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Comparative Assessment between Palliative Radiotherapy with Concurrent Erlotinib and Radiotherapy Alone in Advanced and/or Metastatic Non-Small Cell Lung Cancer

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ABSTRACT

Introduction: It was earlier documented that concurrent systemic therapy has a beneficial effect in advanced non-small cell lung cancer (NSCLC) patients when given along with palliative local radiation. However, the data on the Indian population is limited. So, we conducted the study to assess the effect of concurrent erlotinib and palliative thoracic radiotherapy as compared to palliative radiotherapy alone in patients with advanced and/or metastatic NSCLC.

Material & Methods: Previously untreated patients of advanced and/or metastatic NSCLC, were included in this study, to receive either palliative radiotherapy 30Gy/10fractions with concurrent erlotinib 150mg daily (Group 1) or radiotherapy alone with similar dose-fractionation (Group 2). Symptomatic relief & quality of life (QoL) were assessed using different internationally validated tools.

Results: A total of 60 patients were enrolled in the study. After 4-weeks of radiotherapy, patients in group 1 showed better improvement in QoL scoring and had more symptomatic relief than group 2. Nineteen and eleven patients of groups 1 and 2 showed partial response. Median survival was 7.4 and 5.1 months in groups 1 & 2, respectively.

Conclusion: Our study concluded that concurrent erlotinib with palliative thoracic radiotherapy in advanced and/or metastatic NSCLC patients results in increased symptomatic relief & survival as well as improvement in QoL.

Keywords: Concurrent; erlotinib; non-small cell lung cancer; palliative; radiotherapy; quality of life

INTRODUCTION:

Lung cancer has been the most frequently occurring cancer for last few decades across the world. Recent global data reported approximately 2.2 million new lung cancer cases (11.6% of the total cancer incidence) along with 1.8 million deaths in 2020 worldwide.[1] Non-small cell lung cancer (NSCLC) comprises 80% of all lung cancers with a 5-year overall survival (OS) ranging between 15-25% combining all cancer stages [2-4].

Patients presenting with early-stage disease limited to a single lung i.e., stage I or resectable stage II, can be managed successfully by surgical resection along with adjuvant chemotherapy and/or radiation therapy, whenever indicated [5]. However, around 80% of lung cancer patients present with advanced or metastatic disease burden i.e., in stage III or stage IV, therefore rendering them unsuitable for potentially curable surgical resection [2-6]. Furthermore, most of the time, lung cancer patients suffer from significant comorbidities that might interfere with the indicated treatment [7]. Radiation therapy (RT) is conventionally regarded as the prime treatment modality of lung carcinoma where resection is not feasible like in advanced stages, metastatic disease at diagnosis, in the critically located tumor, associated comorbidities hindered anesthetic fitness, or patient preference [8]. RT can be given to the local site in advanced disease as well as the metastatic site in case of distant spread [5-8]. It provides palliative benefits in terms of alleviating local symptoms like relief in pain & dyspnoea, decrease in the amount and frequency of cough & hemoptysis, ameliorating neurologic symptoms arising from secondary central nervous system involvement, relieving refractory pain from osseous deposits, and also avoidance of impending pathological fracture [8,9].

