Comparative evaluation between Radiotherapy with cyclophosphamide and Radiotherapy alone for the palliative treatment of Non Small Cell Lung Carcinoma

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Introduction

About a hundred years ago, lung cancer was a reportable disease, and it is now the commonest cause of death from cancer in both men and women in the developed world, and before long, will reach that level in the developing world as well. Lung cancer has been the most common cancer in the world for several decades. There were estimated to be 1.8 million new cases in 2015 (12.9% of the total), 58% of which occurred in the less developed regions. In India, the estimated number of new cases of lung carcinoma in 2012 were 70,275 (6.9% of the total). Majority of the patients who were recruited in the present study were bidi smokers, which poses a 6-fold higher risk of lung cancer as compared to cigarette. The incidence of lung cancer increases with larger amounts of bidis smoked per day, with longer duration of bidi smoking and with starting to smoke bidis from a younger age. Hookah smokers have an increased risk of developing lung cancer as compared to non-smokers and also pose a threat to non-smokers in their households by exposing them to second/third hand smoke. In developing countries like India, most of the patients present with locally advanced as well as metastatic disease, which could be due to lack of awareness, economic constraints and asymptomatic early stages of the disease. Locally advanced stages, along with poor general condition of the patient presents a unique kind of challenge about its management as in majority of the cases the patients are unfit for any sort of radical treatment. Therefore, there is a need for tailoring out treatment for such patients which can give them symptomatic relief and improve their quality of life. The palliative treatment approaches traditionally include palliative radiotherapy, palliative intravenous or oral chemotherapy, or both. More recently, the availability oral tyrosine kinase inhibitors (such as Gefitinib and Crizotinib) has revolutionized the treatment of Non-small cell lung cancer. Though very effective, these targeted therapies are applicable
only in certain mutational variants of adenocarcinoma. Also being expensive, targeted therapies are often not afforded by a large proportion of patients. As there are no effective targeted therapies for squamous cell carcinoma, therefore metronomic Cyclophosphamide is a suitable and effective alternative in such situations.

Patients and Methods
The study was conducted on 60 patients of non-small cell lung cancer reporting to the department of Radiotherapy, PGIMS, Rohtak where palliative Radiotherapy would be indicated as the treatment. Inclusion criteria is given below. Radiological assessment including chest X-ray PA view and lateral view, CECT chest (for staging purposes), ultrasound abdomen and pelvis for metastatic disease will be done in all patients. To assess the improvement in quality of life, FACT-G (Functional assessment of cancer therapy-General) (Annexure-IX) scoring will be done on first day of presentation of the patient in OPD and also after the four weeks of completion of palliative radiotherapy with oral cyclophosphamide. The patients will be staged according to AJCC (American Joint Committee Commission) 2010 (Annexure-I). The symptomatic relief will be assessed according to Visual assessment of cough scale (Annexure-V), MRC breathlessness scale (Annexure-VI), Universal pain assessment tool(Annexure-VII) and Hemoptysis assessment criteria(Annexure-VIII), and tumor response to treatment will be assessed by digital x-ray chest using the RECIST criteria version 1.1(Annexure-X).

Inclusion criteria
Based on the above assessment the patients for the study will be selected depending on the following criteria:
1) Poor general condition with Karnofsky Performance Status 30 to 70.
2) Complete hemogram with Hb>8gm/dl; TLC>4000/cmm, Platelet count >100,000/cmm.
3) Renal function tests with Blood urea < 40mg/dl and Serum creatinine < 1.5mg/dl.
4) Liver function tests with SGOT < 35 IU/L and SGPT < 40 IU/L.
5) AJCC stage III/IV and a positive biopsy/cytology of non-small cell carcinoma lung.
6) Patients who sign the informed consent and are ready to be on follow up as required.

