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Research Article

A Comparative Analysis of Two Hypofractionated Palliative Radiotherapy Regimens for Inoperable Metastatic Non-Small Cell Lung Cancer

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Introduction: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality globally, including in India. Most patients present with advanced-stage disease, often experiencing severe, quality-of-life-limiting symptoms. Palliative radiotherapy plays a vital role in symptom management for these patients. This study aims to evaluate the effectiveness of a high-dose, weekly palliative radiotherapy regimen compared to the standard palliative schedule.
Methodology: This prospective randomized control trial was conducted from July 2023 to July 2024, involving 50 patients with biopsy-confirmed NSCLC. Patients were randomized into two treatment arms: Arm A received 21 Gy in 3 fractions (one fraction per week, 25 patients), while Arm B received the standard 30 Gy in 10 fractions over two weeks (25 patients). Symptom assessment was performed using the EORTC QLQ-LC13 questionnaire before treatment, immediately after completion, and at 1 and 3 months post-treatment.
Results: Overall, there was no significant difference in symptomatic relief between the two arms. Patient-reported outcomes at the end of treatment were comparable, with no significant differences in palliation of cough, dyspnea, or other symptoms, except for pain, which was statistically improved in Arm A ($p = 0.021$). At the 1-month follow-up, no significant differences were observed across parameters, while at 3 months, cough relief remained better in Arm B ($p = 0.021$), with other symptoms showing no significant difference.
Conclusion: The hypofractionated regimen of 21 Gy in 3 weekly fractions offers comparable symptomatic relief to the standard 30 Gy in 10 fractions regimen, making it a viable, shorter treatment option for patients with advanced NSCLC and thoracic symptoms.

Keywords: Palliative Radiotherapy, Metastasis, Lung Cancer.

INTRODUCTION

Non-small cell lung carcinoma (NSCLC) is the most prevalent cancer among men worldwide, both in terms of incidence and mortality.[1] According to GLOBOCAN 2022, lung cancer ranks as the fourth most common cancer in India for both incidence and mortality.[2] A significant proportion—over three-fourths—of NSCLC patients present with symptomatic Stage III or IV disease at diagnosis.[3] The most frequently reported symptoms include cough, chest pain, dyspnea, and hemoptysis, alongside systemic manifestations such as loss of appetite and generalized weakness.

Radiotherapy (RT) remains a cornerstone of palliative care for advanced NSCLC, offering symptom relief in up to 80% of patients by significantly reducing pain, cough, and dyspnea.[4–6] Despite its efficacy, access to timely RT remains a challenge in India due to the high cancer burden. Currently, the country has approximately 4,044,664 cancer patients, served by an estimated 545 teletherapy machines, including 180 telecobalt units and

365 linear accelerators, alongside 22 advanced therapy machines and 250 remote afterloading brachytherapy units.[7] Given this distribution, each RT machine is responsible for approximately 4,950 patients.[8] With three out of four NSCLC patients presenting with locally advanced, symptomatic disease,[9] the need for effective, accessible palliative RT is pressing.

Conventional palliative RT regimens, such as 30 Gy in 10 fractions or 20 Gy in 5 fractions, are widely used. However, due to the high patient load and long waiting times at treatment centers, alternative hypofractionated regimens are being explored.[9] Severely hypofractionated schedules—where patients receive palliative radiation on a weekly basis over fewer sessions—offer a practical solution by enabling day-care treatment without hospitalization. This approach not only ensures a rapid response but also helps manage the patient burden more effectively while offering a more financially viable option for both patients and healthcare institutions.[10]

Beyond symptom control, assessing the quality of life (QOL) in advanced lung cancer patients is crucial. QOL encompasses multiple domains, including physical, social, emotional, and functional well-being.[11] In cancer care, QOL is frequently measured using standardized quantitative questionnaires, typically self-reported by patients or assessed through proxies when necessary.[12] These assessments play a pivotal role in treatment decision-making by evaluating therapeutic effectiveness and patient well-being.[13]

Particularly in advanced-stage cancer, patient-reported outcomes such as QOL serve as valuable indicators of treatment efficacy.[14] Several validated QOL assessment tools exist, with lung cancer-specific questionnaires supplementing core instruments like the EORTC QLQ-C30 and FACT-G. The EORTC QLQ-LC13, a lung cancer-specific module, is often paired with the EORTC QLQ-C30, which includes functional, symptom, and global health/QOL scales.[15] These tools facilitate a comprehensive evaluation of the patient's overall well-being during treatment.