RT can improve different symptoms of advanced lung cancer acutely. However, in co-morbid patients with progressive disease RT cannot be administered for longer duration as indicated in conventional dose schedules due to poor patient compliance, less tolerability of adjacent normal tissues as well as for technical difficulties. The usefulness of different targeted therapies according to molecular biomarkers in advanced and/or metastatic NSCLC is an established treatment option.[5] Erlotinib, an oral tyrosine kinase inhibitor (TKI), acted by inhibiting epidermal growth factor receptor (EGFR), is already approved as single-agent therapy in refractory, advanced and/or metastatic NSCLC with favorable outcomes [6-10]. Research is ongoing to combine different drugs or modalities along with erlotinib and other targeted agents to increase the survival in these patients. Various studies have shown increased survival along with improved quality of life (QoL) in patients receiving erlotinib combined with radiotherapy in NSCLC patients [11-14]. During the COVID pandemic, the diagnosis and treatment of lung cancer were hampered seriously and the QoL of NSCLC patients was compromised [15]. Several changes were needed in the management strategies of cancer patients during the COVID pandemic; likely comparatively short duration, high-dose radiation schedules (hypofractionated RT), switching from intravenous chemotherapy to oral low-dose chemotherapy, and minimizing the number of hospital visits [16]. In our department, we had started prescribing oral agents for palliative management of advanced and/or metastatic lung as well as other cancers. Among different oral agents used in NSCLC patients, erlotinib is the most common one. However, patients receiving only erlotinib did not respond well in their local thoracic symptoms and palliative RT was needed more or less in every patient. Furthermore, some patients on oral erlotinib showed adverse drug reactions also. In these scenarios, it was needed to check whether palliative RT could be combined with oral erlotinib or not.

So, we intended to compare the effect of palliative radiotherapy and the concurrent addition of erlotinib to palliative radiotherapy alone in patients with advanced and/ or metastatic NSCLC.

Materials and Methods:

The study was conducted on advanced and/ or metastatic non-small cell lung cancer patients registered in our

department who had not received any prior treatment for the disease and where the intention of treatment was palliative and radiotherapy would be indicated as the treatment. Radiological assessment including contrast-enhanced computed tomography (CECT) of the chest for estimating primary disease and nodal status; ultrasonography of abdominopelvic region for assessing metastatic lesions was considered in all patients, to know overall disease burden and also for staging purposes. Additional imaging studies like contrast-enhanced magnetic resonance imaging (CEMRI) of the brain, abdomen & pelvis, lumbosacral spine, bone scan, and whole-body positron emission tomography (PET) scan were done in selected patients as per indications and where confusion arises to assess extent of disease. Routine haematological (complete blood count) and biochemical profile (blood urea, serum creatinine, liver enzymes) were evaluated in all patients to assess the tolerability of erlotinib administration.

Based on mentioned clinical & radiological assessment, the patients were enrolled in the study who fulfilled the following criteria:

i. Age ≥18 years
ii. histologically confirmed locally advanced and/ or metastatic NSCLC
iii. Medically unfit for radical treatment.
iv. Adequate organ function.

Eligible patients were randomly divided in an equal ratio into two groups by internet application to receive either palliative radiotherapy with concurrent oral erlotinib (Group 1 i.e., study group) or to receive palliative radiotherapy alone (Group 2 i.e., control group). Palliative radiotherapy was administered in both the groups in dose schedules of 30 Gy/10 fractions/ 2 weeks [5 fractions in a week]. Oral erlotinib treatment commenced to group 1 patients at 150 mg daily dose starting 1-week before beginning of radiotherapy. It was continued until radiotherapy completion and a minimum 1-week thereafter, such that participants received a total of 4 weeks of erlotinib therapy; 1 week before and 2 weeks concurrent with radiotherapy, and 1 week thereafter.

All patients, included in the study, were assessed weekly to observe for acute treatment-induced toxicity and tolerability. Clinical & hematological examinations were done for each patient to check the tolerability of delivered treatment and acute treatment-induced adverse reactions were noted thoroughly.

Following 4 weeks after the completion of treatment, a CECT of the chest was done in every patient to assess the response. Tumor response to treatment was assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. The subjective relief in symptoms was assessed according to various globally validated tools like a visual assessment of cough scale, Medical Research Council (MRC) dyspnoea scale, and universal pain assessment tool. Improvement in QoL was assessed by functional assessment of cancer therapy-lung (FACT-L) scoring before the initiation of treatment and after the four weeks of completion of the treatment, and evaluation was done by comparing post-treatment with the pre-treatment score.