Patient Characteristics
Table - I

<table>
<thead>
<tr>
<th></th>
<th>Group-I</th>
<th>Group-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Mean age</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Gender</td>
<td>Male – 25, Female - 5</td>
<td>Male – 28, Female - 2</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Smoker – 29, Nonsmoker - 1</td>
<td>Smoker – 30, Nonsmoker - 0</td>
</tr>
<tr>
<td>KPS</td>
<td>- 70 – 5, - 60 – 17, - 50 – 6, - 40 – 2</td>
<td>- 70 - 11, - 60 - 9, - 50 - 8, - 40 - 2</td>
</tr>
<tr>
<td>Histology</td>
<td>- Adenocarcinoma - 7, - Squamous cell - 22, - Large cell - 1</td>
<td>- Adenocarcinoma - 2, - Squamous cell - 28, - Large cell - 0</td>
</tr>
</tbody>
</table>
Methodology
The patients will be divided randomly in two groups of 30 patients each by internet service website https://www.random.org/lists/.

Group-I - This group will comprise of 30 randomly selected patients having histopathologically proven non-small cell carcinoma lung suitable for palliative radiotherapy. These patients will be given oral Cyclophosphamide 50 mg before initiation of palliative radiotherapy 30 Gy in 10 fractions, 5 fractions per week over a period of 2 weeks.

Group-II - This group will comprise of 30 randomly selected patients having histopathologically proven non-small cell carcinoma lung suitable for palliative radiotherapy. These patients will be treated with palliative radiotherapy 30 Gy in 10 fractions, 5 fractions per week over a period of 2 weeks.

Assessment during Treatment
From the commencement of treatment, all the patients included in the study will be carefully and regularly assessed. Detailed clinical evaluation for the tolerance of each patient to the delivered treatment will be done by thorough local examination of the patient and observation of acute toxic side effects of radiation. Radiation reactions will be assessed by Radiation Therapy Oncology Group (RTOG) criteria (Annexure-II) and WHO toxicity criteria (Annexure-III).

Assessment at the Completion of Treatment
All the patients will be assessed four weeks after the completion of treatment, to detect acute complications like mucositis, skin reaction. Treatment related toxicity will be graded using RTOG criteria (Annexure-IV). The quality of life will be assessed by FACT G (Annexure-IX) and the symptomatic relief by Visual assessment scale of cough (Annexure-V), MRC breathlessness scale (Annexure-VI), Universal pain assessment tool (Annexure-VII) and Hemoptysis assessment (Annexure-VIII). The tumor response to treatment will be assessed by RECIST criteria version 1.1(Annexure-X).

Results
Subjective relief in Cough
• All the patients in both the groups who had cough on presentation were assessed for subjective relief in cough after 4 weeks of completion of treatment.
• The categorization of relief was done based on the visual assessment scale of cough (Annexure-V).
• In Group-I 11(59%) patients had >=50% relief, 5(26%) patients had 25%-50% relief, whereas 3(15%) patients had < 25% relief.
• In group-II 7(37%) patients had >=50% relief, 5(26%) patients had 25%-50% relief, and 6(32%) had <25% relief, and 1(5%) patient had no relief.

Table-II

<table>
<thead>
<tr>
<th>Subjective relief</th>
<th>Number of patients in Group-I</th>
<th>Number of patients in Group-II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=50%</td>
<td>11</td>
<td>7</td>
<td>0.194</td>
</tr>
<tr>
<td>25%-50%</td>
<td>5</td>
<td>5</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>3</td>
<td>6</td>
<td>0.252</td>
</tr>
<tr>
<td>No relief</td>
<td>0</td>
<td>1</td>
<td>0.311</td>
</tr>
</tbody>
</table>
Subjective relief in Chest pain
- All the patients in both the groups who initially had chest pain were assessed for subjective relief in cough after 4 weeks of completion of treatment.
- The categorization of relief was done based on the universal pain assessment tool (Annexure-VII).

- In Group-I (53%) patients had >=50% relief in chest pain and 9(47%) patients had 25%-50% relief.
- In Group-II 5(26%) patients had >=50% relief, 10(53%) patients had 25%-50% relief in symptoms, and 4(21%) patients had <25% relief.