A systematic review by Salvo et al. highlighted the importance of using QOL instruments in lung cancer patients receiving palliative RT, with the EORTC QLQ-C30 emerging as the most commonly utilized tool.[16] As QOL assessments gain prominence in clinical oncology, selecting the appropriate tool can enhance the understanding of treatment impact and guide clinical decisions.

Given the potential advantages of hypofractionated palliative RT regimens, this study aims to compare the conventional palliative RT schedule of 30 Gy in 10 fractions over two weeks with a weekly hypofractionated regimen of 21 Gy in 3 fractions (one fraction per week). By assessing symptom relief and QOL outcomes, this study seeks to determine whether a more condensed treatment schedule can provide comparable or superior palliation while addressing logistical challenges in resource-limited settings.

AIMS & OBJECTIVES

To compare the efficacy of hypofractionated palliative radiotherapy (21 Gy in 3 fractions, delivered weekly) with the standard palliative schedule (30 Gy in 10 fractions over 2 weeks) in patients with inoperable metastatic non-small cell lung cancer (NSCLC).

The primary objective of this study is to evaluate symptom relief, specifically in pain, dyspnea, and cough. The secondary objective is to assess and compare health-related quality of life (HRQOL) using standardized questionnaire-based outcomes.[12–16]

MATERIALS AND METHODS

The study was conducted in the Department of Radiation Oncology, Rabindra Nath Tagore Medical College, Udaipur, Rajasthan**,** and included patients with moderate to severe symptoms of non-small cell lung cancer (NSCLC) that was loco-regionally unresectable or metastatic**.** Patients were enrolled after providing written informed consent, provided they met the eligibility criteria. Study Design. The total study duration was one year**,** including treatment and follow-up.

This prospective, randomized controlled trial utilized simple randomization based on the hospital's HID number, with patients assigned to one of two arms using an odd-even randomization approach**:** Test Arm (Arm A) received 21 Gy in 3 fractions, delivered weekly (1 fraction per week), while Control Arm (Arm B) received 30 Gy in 10 fractions over 2 weeks. The study was approved by the Institutional Ethics Committee, and patient enrollment was conducted over one year following approval.

Radiation therapy was delivered using a Cobalt-60 (Co-60) unit with an energy of 1.25 MeV on a Bhabhatron-II Teletherapy Co-60

machine, utilizing high-energy gamma radiation (Megavoltage Photon Radiation). The treatment was administered with a portal orientation of Anterior-Posterior and Posterior-Anterior (AP-PA).

Eligibility Criteria

Inclusion Criteria

- **Histologically confirmed NSCLC**
- **Stage IV disease**
- **ECOG performance status:** 2, 3, or 4
- **Newly diagnosed cases**
- **Age range:** 30–80 years

Exclusion Criteria

- **ECOG performance status:** 0 or 1
- **Prior treatment with:**
  - Chemotherapy
  - Targeted therapy
  - Immunotherapy
  - Radiation therapy
- **Non-NSCLC histology**
- **Age below 30 years or above 80 years**

All patients underwent clinical examination and staging, which included medical history, physical examination, radiological investigations (chest CT scan and abdominal imaging), and laboratory tests (liver and kidney function tests). Additionally, performance score assessment and weight loss evaluation (over the last six months) were conducted. Brain MRI and bone scans were performed only for symptomatic patients. Staging was done according to the American Joint Committee on Cancer (AJCC) guidelines. Patient evaluation was conducted at three time points: end of radiation treatment, one month post-radiotherapy (RT), and three months post-RT. Symptom relief and quality of life (QOL) were assessed using standardized patient-reported outcome (PRO) questionnaires.

What are the changes in scores on the EORTC QLQ-C30 representing a change in patients supportive care needs?

Scoring of the QLQ-C30 Summary Score

EORTC QLQ-C30 score changes ranged from 21-points worsening to 21-point improvement for patients reporting worsening supportive care needs; statistically significant changes were 9-21 points in the hypothesized direction and a 21-point statistically significant change in the opposite direction.

