DOI:10.31557/APJCC.2024.9.2.253

RESEARCH ARTICLE

Palliative Hypo-fractionated Radiotherapy for Locally Advanced Non-Small Cell Lung Cancer: A Feasibility Study

Saroj Dhaka[1], Rakesh Kumar Sihag[1], Vidushi Saharan[2], Shankar Singh Dhaka[3], Surender Beniwal[4]

[1]Department of Neurosurgery, AIIMS, Rishikesh, India. [2]Department of Pathology, SMS Medical College, Jaipur, India. [3]Department of Radiation Oncology, Sardar Patel Medical College, Bikaner, India. [4]Department of Medical Oncology, Sardar Patel Medical College, Bikaner, India.

Abstract

Objective: To assess the feasibility and potential benefits of palliative hypo-fractionated radiotherapy (HF-RT) compared to conventional fractionated radiotherapy (CF-RT) in patients with locally advanced non-small cell lung cancer (NSCLC). **Materials and Methods:** Fifty patients with unresectable stage III NSCLC received three cycles of neoadjuvant chemotherapy. After completion, 25 patients were randomized to receive HF-RT (17 Gy in 2 fractions, 8.5 Gy per fraction, on days 1 and 8) and 25 to CF-RT (50 Gy in 25 fractions, 2 Gy per fraction, administered daily for 5 weeks). Disease response was assessed using RECIST criteria at 1, 3, and 6 months, and overall survival was followed for up to 3 years. **Result:** No complete responses were observed in either group. Locoregional disease control rates were 18% in the HF-RT arm and 27% in the CF-RT arm ($p > 0.05$). Median survival was 10 months in the HF-RT arm and 12.5 months in the CF-RT arm, with no statistically significant difference. There was no significant difference in the grade of toxicities between the groups. Although a significant proportion of patients were lost to follow-up, among those followed, HF-RT showed a trend toward improved quality of life and shorter treatment duration. **Conclusion:** This feasibility study suggests that HF-RT may be a viable and potentially beneficial palliative option for locally advanced NSCLC patients, particularly those with poor performance status and a limited life expectancy. However, further research with larger cohorts and stricter follow-up is needed to confirm these preliminary findings and establish the true clinical benefits of this approach.

Keywords: Unresectable stage III Non small cell lung cancer- conventional radiation- palliative hypo-fractionated radiation

Asian Pac J Cancer Care, **9 (2)**, 253-256

Submission Date: 08/26/2023 Acceptance Date: 03/16/2024

Introduction

Worldwide lung cancer is the most common and deadliest form of cancer accounting for 13%of all new cancer cases and 19% of cancer related deaths worldwide [1]. Among males lung cancer is the most commonly diagnosed cancer and leading cause of cancer death. Among females, it is the 4th most commonly diagnosed cancer (after breast, oral, colorectal and cervical cancer) and second leading cause of cancer death (1st being breast cancer) [2]. In India, currently lung cancer is the 4th largest cause of cancer, accounting for nearly 8% of all cancer related deaths in the country. At diagnosis, nearly 70% of patients present with locally advanced or metastatic disease [3].

About 55% patients with NSCLC present advanced lung cancer are treated with palliative intent. In advanced stage patients of NSCLC the performance status is used to estimate a patient's prognosis, tolerance and potential benefits of chemotherapy. Majority of patients are incurable at presentation and majority of them will die from their locoregional disease. Most of patients develop thoracic symptoms during their illness. The goal of providing effective palliation while avoiding unacceptable toxicity should be incorporated while choosing treatment modality. The overall survival rate of lung cancer is 23% and 10% with stage IIIA and IIIB, IV respectively. The median survival is roughly 13 months with treatment.

Corresponding Author:
Dr. Saroj Dhaka
Assistant Professor, Department of Radiation Oncology, Dr S.N. Medical College, Jodhpur, India.
Email: sarojdhakasihag@gmail.com

The rationale behind the sequential chemo-radiotherapy is based on that RT addresses locoregional control whereas CT acts systemically to eradicate micro-metastasis [4-7].

