded weekly. There are ten single-item scales addressing: cough, hemoptysis, sore

Table 1: Patients characteristics

Patients characteristics	Control		Study	
	Number of patients	Percentage	Number of patients	Percentage
Age in years				
45-50	3	14	2	10
51-55	3	14	3	14
56-60	5	24	7	33
61-65	7	33	3	14
66-70	3	14	6	29
Sex				
Male	17	81	15	71
Female	4	19	6	29
Smoker vs non-smoker				
Smoker	21	100	21	100
Non-smoker	0	0	0	0
KPS				
70	3	14	1	5
80	8	38	11	52
90	10	48	9	43
Histology				
Squamous	14	67	14	67
Adenocarcinoma	7	33	7	33
Stage				
IIA	1	5	1	5
IIB	4	19	4	19
IIIA	11	52	11	47
IIIB	5	24	5	24

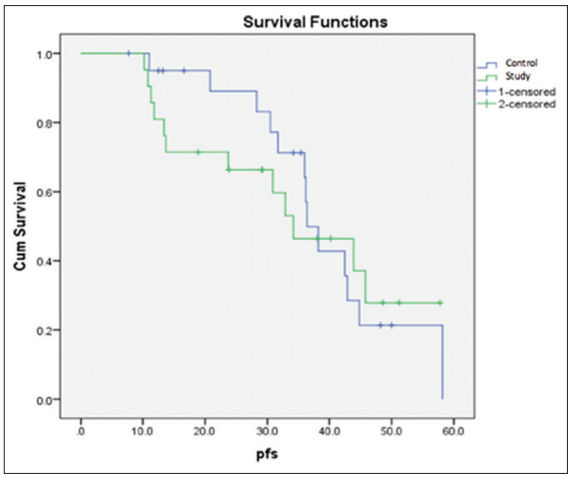

Figure 1: Progression-free survival

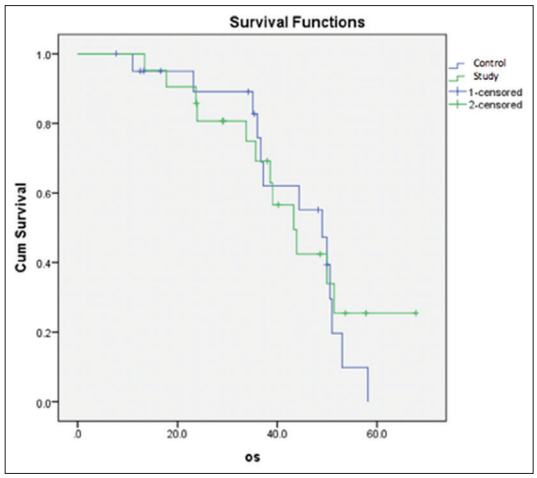

Figure 2: Overall survival

Table 2: Overall disease responses at the first follow-up

Response	Control group (21)	Study group (21)	*P*
Complete response	3 (14.2%)	4 (19%)	0.634
Partial response	11 (52%)	10 (47.6%)	0.533
Stable Disease	3 (14.2%)	3 (19%)	0.634
Progressive disease	4 (19%)	4 (19%)	1.000

Table 3: Subset analysis

Subset	Control arm					Study arm				
	CR	PR	SD	PD	Deaths	CR	PR	SD	PD	Deaths
IIA+ADENO	1	3	0	0	0	1	2	0	0	0
IIB+SCC	1	3	1	0	1	2	3	0	0	0
IIB+ADENO	1	2	0	0	1	1	2	0	0	0
IIIA+SCC	0	1	0	1	3	0	1	0	1	1
IIIA+ADENO	1	1	0	1	3	0	0	1	1	1
IIIB+SCC	0	1	1	2	5	0	2	2	1	2

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, SCC=squamous cell carcinoma, adeno=adenocarcinoma

mouth/tongue, dysphagia, peripheral neuropathy, alopecia, chest pain, arm/shoulder pain, other pains, and improvement of pain upon medication.[9] There is one 3-item scale addressing dyspnea: dyspnea at rest, on walking, and on climbing stairs. The most common symptom at presentation was cough (41 out of 42 patients [98%] had cough) followed by dyspnea (37 out of 42 patients [88%] had some grade of dyspnea). Maximum improvement was noted for [Table 5] (a) hemoptysis: all 5 out of 5 patients in the control group and 3 out of 4 patients in the study group improved; (b) arm/shoulder pain: 4 out of 5 patients (80%) in the control group and 4 out of 4 patients (100%) in the study group improved; and (c) dyspnea: 14 out of 17 patients (82.35%) in the control group and 13 out of 16 patients (81.25%) in the study group improved. Chest pain improved in 9 out of 11 patients (81.81%) and 3 out of 7 patients (42.8%) in the control and study groups, respectively. These observations are, however, not statistically significant. The parameters which developed or worsened on treatment were as follows: dysphagia, paresthesia, alopecia, and sore mouth. Dysphagia developed/worsened [Table 6] in 10 out of 21 patients (48%) and 13 out of 18 patients (62%) in the control and study groups, respectively. Paresthesia developed in 4 out of 21 patients (19%) and 3 out of 21 patients (14%) in the control and study groups, respectively. Hair loss was noted in 100% of patients in both the groups. Sore mouth was noted in 11 out of 21 patients (52%) and 10 out of 21 patients (48%) in the control and study groups, respectively.