Table-III

<table>
<thead>
<tr>
<th>Subjective relief</th>
<th>Group-I</th>
<th>Group-II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=50%</td>
<td>10</td>
<td>5</td>
<td>0.097</td>
</tr>
<tr>
<td>25%-50%</td>
<td>9</td>
<td>10</td>
<td>0.746</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>0</td>
<td>4</td>
<td>0.034</td>
</tr>
<tr>
<td>No relief</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Subjective relief in Breathlessness
- All the patients in both the groups who initially had breathlessness were assessed for subjective relief in cough after 4 weeks of completion of treatment.
- The categorization of relief was done based on the MRC breathlessness criteria (Annexure-VI).
In Group-I 11(46%) patients had >=50% relief, 7(29%) had 25%-50% relief, 5(21%) patients had <25% relief and 1(4%) patient had no relief. In Group-II 6(27%) had >=50% relief, 10(46%) had 25%-50% relief, 2(9%) patients had >25% relief and 4(18%) patients had no relief.

Table-IV

<table>
<thead>
<tr>
<th>Subjective relief</th>
<th>Group-I</th>
<th>Group-II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=50%</td>
<td>11</td>
<td>6</td>
<td>0.193</td>
</tr>
<tr>
<td>25%-50%</td>
<td>7</td>
<td>10</td>
<td>0.253</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>5</td>
<td>2</td>
<td>0.268</td>
</tr>
<tr>
<td>No relief</td>
<td>1</td>
<td>4</td>
<td>0.127</td>
</tr>
</tbody>
</table>

Figure-IV

Comparison of relief in breathlessness

Subjective relief in Hemoptysis

- All the patients in both the groups who initially had cough were assessed for subjective relief in hemoptysis after 4 weeks of completion of treatment.

Table-V

<table>
<thead>
<tr>
<th>Relief in hemoptysis</th>
<th>Number of patients in Group-I</th>
<th>Number of patients in Group-II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete relief</td>
<td>3</td>
<td>5</td>
<td>0.448</td>
</tr>
</tbody>
</table>

Assessment of post treatment quality of life

- The quality of life was assessed on the basis of the FACT-G criteria (Annexure-XI).
- The mean FACT-G score was 76 was Group-I and 66 in Group-II.
- The median FACT-G score in Group-I was 76 and in Group-II was 67.

The categorization of relief was done based on the assessment of hemoptysis criteria (Annexure-VIII).

In both groups all the patients who had presented with hemoptysis were completely relieved.

The mean improvement in the FACT-G score in Group-I and Group-II is 16(26%) and 6(10%) respectively.
Table VI

<table>
<thead>
<tr>
<th>Median FACT-G score</th>
<th>Group-I</th>
<th>Group-II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>61</td>
<td>61</td>
<td>NA</td>
</tr>
<tr>
<td>Post treatment</td>
<td>76</td>
<td>67</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table VII

<table>
<thead>
<tr>
<th>Group</th>
<th>Improvement in mean FACT-G score (%)</th>
<th>Improvement in mean FACT-G score (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-I</td>
<td>16</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group-II</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Figure VII

Comparison of median post-treatment FACT-G score

Tumor response to treatment after 4 weeks

Figure VIII

Improvement in mean FACT-G score
Tumor response to treatment after 4 weeks

Table-VIII

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group-I</th>
<th>Group-II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean overall survival (months)</td>
<td>6.7</td>
<td>5.2</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Figure - IX

Comparison of mean overall survival

Table-IX

<table>
<thead>
<tr>
<th>Disease status</th>
<th>Number of patients in Group-I</th>
<th>Number of patients in Group-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>No change</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Progression</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

Figure-X

Toxicity assessment

Patients were assessed for toxicity of the treatment weekly during palliative radiotherapy and after 4 weeks of completion of treatment.
Skin reactions were the only toxicity observed, which was grade 1 in 5(16%) patients, in week 2 and grade 2 in 2(6%) patients in the first follow up.