Hypofractionation refers to administration of radiotherapy utilizing a small number of fractions with a larger dose per fraction. Invitro experiments indicated that the dose needed to kill severely hypoxic cells is on the order of 2 or 3 time the dose needed for oxigenated cells. Therefore, delivering a higher RT dose to tumour may result in higher tumour cell kill and improved local control. One approach to increase RT dose is to use hypo-fractionated RT, which not only increases the dose, but also reduces the overall treatment time. This study is intended to evaluate the benefits of hypofractionated RT in advanced stage lung cancer patients previously treated with induction chemotherapy in favour of symptom control, quality of life, toxicity profile, median and overall survival [8, 9].

Materials and Methods

This was a randomised prospective study conducted at Acharya Tulsi Regional Cancer Treatment and Research Institute, Sardar Patel Medical College and associated group of hospital, Bikaner.

The study protocol included 50 patients of locally advanced NSCLC patients of stage IIIA-IIIB, histologically proven cases of non small cell carcinoma, who were enrolled from July 2012 to July 2013. Inclusion criteria included inoperable, locally advanced, histologically proved, stage IIIA and IIIB NSCLC patients, ECOG performance status 2-3, tumor related chest symptoms (cough, dyspnoea, haemoptysis, chest pain, dysphagia), age up to 75 years, without any haematological, cardiac, renal or liver function abnormality, no previous history of treatment for the lung cancer and no any other concurrent malignancy (Table 1).

All 50 patients were randomly selected in two arms of 25 patients in each. The both arms were treated by sequential chemo-radiotherapy. Neoadjuvant chemotherapy was 3 cycle, each consisting of inj cisplatin 40mg/m^2 on day 1 and 2 and inj paclitaxel 175mg/m^2 on day 1. Radiotherapy was planned after 3-4 weeks from last cycle of chemotherapy. In study arm, patients received a total 17Gy in 2 fractions (8.5Gy for each fraction) on day 1& day8 (Hypofractionated Radiotherapy) and control arm, patients received a total 50Gy in 25 fractions (2Gy for each fraction), administered daily (5 days per week) for 5 weeks (conventional fractionated radiotherapy).

Treatment volume were included primary tumor site plus mediastinum region. Parallel opposed antero-posterior fields were planned. The dose was prescribed at midline. External beam radiotherapy was given with radiation therapy parameter on cobalt-60 machines Theratron 780E/ 780C/ Bhabhatron II with photon energies of 1.25MeV. Minimum treatment distance was>=80 cm SSD.

Patients were under monitoring after every course of chemotherapy and prior to and during radiotherapy. In each monitoring, patients were assessed for treatment response, control of symptoms and any treatment related morbidity by doing complete blood counts, biochemistry profile consisting of RFT and LFT, chest X-ray, USG Abdomen. Toxicity haematological, renal, biochemical, skin reactions and disease response were assessed. After 1 month of completion of radiotherapy patients were called for first follow up visit and were assessed for treatment response and palliation of symptoms. On first follow up visit complete general-physical examination, hemogram, RFT, Chest X-ray and CECT Thorax were done for treatment response and toxicity evaluation and metastatic workup were consist of USG Abdomen and LFT.

On subsequent follow up in 3rd, 6th month, detailed systemic examination, CBC, LFT, RFT, chest x-ray and USG Abdomen was done to evaluate for distant metastasis and complications RT like mediastinitis, esophagitis and radiation pneumonitis. The result of both arms were analysed and compared in terms of various aspects like quality of life, tumor response and symptom relief.

Results

Most of patients had ECOG performance status 3, median age 59 yr, male gender, median weight 59kg and stage IIIA and IIIB in both arms. During the treatment 2 and 3 patients lost from follow up in arm A and arm B respectively. While 1 patient expired after receiving 3 cycle of chemotherapy.

At 6th month follow up- None of patients had complete response in study & control arm for any stage (X2 =0, p= 1) 4 and 6 patients had regression (X2 =1.818, p=0.177) 5 and 7 patients had stable disease (X2 =1.515, p=0.218) and 13 and 9 patients had progression of disease (X2 =3.309, p=0.068) in study and control arm respectively. When analysed at 6th month follow up, 82% and 73% patients had progressive/stable disease in study and control arm respectively while 18% patients in study and 27%patients in control arm had regression of disease (Table 2 and Figure 1).