The EORTC QLQ-C30 Summary Score is calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale are not included). Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. The summary score should only be calculated if all of the required 13 scale scores are available (using scale scores based on the completed items, provided that at least 50% of the items in that scale have been completed (see Fayers et. al., The EORTC QLQ-C30 Scoring Manual (3rd Edition) 2001).

Compute

QLQ-C30 Summary Score = (Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ 100-Fatigue+ 100-Pain+ 100-Nausea_Vomiting+ 100-Dyspnoea+ 100-Sleeping Disturbances+ 100-Appetite Loss+ 100-Constipation+ 100-Diarrhoea)/13.

EORTC QLQ- LC13 Scoring Manual

The Lung Cancer Module is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-LC13 incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis.

The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales / single-items of the QLQ-C30. All scoring information specific to the QLQ-LC13 is presented in Table 1.

Table 1. Scoring the QLQ-LC13

	Scale	Number of items (n)	Item range*	QLQ-LC13 item numbers (I1, I2, In)
Symptom scales / items				
Coughing	LCCO	1	3	31
Haemoptysis	LCHA	1	3	32
Dyspnoea [a]	LCDY	3[a]	3	33 - 35

	Scale	Number of items (n)	Item range*	QLQ-LC13 item numbers (I_1, I_2, I_n)
Dyspnoea when resting [a]	LCDYR	1	3	33
Dyspnoea when walking [a]	LCDYW	1	3	34
Dyspnoea when stairs [a]	LCDYS	1	3	35
Sore mouth	LCSM	1	3	36
Dysphagia	LCDS	1	3	37
Peripheral neuropathy	LCPN	1	3	38
Alopecia	LCHR	1	3	39
Pain in chest	LCPC	1	3	40
Pain in arm or shoulder	LCPA	1	3	41
Pain in other parts	LCPO	1	3	42

* "Item range" is the difference between the possible maximum and the minimum response to individual items. All items are scored 1 to 4, giving range = 3.

[a] The dyspnoea scale should only be calculated if all three items have been answered. Some respondents ignore question 35 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 35 is missing then items 33 and 34 should be used as single-item measures.

Principle for scoring

1) Raw score

For the multi-item scale, calculate the average of the corresponding items.

Raw Score = $RS = \{\frac{I1+I2+\ldots+In}{n}\}$

For each single-item measure, the score of the concerning item corresponds to the raw score. There are no reverse scoring items.

2) Linear Transformation

To obtain the Score S, standardize the raw score to a 0 – 100 range using the following transformation:

$S = \{\frac{(RS-1)}{Range}\} \times 100$

For directions on Missing Data or for more detailed information on the Interpretation of Scores, we redirect to the EORTC QLQ-C30 Scoring Manual (2001).

Remark

The scoring of item 43 is optional.

Interpretation: A high score for item 43 represents a high level of pain relief.

Table 2. Scoring information for scoring item 43.

Number of items		Item range	Item
Pain relief after medication*	1	3	43

* Item 43 might not be applicable and must only be scored if the answer to the question "Did you take any medication for pain?" is "Yes".

Quality Of Life Questionnaire- Ca Lung as Per Eortc Qlq- Lc13

QLQ CA LUNG LC-13	QUESTION NO.
Cough	31 – 32
Dyspnoea	33 – 35
Mucositis	36
Dysphagia	37
Peripheral Neuropathy	38
Hair loss	39
Pain	40-43

A set of questions will be made for the patients as per the specific guidelines mentioned and they will be asked to score the complaints out of 1(not at all)/ 2(a little)/ 3(quite bit)/ 4(very much).

This questionnaire was done at the start of radiation treatment, 1 month and 3 months after the completion of treatment to draw a final conclusion.

Statistical Analysis

It was done using intention to treat analysis on SPSS 20. The differences between hearing thresholds at baseline, short-term follow-up, and long-term follow-up was assessed using repeated measurement analysis. In the repeated measures analysis we adjusted for ear, gender, age and hearing level at the earliest of the measurements, and time between both measurements. Categorical data was analysed by chi-square test and Fischer exact where applicable. A p value of <0.05 was considered statistically significant.