The data thus obtained was entered in Microsoft Excel (version 2019). Chi-squared test, paired and unpaired t-test, and fisher's exact test was applied to test the significance of the results using Statistical Package for Social Sciences (SPSS) software version 26. $P<0.05$ was considered significant. Informed signed consent was taken from each patient. Institutional Ethics Committee (IEC) approval for the study was obtained.

Results:

60 patients, fulfilling inclusion criteria, were enrolled in the study. The majority of patients were from rural backgrounds and were chronic smokers. Details of patient characteristics were illustrated in tabulated format (table 1).

All patients in the study completed the intended treatment. Erlotinib 150 mg in combination with palliative radiotherapy 30 Gy/ 10 fractions had shown adequate response in terms of subjective relief of symptoms especially in dyspnoea, chest pain, and cough in comparison to palliative radiotherapy in the same dose-fractionation alone (table 2). Improvement in the

Table 1. Baseline patients & tumor characteristics of lung cancer patients in both the groups

Characteristics	Group 1		Group 2		P value
	Total Number	Percentage	Total Number	Percentage	
Mean age (in years)	58	-	62	-	<0.05
Gender	M: 23 F: 7	76.67 23.33	M: 29 F: 1	96.67 3.33	0.66
Background	Ru: 18 U: 12	60 40	Ru: 21 U: 9	70 30	0.59
Smokers	Y: 21 N: 9	70 30	Y: 27 N: 3	90 10	0.58
Alcoholic	Y: 17 N: 13	56.67 43.33	Y: 20 N: 10	66.67 33.33	0.48
Laterality (involved lung)	R: 16 L: 12 B/L: 2	53.33 40 6.67	R: 19 L: 10 B/L: 1	63.33 33.33 3.33	0.78
Histopathology	SCC: 4 ADC: 24 Others: 2	13.33 80 6.67	SCC: 5 ADC: 24 Others: 1	16.67 80 3.33	0.98
Stage	IIIA: 9 IIIB: 8 IIIC: 5 IVA: 6 IVB: 2	30 26.67 16.67 20 6.67	IIIA: 5 IIIB: 9 IIIC: 2 IVA: 10 IVB: 4	16.67 30 6.67 33.33 13.33	0.68
Metastasis Present	Yes: 8 No: 22	26.67 73.33	Yes: 14 No: 16	46.67 53.33	0.18
Involved organ	Bone: 3 Brain: 1 Liver: 2 Lymph nodes: 0 Multiple: 2	10 3.33 6.67 0 6.67	Bone: 6 Brain: 1 Liver: 2 Lymph nodes: 1 Multiple: 4	20 3.33 6.67 3.33 13.33	0.24
ECOG	Score 1: 3 Score 2: 19 Score 3: 8	10 63.33 26.67	Score 1: 4 Score 2: 20 Score 3: 6	13.33 66.67 20	0.93
Symptoms at presentation	Breathlessness: 7 Chest pain: 15 Cough: 5 Hemoptysis: 3	23.33 50 16.67 10	Breathlessness: 6 Chest pain:16 Cough: 5 Hemoptysis: 3	20 53.33 16.67 10	0.87
Mean FACT-L Score	61.6	-	61.4	-	0.7
Mean interval between diagnosis and RT commencement:	3.1 weeks	-	3.5 weeks	-	0.44

[ADC: Adenocarcinoma, B/L: Bilateral, ECOG: Eastern Cooperative Oncology Group, F: Female, FACT-L: Functional assessment of cancer therapy-lung, L: Left, M: Male, R: Right, RT: Radiation therapy, Ru: Rural, SCC: Squamous cell carcinoma, U: Urban]

Table 2. Post treatment subjective relief in symptoms (>50%) in both the groups

Symptoms	Group 1	Group 2	P value
Breathlessness	43.33%	26.67%	0.35
Chest pain	46.67%	30%	0.21
Cough	60%	30%	0.59
Hemoptysis	100%	100%	-