Overall survival rates at 1, 2 and 3 years were 40%, 10% and 0% in study arm while in control arm those values were 50%, 20% and 5% respectively. But on statistical analysis those difference in overall survival were not significant (p value were 0.4, 0.7 and 1.5 for 1, 2 and 3 year OS respectively). Range of survival were 7 to 25 months in study arm and 10 to 48 months in control arm. Median survival were10 months and 12.5 months in study

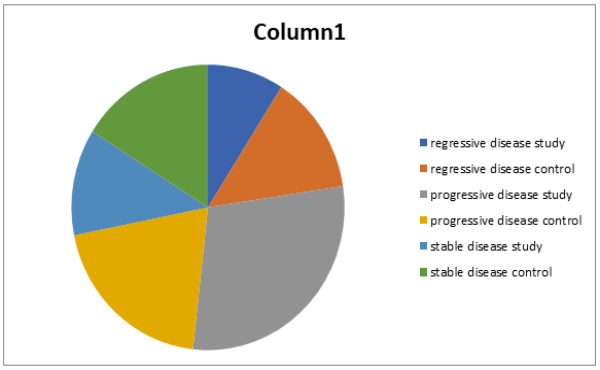

Figure 1. Treatment Response

Table 1. Patients Characteristics

Patients Characteristics	Study Arm	Control Arm
Age (in years)		
Median age	59 yr	59 yr
Range	48 – 75 yrs	40 – 75 yrs
Sex (%)		
Male	96	92
Female	1	2
Weight		
Median	59 kg	59 kg
Range	46-68 kg	45-68 kg
ECOG (%)		
2	28	40
3	72	60
Tumor stage (%)		
T2	8	12
T3	36	52
T4	56	36
Nodal stage (%)		
N0	4	0
N1	8	24
N2	68	60
N3	20	16
Group stage (%)		
Stage IIIA	44	52
Stage IIIB	56	48

and control arm respectively. The palliation of symptoms was slightly better and was for longer duration in control arm, though early palliation was achieved in study arm. It was observed that in patients with good PS, palliation achieved was better.

Discussion

The present study was carried out to identify possible prognostic indicators by assessing health related quality of life (HRQOL). With regard to treatment effect on disease related symptoms in advanced NSCLC, hypofractionated palliative RT is equivalent to conventional higher dose RT. Even though the treatment is palliative, there is limited potential for long term survival in localized disease. In the present study, which was restricted to stage IIIA and IIIB patients considered not suitable for curative radical RT, some long term survivors were observed in the higher dose treatment arm. The most common symptoms that are considered for palliative thoracic RT include dyspnoea, cough, haemoptysis and chest pain. The symptoms occur as a result of tumor related obstruction and irritation of normal intra thoracic structures.

Sundstrom S et al. study evaluating three treatment arms 17Gy/2fr, 42Gy/15fr and 50Gy/25fr concluded that protracted palliative TRT renders no improvement in symptom relief, HRQOL or survival when compared with short term hypofractionated treatment in NSCLC patient with disease too advanced for curative RT. Symptom relief and HRQOL were equivalent in all treatment arms. No significant difference in survival among arms was found.

In this study, symptom free survival was slightly better and for longer duration in control arm, though early palliation was achieved in study arm. It was observed that in patient with good performance status palliation achieved was better. For symptomatic patients with poor PS, stage IIIB disease too advanced for curative RT, palliative RT is recommended. The fractionation pattern should be chosen on the basis of the patient`s need. Patients with vigorous disease may be treated with a longer RT schedule to palliate symptoms for longer period and to increase survival. But patients with very tenuous health & very short estimated survival should be treated with a short course of RT to palliate their symptoms without using up

Table 2. Treatment Response

Treatment response	Number of patients	
	Study arm (22) 100%	Control arm (22) 100%
Regressive disease	4 (18)	6 (27)
Stable disease	5 (23)	7 (32)
Progressive disease	13 (59)	9 (41)