DISCUSSION

Lung cancer remains the leading cause of cancer-related deaths worldwide, with approximately 2.1 million new cases annually.[1] Tobacco smoking is the primary risk factor, contributing to 80-90% of cases.[2] Non-small cell lung cancer (NSCLC) accounts for 80-85% of cases, while small cell lung cancer (SCLC) makes up 15-20%.[3] The most common symptoms include cough (45-75%), dyspnea (25-50%), chest pain (20-40%), and hemoptysis (10-30%).[4]

Patients with locally advanced, inoperable, or metastatic NSCLC often experience severe pulmonary symptoms due to tumor burden, regional metastases, or complications from previous treatments. These patients are not candidates for radical therapy and have a poor prognosis, with median survival ranging from 4 to 7 months. Palliative radiotherapy (RT) plays a crucial role in relieving dyspnea, cough, hemoptysis, and chest pain, improving quality of life (QOL), and reducing the need for opioid analgesics.[5–7]

The standard palliative RT regimen of 30 Gy in 10 fractions (over two weeks) is widely used due to its effectiveness, convenience, and minimal toxicity. However, given the high patient load and limited RT availability, there is growing interest in hypofractionated regimens that deliver fewer but larger fractions to provide equivalent symptom relief with fewer hospital visits.

Hypofractionated RT schedules aim to optimize symptom control while reducing treatment burden. Weekly regimens allow patients to receive RT in a day-care setting, minimizing hospital stays and offering a cost-effective solution for both patients and healthcare facilities.

Given the potential benefits of weekly hypofractionated RT, this study compares the conventional palliative regimen (30 Gy in 10 fractions over two weeks) with a weekly hypofractionated regimen (21 Gy in 3 fractions, one fraction per week).

To assess treatment impact, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-LC13 is commonly used. It evaluates dyspnea, cough, hemoptysis, mucositis, dysphagia, pain, and analgesic use, with higher scores on functional and global health scales indicating better QOL, while higher symptom scores reflect greater symptom severity.

Patient Demographics

The majority of patients in this study were aged 51-70 years (50%)**,** with a mean age of 56.4 ± 15.3 years**,** consistent with previous studies (Yadav et al., Coon et al., Lei et al.). The male-to-female ratio was 2.33:1, similar to findings in other studies.

Symptom Palliation and QOL Improvement

At baseline, the EORTC QLQ-LC13 scores were:

- **Cough: 80.67 ± 18.42**
- **Dyspnea: 97.00 ± 12.44**
- **Pain: 78.50 ± 24.38**
- **Physical Performance: 72.45 ± 19.72**

At three months post-treatment, the scores for 21 Gy in 3 fractions were:

- **Cough: 44.67 ± 20.01**
- **Dyspnea: 65.44 ± 19.94**
- **Pain: 52.67 ± 18.92**
- **Physical Performance: 46.50 ± 20.61**

For 30 Gy in 10 fractions**,** the corresponding scores were:

- **Cough: 34.33 ± 20.33**
- **Dyspnea: 69.56 ± 22.05**
- **Pain: 47.00 ± 19.93**
- **Physical Performance: 50.67 ± 21.02**

Our study evaluated symptom palliation and QOL improvements in NSCLC patients using two palliative RT regimens, with baseline EORTC QLQ-LC13 scores of cough 80.67 ± 18.42, dyspnea 97.00 ± 12.44, pain 78.50 ± 24.38, and physical performance 72.45 ± 19.72; at three months post-treatment, the 21 Gy in 3 fractions group demonstrated reductions to 44.67 ± 20.01 for cough, 65.44

± 19.94 for dyspnea, 52.67 ± 18.92 for pain, and 46.50 ± 20.61 for physical performance, while the 30 Gy in 10 fractions group showed corresponding scores of 34.33 ± 20.33, 69.56 ± 22.05, 47.00 ± 19.93, and 50.67 ± 21.02, indicating significant symptom relief and QOL improvement in both arms; comparably, Rajan Yadav et al. (2020) demonstrated that hypofractionated RT (17 Gy in 2 fractions) was as effective as standard regimens in symptom relief—with no significant differences in overall survival—an outcome that aligns with our findings of marked symptom score reductions across both treatment schedules.

I. Beli et al. (2010) reported high relief rates for hemoptysis, chest pain, cough, and dyspnea with a short-course regimen (8.5 Gy × 2 fractions) and minimal toxicity, which is in line with the substantial improvements in cough and dyspnea observed in our study.