FACT-L scoring was found to be more in the erlotinib group than in group 2, denoting better QoL improvement in the erlotinib group (figure 1). However, this finding was statistically insignificant (p= 0.13). The tumor response had also been seen to be better in group 1 i.e., in erlotinib group compared to that in group 2 (figure 2); however, this was also statistically not significant (p= 0.12). Overall, the mean survival in group 1 & group 2 was 7.4 months and 5.1 months, respectively (figure 3). Treatment-induced toxicities were assessed in all the study enrolled patients, weekly during the treatment course and 4 weeks after completion of radiation. No hematological toxicities were observed during or after completion of treatment. The cutaneous reaction was the most prevalent toxicity encountered in both groups. Six patients in group 1 and one patient in group 2 showed skin reactions. In erlotinib group, two patients also experienced diarrhoea. No ≥ grade 3 toxicity was found in any of the patients in both the groups.

Discussion:

Lung cancer is the major cause of oncologic-related death worldwide [2]. More than 50% of newly diagnosed lung cancer patients have a survival of just one year from diagnosis, and 5-year survival of lung cancer is very disappointing [4]. Over half of patients with NSCLC at first visit are already in stage III (locally advanced) or stage IV (metastatic) disease [7]. Amongst them, a majority of stage III patients are unfit for curative treatment due to poor performance status; and a similar

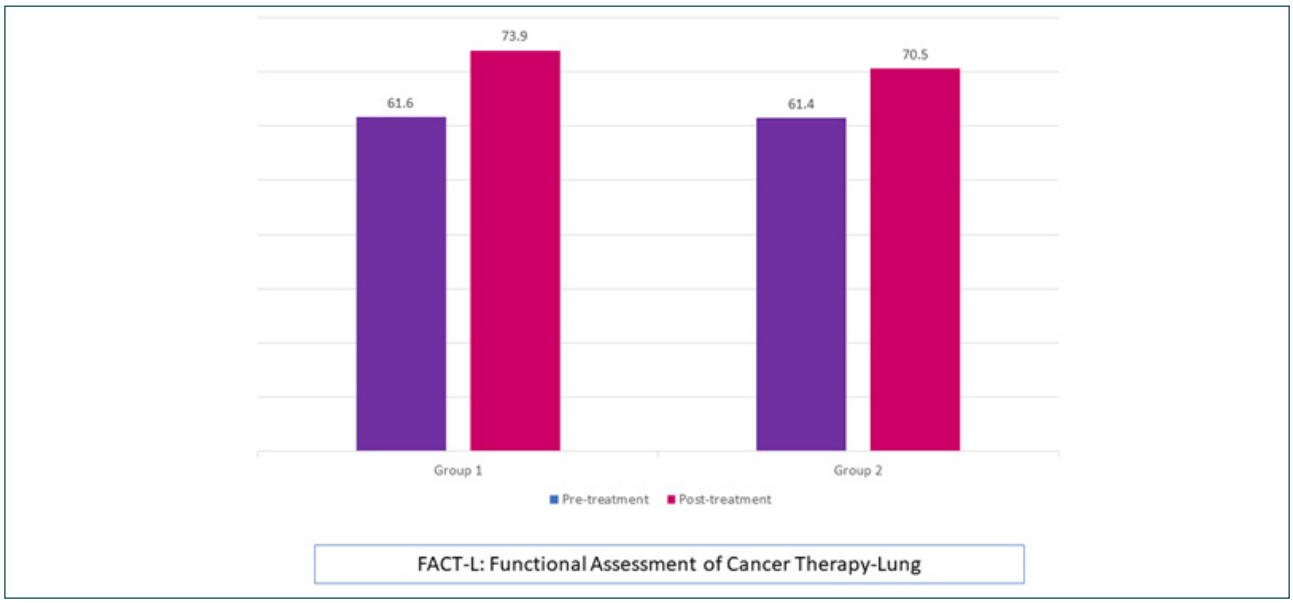

Figure 1: Improvement in FACT-L score in both the groups [FACT-L: Functional Assessment of Cancer Therapy-Lung])