**Group-II**

**Table-XXV**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Number of patients having toxicity in week 1</th>
<th>Number of patients having toxicity in week 2</th>
<th>Number of patients having after 4 weeks(1st follow up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLC</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cystitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Skin reactions were the only toxicity observed, which was grade 1 in week 2, in 4(13%) patients and grade 2 in only 1(3%) patient in the first follow up.

**Discussion**

For carcinoma lung patients, even after decades of development of a lot of modalities for delivering radiation therapy more efficiently and precisely, a number of new molecules for targeting the carcinomatous cells, improvement in survival is still awaited. Talking about cure is always a good thing, but only when the disease is diagnosed at an early stage however in the developing world that seems to be a distant goal, proven by most of patients presenting with late stages. In locally advanced stages, patients have a lot of symptomatic distress due to huge volume of disease, simultaneous involvement of critical structures and falling pulmonary reserves, making the patient unfit for radical treatment. Patients need urgent intervention to get relief from troublesome distressing symptoms as well as reduction in tumor burden, so that even when the survival may not improve but quality of life of the patient would be improved in such a manner that dignity of the person would be maintained.

As majority of the patients present in locally advanced stages along with poor general condition, hence they cannot tolerate conventional protracted radical treatment regimens and majority cannot afford costly targeted therapies. The present study was designed based on these unfortunate but very real factors of the patients of non-small cell lung carcinoma presenting in the department of Radiotherapy, PGIMS, Rohtak, where patients of locally advanced stages of carcinoma lung with poor performance status were randomly assorted into 2 groups, in which Group-I patients received palliative radiotherapy 30 Gy in 10 fractions over 2 weeks along with Tab. Cyclophosphamide 50 mg once a day concomitant with radiotherapy, and Group-II patients received palliative radiotherapy 30 Gy in 10 fractions over 2 weeks alone. After 4 weeks of receiving the prescribed treatment these patients
were assessed for symptomatic relief in terms of cough, breathlessness, chest pain and hemoptysis, and improvement in the quality of life.

**Pre-Treatment Evaluation**

**Age-wise distribution**

Table I shows the age-wise distribution of 60 patients. The mean age of patients in Group-I was 60 years and in Group-II was 59 years. A nearly similar trend was observed by Das et al. in a retrospective analysis of 15,968 cancer patients who reported at the department of Radiotherapy, PGIMS, Rohtak between 1980 to 2000, where 72.9% patients of carcinoma lung patients presented in the age group of 41 to 70 years and by Malik et al., as they observed a median age of 55 years in 369 patients of non-small cell lung cancer who reported to the department of medical oncology in AIIMS, Delhi. Similar results of a median age of 56 years in 489 patients of non-small cell lung cancer were reported by Noronha et al. in their study of epidemiology of lung cancer in India.

**Gender wise distribution**

Among a total of 30 patients each in both groups, in Group-I 25(84%) patients were males and 5(16%) were females, and in Group-II 28(94%) were males and 2(6%) were females. Thereby, showing a male dominance in the occurrence of lung cancer, a nearly similar ratio of 4.43:1 was found by Singh et al. in their study of epidemiology of lung cancer in India.

**Rural-urban status**

Majority of the patients in both groups resided in rural areas, 23(76%) in Group-I and 25(83%) in Group-II, whereas only 7(24%) patients in Group-I and 5(17%) patients in Group-II resided in urban areas. Haryana’s economy is predominantly agricultural based and majority of the population lives in rural areas and this is reflected in the present study.

**Smoking status**

In the present study only 1 patient in Group-I was a non-smoker whereas in Group-II all the patients were smokers. As more patients are from rural background where smoking is more common among males, smokers outnumber non-smokers. Thereby again confirming the strong correlation of smoking and lung cancer, as was observed by Lubin et al in a study of cancer risk assessment conducted in Southern China. A similar trend of predominance of smokers in lung cancer was reported by Kenfield et al. among 543 adenocarcinoma lung patients in the study “comparison of aspects of smoking among four histological types of cancer” and Kim et al. in the study “Prognostic value of smoking status in non-small-cell lung cancer patients treated with immune checkpoint inhibitors: a meta-analysis.” Malik et al. also reported majority of patients (68%) of carcinoma lung reporting to the department of medical oncology at AIIMS, Delhi being smokers, thereby further again proving the strong correlation of smoking with lung cancer.