Discussion

The standard treatment for locally advanced unresectable or inoperable NSCLC is concomitant chemoradiation.[9,10] Despite undergoing definitive concomitant chemoradiation, patients experience a high incidence of local and distant relapse. Hence, trials need to focus on the effect of altered fractionation. One of the less explored options is accelerated chemoradiotherapy. The place of more intensive fractionation schedules has been evaluated in a number of other sites like in head and neck cancers. There have been encouraging results indicating trends toward better local control for more advanced disease. The meta-analyses by Mauguen *et al*.[10] and a study[11] had used modified radiation therapy and has shown significant in terms of 12%–13% relative reduction of mortality in patients with lung cancer, resulting in a 5-year survival absolute benefit of 2.5% in NSCLC. There was more acute esophageal toxicity in modified radiotherapy groups, likewise, in our study patients also experienced acute esophageal toxicity but it was comparable in both the groups (accelerated CCRT and conventional CCRT) with no statistically significant difference. The overall response rate and CR both were equivocal in both the groups. The CR rates were seen to be 14.2% in the control group and 19% in the study group. The overall response rates were noted to be 66.2% in the control

Table 4: Toxicity profile

Toxicity	Control group		Study group		*P*
	Frequency	%	Frequency	%	
Pulmonary Toxicity					
GRADE 0	0	0	0	0	
GRADE 1	9	43	10	47	0.7
GRADE 2	11	52	9	43	0.5
GRADE 3	1	5	2	10	0.54
GRADE 4	0	0	0	0	
Haematological Toxicity					
GRADE 0	9	43	7	33	0.52
GRADE 1	3	14	3	15	1.0
GRADE 2	8	38	10	47	0.553
GRADE 3	1	5	1	5	1.0
GRADE 4	0	0	0	0	
Oesophageal toxicity					
GRADE 0	0	0	0	0	
GRADE 1	16	76	14	67	0.495
GRADE 2	5	24	7	33	0.495
GRADE 3	0	0	0	0	
GRADE 4	0	0	0	0	
Skin toxicity					
GRADE 0	8	38	8	38	
GRADE 1	3	14	3	14	1.0
GRADE 2	9	43	9	43	1.0
GRADE 3	1	5	1	5	1.0
GRADE 4	0	0	0	0	

group and 66.6% in the study group, and the difference was statistically insignificant. The treatment in both the groups was very well tolerated with no high-grade toxicities. QoL analysis depicted that maximum improvement was noted for hemoptysis, arm/shoulder pain, dyspnea, and chest pain. The difference was statistically insignificant.

Similarly, the QoL parameters noted were hemoptysis which improved in all patients; chest pain (81.2%) in the conventional arm and (42.8%) in the study arm improved; dyspnea (82.35%) in the conventional arm and (81.25%) in the study arm improved. The parameters which developed or worsened on treatment were as follows: dysphagia, paresthesia, alopecia, and sore mouth. These parameters were comparable in both the arms. This correlates well with the study by Nyman *et al*.[12] in which all the toxicities in the convention arm as well as accelerated radiation arms were manageable with 12% Grades 3–4 esophagitis and 1% Grades 3–4 pneumonitis, and there was no clear difference between the arms. The QoL data did not differ either. In this study, the treatment results were quite equal by intensifying the locoregional treatment either by accelerated fractionated radiotherapy or daily or weekly concomitant chemoradiotherapy both in terms of survival, toxicity, and QoL. However, in a randomized multicenter trial by

Table 5: Quality of life parameters which improved on Treatment

Symptom	Control group	Study group	*P*
Cough	14/21 (66.7%)	13/20 (65%)	0.910
Haemoptysis	5/5 (100%)	3/4 (75%)	0.236
Dyspnoea	14/17 (82.35%)	13/16 (81.25%)	0.935
Chest pain	9/11 (81.18%)	3/7 (42.8%)	0.087
Arm/shoulder pain	4/5 (80%)	4/4 (100%)	0.343

Table 6: Quality of life parameters which developed/ worsened on treatment

	Control	Study	*P*
Dysphagia	10/21 (48%)	13/21 (62%)	0.352
Hair loss	21/21 (100%)	21/21 (100%)	1.000
Paraesthesia	4/21 (19%)	3/21 (14%)	0.679
Sore mouth	11/21 (52%)	10/21 (48%)	0.758

Saunders *et al*.[13] in continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in patients with locally advanced NSCLC, severe dysphagia occurred more often in the CHART group than in the group of conventional radiotherapy (19% vs. 3%). Otherwise, there were similar short-term or long-term toxicities.

Conclusion

The outcome of the study depicts that response rates were comparable and toxicity profile and Qol parameters were also similar in both arms. The accelerated chemoradiotherapy can be considered as an alternate option in patients of inoperable or nonresectable locally advanced NSCLC. Further, the accelerated chemoradiotherapy will increase the turnover on treatment machines and 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 1 week, thus saving patient's time and money as well. However, we need to confirm these findings in a large prospective randomized trial with a longer follow-up period to make any definitive conclusion.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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