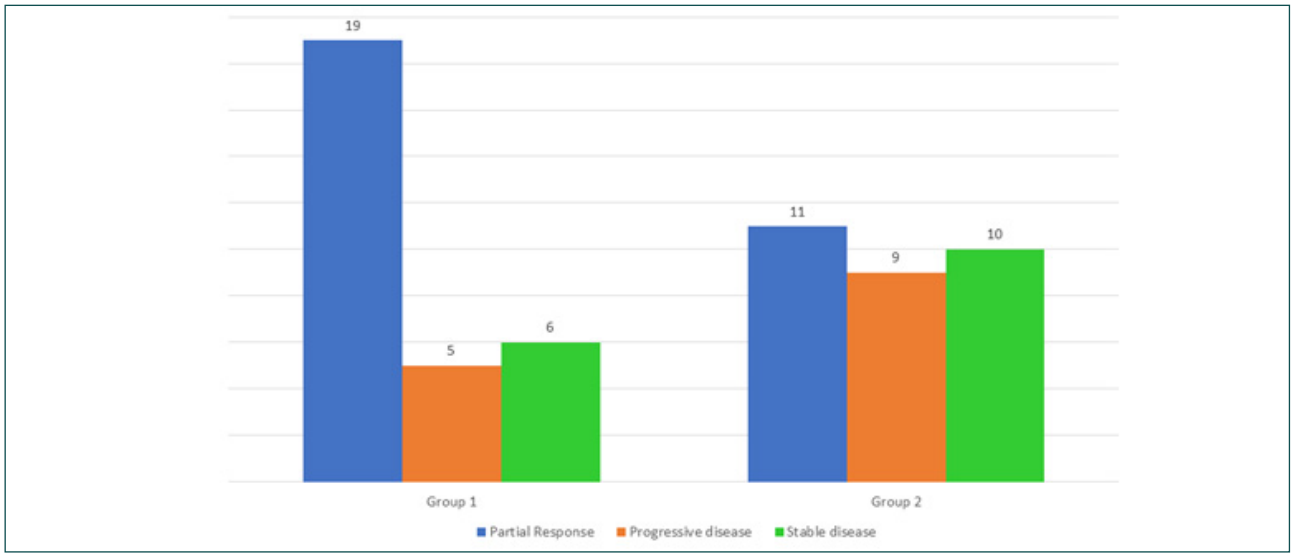

Figure 2: Post treatment tumor response in both the groups

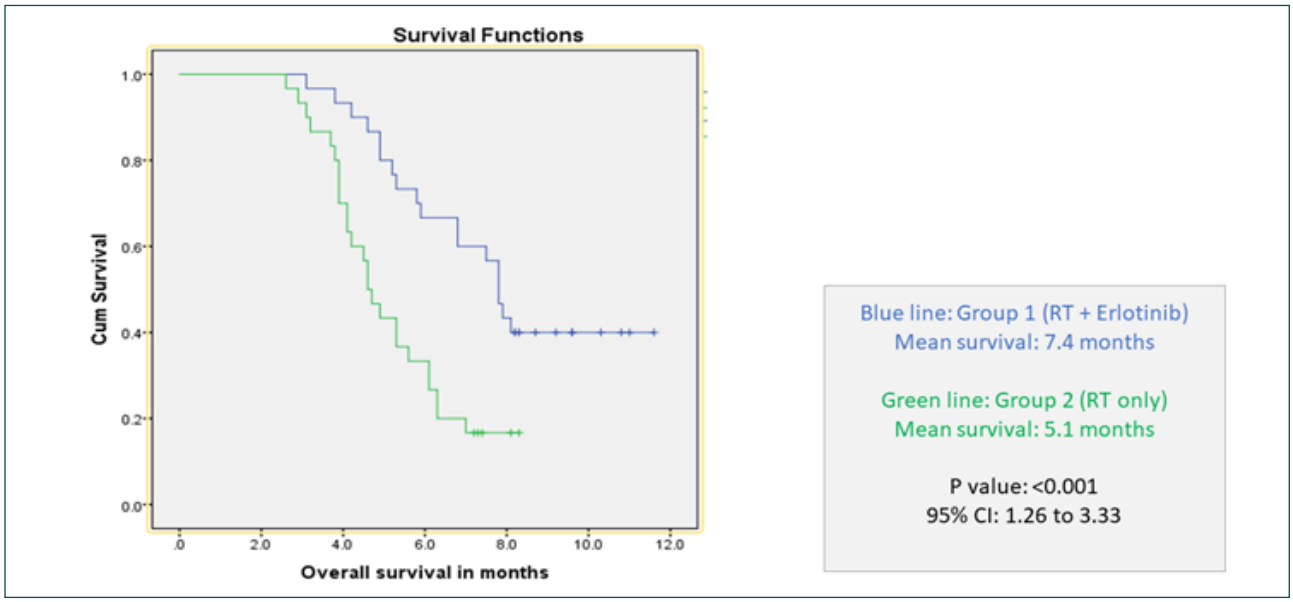

Figure 3: Kaplan-Meier curve showing mean survival (in months) in both the groups

percentage of patients with stage IV disease is managed for thoracic complaints [6,8,9].

Progression of the ailment, intensity of its symptoms, and treatment-induced adverse events significantly diminish the QoL in lung cancer patients [17]. The QoL is lower in these patients compared to healthy populations and patients having other malignancies. Number of symptoms which are specific for lung tumors such as dyspnea, cough, chest pain, and blood in sputum, all affect the QoL [6,9]. The disease also causes annoyance, misery, and depression in patients. Management of these associated symptoms may upgrade QoL [17]. Braun et al concluded that early evaluation of QoL including assessment of physical status is a source of crucial prognostic guidance in patients with lung cancer [18]. The goal of palliative thoracic radiation,

commonly administered in clinical practice, is to boost the sufferer's QoL by relieving symptoms [9,17]. RT has been a cornerstone in progressive stage i.e., stage III and IV lung cancer management [6,8,9]. For patients having poor performance status, radiation fractionation must be brief and effective with least toxicities.[3,8] Clinical practice remains heterogeneous despite international guidelines [19].

A plenty of external beam radiation therapy (EBRT) fractionation schedules have been tried by many clinical trials for palliation in lung cancer [8,19]. Among them, most of the documented radiotherapy schedules were hypofractionated; 16 or 17 Gy in 2 fractions separated