**Karnofsky Performance status**

In Group-I majority, 17(57%) patients had a KPS of 60 and in Group-II majority 11(37%) patients had KPS of 70. In both groups maximum patients presented with KPS in the range of 60 to 70 and minimum patients presented with a KPS of 40, 2(6%) patients in both groups. As radical conventional therapy is the standard of care in patients with KPS > 70, the recruited patients in the present study were only suitable for palliative treatment.

**Tumor histology wise distribution at presentation**

Majority of the patients in both the groups were of squamous cell histology, 22(74%) in Group-I and 28(94%) in Group-II, followed by adenocarcinoma, 7(23%) patients in Group-I and 2(6%) patients in Group-II. This shows that the squamous cell histology is still prevalent in the lung cancer patients of North India due to non-changing smoking patterns.
Stage IIIB, 13(43%) and 12(40%) in Group-I and Group-II, respectively, followed by stage IV, 12(40%) in Group-I and 10(33%) in Group-II. A similar trend was reported by Singh et al among 101 non-small cell lung cancer patients who reported to the lung clinic of PGIMER, Chandigarh during 2007 to 2009. 13

Pre-treatment hematopoietic and biochemical status

The hematological & biochemical profile done in all 60 patients have been shown in Master Chart. Pretreatment hematopoietic status of patients is shown in TABLE-XXIII. Hemoglobin level was more than 8 gm/dl in all the patients at time of presentation. Total leukocyte count (TLC) was more than 4000/cumm in all patients at presentation. Platelet count was >100,000/cumm. The master chart shows the details of biochemical parameters. All the patients fulfilled the inclusion criteria with respect to biochemical status.

Symptoms at presentation

The most significant feature observed in the present study was the symptoms with which the patients presented, main distressing symptoms were breathlessness, cough, chest pain, and hemoptysis as it is these symptoms which hamper the quality of life of the patients. In both groups breathlessness was observed in majority of the patients, 24(80%) and 22(73%) in Group-I and Group-II respectively. Breathlessness was followed by cough and chest pain which were observed in equal number of patients in both groups which is 19(63%) patients each. Hemoptysis was only observed in 3(10%) patients of Group-I and 5(16%) patients of Group-II. On the basis of Lung Cancer Symptoms scale, Iyer et al also proved that the above mentioned symptoms are the most common to present in carcinoma lung patients, affecting the quality of life of the patient. 57 Coolie also urged in a study of symptoms of adults in lung cancer, of the need of early symptomatic relief of the above mentioned symptoms in lung cancer. 119

Pre-treatment FACT-G scoring

The improvement in patient's quality of life is one of the main target of health care in oncological services. 104 The quality of life in lung cancer patients is lower than in healthy population and patients suffering from other malignancies. It is affected by the severity and the number of symptoms such as fatigue, loss of appetite, dyspnea, cough, pain, and blood in sputum, which are common in lung tumors. Developed by Dr. David Cella, the FACT-G is a patient-reported outcome measure used to assess health-related quality of life in patients undergoing cancer therapy by taking into consideration the patient’s physical, social, emotional and functional well being.