George A. Plataniotis et al. (2009) found symptom relief rates of 68% for cough, 90% for hemoptysis, 57% for pain, and 38% for dyspnea with 17 Gy in 2 fractions, and a median survival of 9 months, reinforcing our results that indicate effective palliation with hypofractionated RT.

Chaundré K. Cross et al. (2003) achieved symptom relief rates of 60% for cough, 100% for hemoptysis, 75% for pain, and 30% for dyspnea using 8.5 Gy × 2 fractions, and our comparable improvements at three months post-treatment similarly support the efficacy and minimal toxicity of such regimens.

M. Lupattelli et al. (2000) reported that 16 Gy in 2 fractions resulted in 77% symptom relief, 73% performance status improvement, and no late toxicity, findings that mirror the improvements in physical performance and pain scores in our study, thereby collectively underscoring that both our hypofractionated and standard palliative RT regimens offer effective symptom palliation and QOL benefits in advanced NSCLC.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 50 patients were included in the study, with an age range of 30–80 years (mean ± SD: 56.4 ± 15.3 years). The majority of patients (50%) were between 51 and 70 years of age, while 10% were between 30 and 40 years, and 16% were older than 70 years.

Among the study cohort, 35 patients (70%) were male, resulting in a male-to-female ratio of 2.33:1. Rural populations accounted for 60% of patients, reflecting the regional healthcare distribution. The majority were laborers (78%), followed by businessmen (18%) and homemakers (4%).

Regarding clinical parameters, all patients presented with stage IV non-small cell lung cancer (NSCLC). Squamous cell carcinoma was the predominant histological subtype (54%), while non-squamous histology accounted for 46% of cases. The Eastern Cooperative Oncology Group (ECOG) performance status was distributed as follows: ECOG 2 in 36% of patients, ECOG 3 in 44%, and ECOG 4 in 20%.

Baseline Patient-Reported Symptoms

Before radiation therapy, symptom severity was assessed using the EORTC QLQ-LC13 questionnaire. The mean baseline scores were as follows:

- Coughing: 92.5 ± 30.1
- Dyspnea: 90.0 ± 18.6
- Pain: 82.5 ± 23.7

Treatment Outcomes and Symptom Relief

End of Radiation Therapy Following completion of radiotherapy, symptom relief was assessed separately for the two treatment arms:

- Arm A (21 Gy in 3 fractions): Mean scores were 70.67 ± 28.31 for coughing, 92.00 ± 17.46 for dyspnea, and 64.50 ± 22.58 for pain.
- Arm B (30 Gy in 10 fractions): Mean scores were 60.67 ± 28.31 for coughing, 85.67 ± 21.08 for dyspnea, and 53.67 ± 23.55 for pain.

Statistical comparison between the two groups at the end of treatment showed no significant difference in coughing ($p = 0.06$) and dyspnea ($p = 0.105$). However, pain relief was significantly better in the 21 Gy group ($p = 0.021$).

One Month Post-Treatment

At one month post-radiotherapy, continued symptomatic improvement was observed:

- Arm A (21 Gy): Coughing (60.33 ± 18.17), dyspnea (64.67 ± 15.81), pain (81.50 ± 18.12).
- Arm B (30 Gy): Coughing (54.67 ± 18.97), dyspnea (60.00 ± 17.29), pain (76.00 ± 19.23).

There was no statistically significant difference between the two groups at this time point.