by one week, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in two courses of 20 Gy (split course schedule), and 39–45 Gy in 13–15 fractions. Most of these radiation dose-fractionation schedules were manifested as worthwhile for palliation [8,19]. In a recent day survey, 304 patients, who received palliative radiotherapy with 30 Gy in 10 fractions for various malignancies including lung cancer, responded well to palliative radiation and had improved pain relief and QoL [20]. Another retrospective, single-center analysis of palliative radiotherapy to chest conducted by Lewis et al drew the inference that increased fractionation regimens (up to and including 30 Gy in 10 fractions) were associated with better survival regardless of performance status [21].

Not only palliative radiotherapy alone, but a handful of studies explored the role of concurrent cytotoxic therapy along with palliative radiotherapy in advanced lung cancer patients (Table 3) [11-13, 22-23]. Different cytotoxic agents, starting from traditional intravenous cisplatin & vinorelbine to oral metronomic cyclophosphamide and targeted agents like tyrosine kinase inhibitors i.e., gefitinib to modern-day practice immunotherapy have been tried in combination with palliative radiotherapy in advanced and metastatic lung cancer with variable outcome 14, 22,25]. However, despite getting some added benefit of concurrent chemotherapy with thoracic palliative EBRT in NSCLC, it cannot be feasible for all advanced cases as some of these patients have very low life expectancy, huge metastatic burden, and overall poor general condition to tolerate systemic therapy. These patients are unlikely to get the QoL improvements associated with concurrent chemotherapy.