All the recruited patients in both the groups were assessed for quality of life on the day of presentation by using the Functional Assessment of Cancer Therapy – General (FACT-G scoring) (Annexure-XI). The mean FACT-G score in both the groups was 60, the median FACT-G score in both groups was 61 and, equal number of patients in both the groups presented with the FACT-G score of between 50 to 60 and 61 to 70, which is 15(50%) patients. Dharm-Wardene et al tried to evaluate whether quality of life measured by the FACT-G instrument is predictive of survival of patients with advanced ling cancer, and they found that the mean baseline FACT-G score as 78.8. 120

During Treatment Evaluation

Patients were assessed weekly for radiation related as well as Cyclophosphamide associated toxicities. All patients had well tolerated the 30 Gy dose to the primary tumor in 10 fractions over a period of 2 weeks, concomitant with Tab Cyclophosphamide 50 mg with radiation therapy daily. No patient developed any kind of toxicity during the two week period of concomitant radiotherapy. All the patients completed radiotherapy without any gap.

Post Treatment Evaluation

Subjective relief in Cough

All the patients in both groups who presented with
cough were assessed for subjective relief after four weeks of completion of treatment by the visual assessment scale of cough (Annexure-V). In Group-I 11(59%) patients had >50% relief, 5(26%) patients had 25%-50% relief, and only 3(15%) patients had <25% relief. In Group-II 7(37%) patients had >50% relief 5(26%) patients had 25%-50%, 6(32%) patients had <25% relief, and 1(5%) patient had no relief.

**Subjective relief in Chest pain**

All the patients in both groups who presented with cough were assessed for subjective relief after four weeks of completion of treatment by the Universal Pain Assessment Tool (Annexure-VII). In Group-I 10(63%) patients had >50% relief, and 9(47%) patients had 25%-50% relief. In Group-II 5(26%) patients had >50% relief, 10(53%) patients had 25%-50% relief, 2(9%) patients had <25% relief, and 4(21%) patients had <25% relief.

**Subjective relief in Breathlessness**

All the patients in both groups who presented with breathlessness were assessed for subjective relief after four weeks of completion of treatment by the MRC Breathlessness Criteria (Annexure-VI). In Group-I 11(46%) patients had >50% relief, 7(29%) patients had 25%-50% relief, 5(21%) had <25% relief and 1(4%) patient had no relief. In Group-II 6(27%) patients had >50% relief, 10(46%) patients had 25%-50% relief, 2(9%) patients had <25% relief and 4(18%) had no relief.

**Subjective relief in hemoptysis**

All the patients in both groups presenting with hemoptysis were assessed for subjective relief after 4 weeks of completion of treatment, by the Assessment of Hemoptysis Criteria (Annexure-VIII). Complete relief was seen in hemoptysis in the patients of both the groups.

**Comparison of symptomatic relief**

The combination of Cyclophosphamide 50 mg orally and radiotherapy in a dose of 30 Gy in 10 fractions has shown significant and satisfactory response in terms symptomatic relief especially in breathlessness, cough, and chest pain when compared to radiotherapy 30 Gy in 10 fractions alone. The results are almost similar to the study conducted by Hotwani et al on the relief of thoracic symptoms in locally advanced lung cancer.121 This study further advocates the effectiveness of radiotherapy as an effective modality in providing immediate relief in breathlessness in patients with advanced stage lung cancer, and that radiotherapy is also free from troublesome side effects and is much more effective in relieving breathlessness than other in trial agents like midazolam, promethazine and benzodiazepines.122 Such results with palliative external beam radiotherapy also outweigh the need of endobronchial brachytherapy for symptomatic relief, which in itself is a comparatively invasive procedure which requires special expertise and state of the art setup.123 The results in terms of symptomatic relief are also comparable to the study conducted by Bhatt et al on the palliative treatment of advanced non-small cell lung carcinoma.124 The subjective symptomatic relief was significantly better in Group-I as compared to Group-II regardless of the tumor histology however, Revannasiddaiah et al had observed good response of cyclophosphamide in only patients of adenocarcinoma while, in the present study majority of the patients are of squamous cell carcinoma and good results are being observed with the addition of Tab Cyclophosphamide 50 mg concomitant with palliative radiotherapy 30 Gy in 10 fractions over 2 weeks.24