Table 3. Relief of Symptoms

Symptoms	Arm	Baseline (%)	After CT3 (%)	At end of treatment (%)	1st month (%)	3rd month (%)	6th month (%)
Chest pain	Study	17 (77.27)	13 (59.09)	8 (36.36)	5 (22.73)	6 (27.27)	11 (50)
	Control	15 (68.18)	11 (50)	5 (22.72)	3 (13.6)	3 (13.63)	7 (31.18)
Dyspnoea	Study	18 (81.81)	14 (63.63)	9 (40.90)	7 (31.18)	7 (31.18)	13 (59.09)
	Control	15 (68.18)	12 (54.54)	7 (31.18)	4 (18.18)	5 (22.72)	9 (40.90)
Cough	Study	16 (72.72)	12 (54.54)	8 (36.36)	6 (27.27)	7 (31.18)	12 (54.54)
	Control	19 (86.36)	15 (68.18)	9 (40.90)	6 (27.27)	6 (27.27)	10 (45.45)
Haemoptysis	Study	8 (36.3)	4 (18.18)	1 (4.54)	1 (4.54)	2 (9.09)	4 (18.18)
	Control	6 (27.27)	3 (13.63)	1 (4.54)	1 (4.54)	1 (4.54)	2 (9.09)

a great amount of their limited life.

Our toxicity data support that cough, dysphagia, dyspnoea, nausea/vomiting and anorexia were most common toxicities reported by study population. Although all the treatment toxicities (except dysphagia which which was more in study arm) were in control arm, the difference in toxicities in both arms were not statistically significant. Improvement in chest pain and haemoptysis were comparable in both arms except that it showed early improvement in study arm but maintained only for shorter duration in study arm compared to control arm (Table 3).

In conclusion, many patients were lost to follow up in our study; although among the patients followed, we found to concluded that for improvement of quality of life in locally advanced NSCLC patients with poor PS & short life span, the palliative hypofractionated regimen of short duration (17Gy/2fr) could be considered as a reasonable alternative and also economically feasible & required shorter duration of stay in the hospital. In conclusion, large number of patients with strict follow up need to be done to ascertain the need and benefits of this palliative TRT.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021 05;71(3):209-249. https://doi.org/10.3322/caac.21660
2. Funatogawa I, Funatogawa T, Yano E. Trends in smoking and lung cancer mortality in Japan, by birth cohort, 1949-2010. Bulletin of the World Health Organization. 2013 05 01;91(5):332-340. https://doi.org/10.2471/BLT.12.108092
3. Chen M, Hayman JA, Ten Haken RK, Tatro D, Fernando S, Kong F. Long-term results of high-dose conformal radiotherapy for patients with medically inoperable T1-3N0 non-small-cell lung cancer: is low incidence of regional failure due to incidental nodal irradiation?. International Journal of Radiation Oncology, Biology, Physics. 2006 01 01;64(1):120-126. https://doi.org/10.1016/j.ijrobp.2005.06.029
4. Dağoğlu N, Karaman Ş, Arifoğlu A, Küçücük S, Oral EN. Definitive radiotherapy in locally advanced non-small cell lung cancer: dose and fractionation. Balkan Medical Journal. 2014 Dec;31(4):278-285. https://doi.org/10.5152/balkanmedj.2014.14496
5. Curran JW. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresectable stage III NSCLC: RTOG 9410. InProc Am Soc Clin Oncol. 2003;22:621.
6. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2010 05 01;28(13):2181-2190. https://doi.org/10.1200/JCO.2009.26.2543
7. Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, Movsas B, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. Journal of the National Cancer Institute. 2011 Oct 05;103(19):1452-1460. https://doi.org/10.1093/jnci/djr325
8. Mauguen A, Le Péchoux C, Saunders MI, Schild SE, Turrisi AT, Baumann M, Sause WT, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2012 08 01;30(22):2788-2797. https://doi.org/10.1200/JCO.2012.41.6677
9. Hatton MQF, Hill R, Fenwick JD, Morgan SA, Wilson PC, Atherton PJ, Dickson J, Murray KE, Paul J. Continuous hyperfractionated accelerated radiotherapy - Escalated dose (CHART-ED): A phase I study. Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology. 2016 03;118(3):471-477. https://doi.org/10.1016/j.radonc.2015.11.015