As stated earlier, erlotinib at the standard oral daily dose of 150 mg is approved for the treatment of unselected chemo-refractory advanced non-small cell lung cancer patients as well as maintenance therapy after first-line chemotherapy and first-line therapy in patients with EGFR mutation [5,15]. Independently, erlotinib and radiation induce the accumulation of tumor cells in the G1 and G2-M phase of the cell cycle, respectively, and decreased cells in the S phase [26]. Erlotinib promotes a further reduction in S-phase fraction when combined with radiation. Following radiation exposure, erlotinib enhances the induction of apoptosis, inhibits EGFR autophosphorylation and Rad51 expression, and promotes an increase in radiosensitivity [27]. The added benefit of erlotinib is its property to cross the blood-brain barrier and concentrate in cerebrospinal fluid; thus, making this cytotoxic agent efficacious in treating brain metastasis arising from lung or other primary solid tumors [28]. Different nationwide studies & big-scale meta-analyses concluded that the combination of oral erlotinib with radiotherapy may improve the overall response and survival outcomes in advanced NSCLC patients [11-14].

The present study was planned based on the factors that the majority of the lung cancer patients reporting in our department were in advanced stage & had poor quality of life. Moreover, in developing countries like ours, there are limited health resources and the bulk of the patients are from poor socio-economic status, thus affordability for costly diagnostic tests and treatments like specific mutation-based targeted therapies, stereotactic body radiotherapy & immunotherapy are practically impossible [29].

Our study showed a clear-cut male predominance which was closely matched with the analysis conducted by Nawrocki et al and Revannasiddaiah et al [22,23]. The right lung supremacy in our analysis was also comparable with the analysis of Lewis et al [21]. Most of the patients in our study were smokers which was similar to the

study by Martinez et al [13]. The results of our analysis were closely matched with the observation concluded by Hotwani et al in patients of locally advanced lung cancer regarding radiotherapy-induced thoracic symptoms relief [30]. Our study further supports the usefulness of external radiation as a potent option in providing immediate relief to lung mass-induced dyspnoea in advanced staged patients.

A few limitations are there in our study. The major drawback of the study is its small sample size i.e., only 60 patients. However, after getting the initial result encouraging, more patients are recruiting. Future analysis with a large sample size and longer follow-up is on the way. Moreover, subgroup analyses like beneficiary effect in metastatic versus non-metastatic disease, brain metastasis versus other metastatic lesions, and advantage based on the mutation status of primary lesion are planned after recruiting more patients.

Conclusion:

Lung cancer, the most lethal malignant disease, often presents with distressing local symptoms associated with poor quality of life. Prolonged radical treatment is not an option for patients who are in an advanced stage, have poor general condition, or have other associated co-morbidities. Therefore, a palliative treatment regime has to be tailored for such patients to provide them with symptomatic relief and improve their quality of life along with minimal treatment-related toxicities. In this short-scale study, our approach was to check if there was any added benefit by combining oral erlotinib concurrently with palliative thoracic radiation compared to palliative thoracic radiation alone. Although the combination treatment arm had shown superior results in terms of greater symptomatic relief and superior quality of life improvement without any severe treatment induced toxicities, the benefit was not pronounced. Maybe, this non-significant advantage was due to a small patient cohort and a large-scale study with more patients will yield a statistically significant benefit. However, the minimal advantage seen in our analysis anchored us to combine oral erlotinib along with palliative thoracic radiation in metastatic NSCLC patients for both systemic and local effects.

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