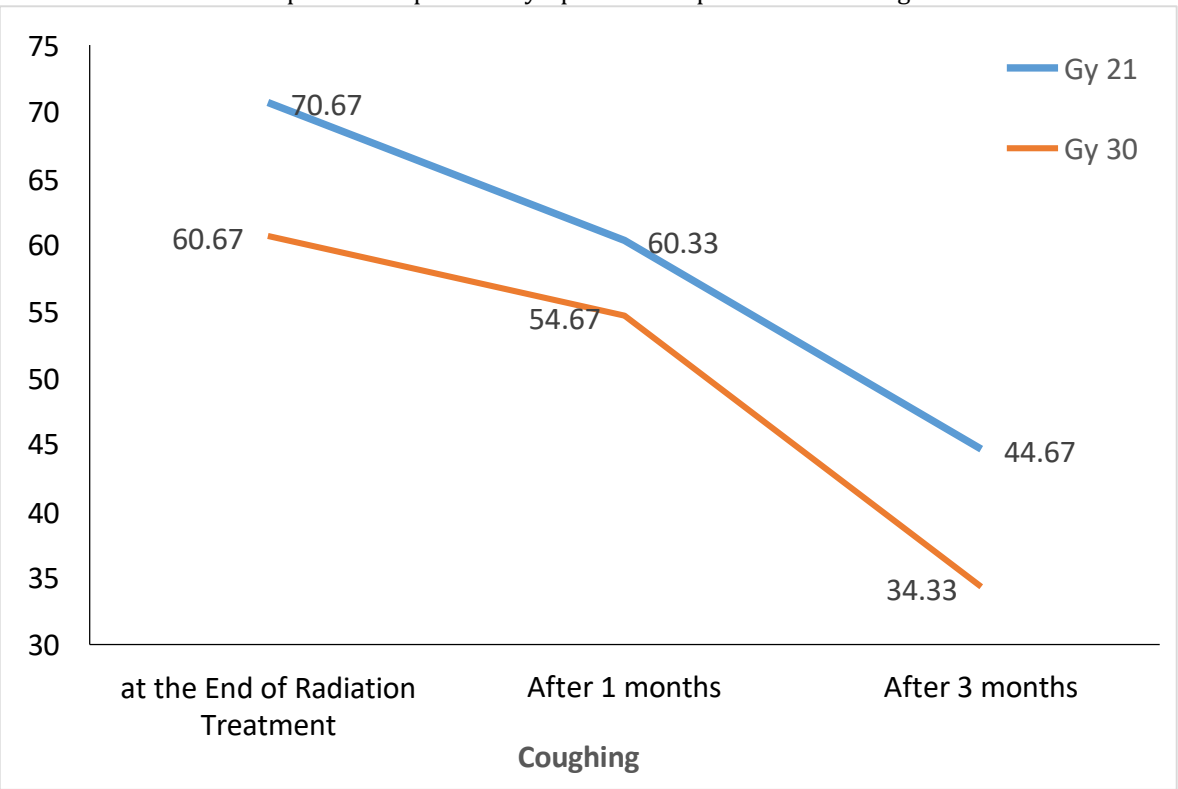
Three Months Post-Treatment

By the three-month follow-up, symptom scores showed further reductions:

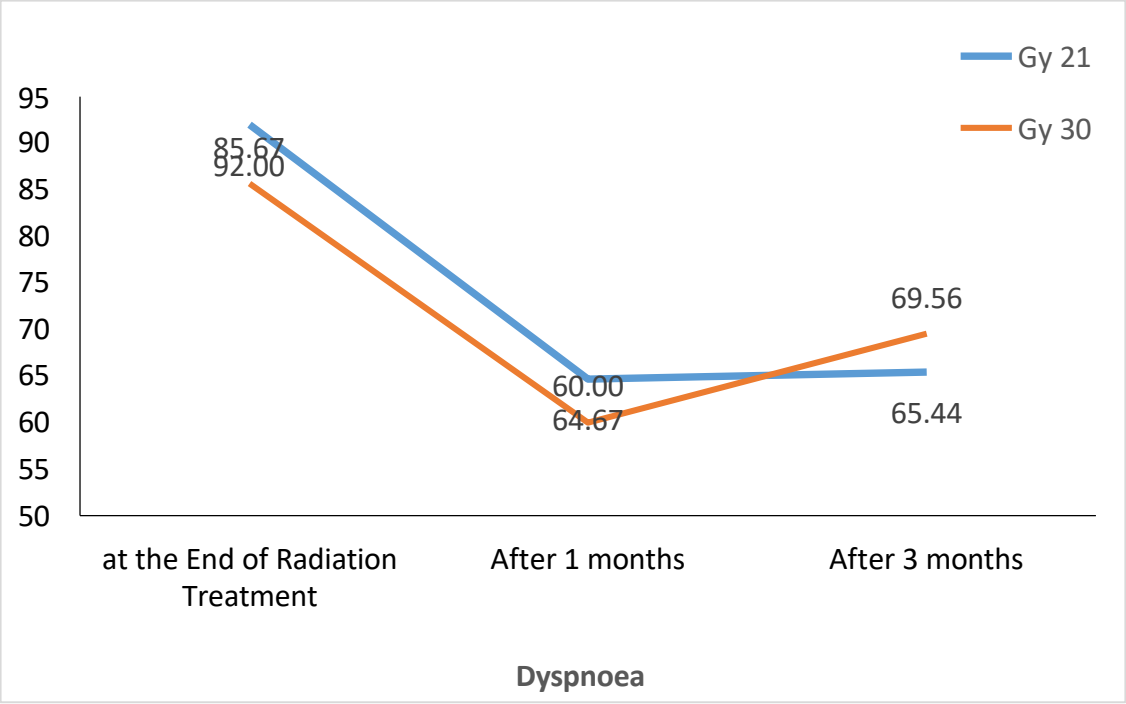
- Arm A (21 Gy): Coughing (44.67 ± 20.01), dyspnea (65.44 ± 19.94), pain (52.67 ± 18.92).
- Arm B (30 Gy): Coughing (34.33 ± 20.33), dyspnea (69.56 ± 22.05), pain (47.00 ± 19.93).