**Post-treatment FACT-G score**

Following four weeks of treatment completion, every patient was asked the questionnaire i.e. FACT-G questionnaire using Annexure-IX. The mean post-treatment FACT-G score was 76 in Group-I and 66 in Group-II, the median post-treatment FACT-G score was 76 in Group-I and 67 in Group-II. The improvement in the quality of life in the present study is appealing and statistically significant (p-value of median post-treatment FACT-G score and improvement in mean post-treatment FACT-G score was <0.001) with the addition of Tab Cyclophosphamide 50 mg 1 OD concomitant with palliative radiotherapy.
30 Gy in 10 fractions over 2 weeks. Same schedule of radiotherapy was used by Sau et al. in a comparative study of different dose fractionations schedule of thoracic radiotherapy for pain palliation and health-related quality of life using FACT-G in 182 patients of non-small cell lung carcinoma, but improvement in FACT-G score was non-significant.\(^{125}\)

The results of improvement in the quality of life is similar to a study conducted by Tucott et al on the quality of life in lung cancer patients with addition of expensive agents like nabilone.\(^{126}\) As suggested by Li et al improving the quality of life in lung cancer patients is important,\(^{127}\) the addition of an effective chemotherapeutic agent like Cyclophosphamide in a non-toxic tolerable doses along with palliative radiotherapy show promising results in terms of quality of life.

**Toxicity assessment**

Patients in both groups were assessed for toxicity of treatment weekly during the course of radiotherapy and 4 weeks after completion of treatment. Skin reactions were the most common toxicity observed in both groups. No hematological toxicities were encountered during or after completion of treatment. None of the patients in both groups experienced any grade 3 toxicity. The dose of cyclophosphamide concurrent with radiotherapy in present study does not show any of the side effects encountered with the conventional dose of Cyclophosphamide as reported by Said et al also.\(^{128}\)

**Tumor response to treatment**

The tumor response was assessed 4 weeks after the completion of the prescribed treatment and was assessed by digital x-ray chest using the RECIST criteria version 1.1.\(^{129}\) In Group-I partial response was seen in 17(57%) patients, no change was seen in 8(26%) patients and progression of disease was seen in 5(17%) patients. Whereas, in Group-II 11(37%) patients had partial response, no change was seen in 10(33%) patients and progression of disease was seen in 9(30%) patients. The combination of radiotherapy and Cyclophosphamide has shown promising results in terms of tumor response as similar tumor response has been seen in a study conducted by Wang et al, in which 48% patients of adenocarcinoma lung had partial response at 1 month follow up after receiving Gefitinib concomitant with radical radiotherapy.\(^{130}\) Single agent low dose Cyclophosphamide has shown tumor response in non-small cell lung carcinoma comparable to those reported by Lee in the study of combination chemotherapy including Cyclophosphamide in the treatment of Small cell lung cancer.\(^{99}\)

**Conclusion**

This analysis has shown promising results with the combination of low dose oral Cyclophosphamide (50 mg) and palliative regime of radiotherapy (30 Gy in 10 fractions) as compared to palliative radiotherapy (30 Gy in 10 fractions) alone, it has shown better and more symptomatic relief (though not statistically significant) and statistically significant improvement in quality of life, and absolutely no life threatening or severe treatment related complications during and after treatment.

As it is evident and quite obvious that the quality of life in lung cancer patients is significantly lower than in healthy population and also patients suffering from other malignancies. A patient’s quality of life is hindered by the severity and the number of symptoms such as fatigue, loss of appetite, dyspnea, cough, pain, and blood in sputum, which are very common in lung cancer. Such troubling and discomforting symptoms effect the physical, social, emotional as well as psychological dimensions of not only the patient but also his/her family.

The present study has shown good symptom control and improvement in the patient’s quality of life with a treatment regime which has minimal treatment related toxicity and less number of visits to the hospital and therefore, concludes that the combination of short palliative course of Radiotherapy and oral Cyclophosphamide is an effective treatment to achieve early relief in
symptoms and improvement in the quality of life of a patient suffering from advanced stage non-small cell lung cancer.

References