At three months, the reduction in coughing was significantly greater in the 30 Gy group compared to the 21 Gy group (p = 0.012), while dyspnea (p = 0.330) and pain (p = 0.148) remained comparable

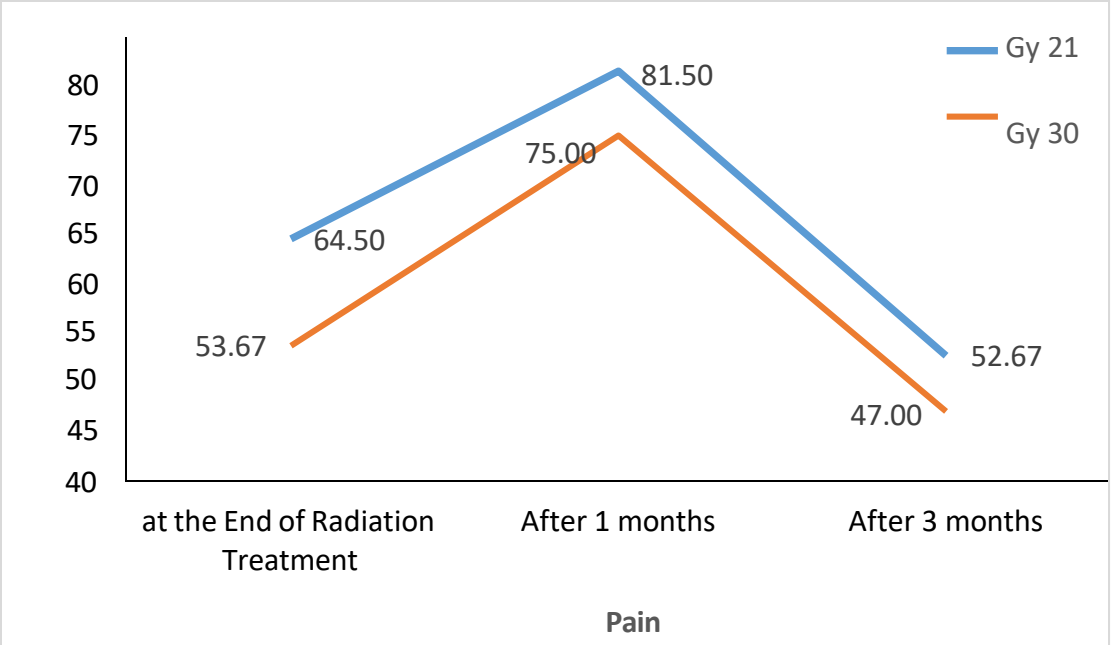
Graph 11: Comparative symptomatic improvement in Cough.



Graph 12: Comparative symptomatic improvement in Dyspnoea.



Graph 14: Comparative symptomatic improvement in Pain.



CONCLUSION

Hypofractionated regimen of 21 Gy in 3 weekly fractions is equally successful in providing symptomatic relief as 30 Gy/10 fractions. Therefore, based on the findings of our study, we advocate short course of palliative hypofractionated regimen as treatment for patients of advanced NSCLC with thoracic symptoms, since it has the advantage of fewer visits to hospital & more financially acceptable.