Background: A Single Institute Prospective Study was carried out in 75 patients of Advanced Non Small Cell Lung Cancer using three different arms using standard regime and the hypofractionated radiotherapy regime.

Methods and Materials: Between July 2010 and September 2011, 75 patients with biopsy proven NSCLC were treated with schemes 1(17 Gy in 2 fractions over 2 weeks; 25 patients), 2 (30 Gy in 10 fractions over two weeks; 25 patients), or 3 (39 Gy per 13 fractions over three weeks; 25 patients). There were 66 evaluable patients. 2 of them died during the study(treatment phase) and 6 were lost to follow up. The minimum follow-up time was 24 months.

Results: There was no overall survival difference in all the three arms(p_ .2). The median survival was 6.2 months(arm A:8.5 Gy in 2 fractions one week apart) 6.7 months(arm B:30 Gy in 10 fractions) and 6.8 months(arm C:39 Gy in 13 fractions). Conclusion: Hypofractionated Palliative radiotherapy regime using 17 Gray in two fractions is as effective in alleviation of symptoms as is the standard regime of 30 Gray in 10 fractions and 39 Gray in 13 fraction with no statistical difference in overall survival.

Keywords: Advanced non-small cell lung cancer, hypofractionation, radiotherapy

INTRODUCTION

Non-small cell lung carcinoma (NSCLC) accounts for about 80% of all lung cancer. More than three-fourths of patients will present with symptomatic Stage III or IV disease.[1,2] The clinical profile of lung cancer in Indian subcontinent differs from the West, in that Indian patients present almost 15–20 years earlier, in the fifth or sixth decade of life. Most patients will have symptoms from the primary tumor, including cough, dyspnea, and hemoptysis as the most frequent symptoms. Other symptoms include chest pain, loss of appetite, and generalized weakness. Radiotherapy (RT) is effective in relieving symptoms in majority of these patients. Up to 80% of patients will benefit, with significant reduction of hemoptysis and dyspnea.[3-5] Metastatic lung cancer and locally advanced inoperable cancers not suitable for radical treatment and yield a poor prognosis with relatively short survival (4–7 months). Consequently, a limited treatment period is available, so treatment should be aimed in improving their quality of life (QOL). Hypofractionated RT with the use of few large single fractions may fulfill these criteria. Few studies favor a hypofractionation treatment policy,[6,7] while others advise against hypofractionation because of the increased toxicity and/or reduced survival.[8-10] The objectives were to address whether our standard palliative fractionation (30 Gy in 10 fractions) was comparable to a hypofractionated schedule (17 Gy in 2 fractions), as we were often criticized for underdosing the patients with 30 Gy in 10 fractions and a third widely accepted palliative schedule arm (39 Gy in 13 fractions) was incorporated in the study. Primary end points were patient-assessed and clinician-assessed symptom relief of dyspnea, cough, and hemoptysis, whereas survival and

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the other domains in the health-related QOL (HRQOL) questionnaire were secondary end points.\textsuperscript{[11-15]} The study is presented with a minimum of 2-year follow-up for all surviving patients.

**Materials and Methods**

Between July 2010 and September 2011, 75 patients with biopsy-proven NSCLC were treated with schemes 1 (17 Gy in 2 fractions over 2 weeks; 25 patients), 2 (30 Gy in 10 fractions over 2 weeks; 25 patients), or 3 (39 Gy per 13 fractions over 3 weeks; 25 patients). There were 66 evaluable patients. Two of them died during the study (treatment phase) and 6 were lost to follow-up. The minimum follow-up time was 24 months.

The eligibility criteria were histologically or cytologically confirmed NSCLC, age >30 years, Stage III or IV disease, Karnofsky performance status (KPS) >40%, expected survival >3 months, and no previous or other concomitant malignant disease. Among patients with Stage IIIA disease, only inoperable patients with poor prognostic factors such as tumor diameter >7 cm and KPS <70%, were included.

Previous RT treatment rendered the patients ineligible as did the presence of pleural effusion. The histopathologic diagnosis was established according to the WHO classification.\textsuperscript{[16]} Pathology was reviewed at our center for all patients. The ethics committee approved the study protocol, and written informed consent was obtained from all the patients before random assignment to treatment.

**Clinical examination and staging**

All patients had the following diagnostic workup: history and physical examination, radiologic examinations (chest X-ray and/or computed tomography scan of the chest including liver and adrenal glands), and liver and kidney profile (cell counts, erythrocyte sedimentation rate, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transpeptidase, serum creatinine, and blood urea nitrogen). KPS and weight loss during the last 6 months were registered. Cerebral magnetic resonance imaging and bone scans were only performed when indicated by symptoms. All patients were staged according to the American Joint Committee on Cancer 7.

**Radiotherapy**

RT was given with two opposing anterior-posterior fields, individually encompassing the regional mediastinal lymph nodes and the primary tumor with a 1.5–2-cm margin. The supraclavicular region was not routinely treated unless palpable regional nodes or primary tumor were located in the apical region of the lung. The RT fractionation schemes were as follows: arm A, two fractions of 8.5 Gy days 1 and 8 to a total dose of 17 Gy; arm B, 10 fractions of 3 Gy to a total dose of 30 Gy; and arm C, 13 fractions of 3 Gy to a total dose of 39 Gy.

The maximum portal length, exposing the spinal cord, was set to 10 cm. Lengths above 10 cm were not allowed unless a lead block was inserted to shield the spinal cord from excessive radiation. Patients in arm A were prophylactically administered prednisolone 50 mg bid days −1, 0, and +1.

**Health-related quality-of-life**

The QOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire (QLQ)-C30 and the lung cancer-specific module QLQ-LC13.\textsuperscript{[11-15]} The core questionnaire incorporates functional scales, i.e., physical, emotional, cognitive, and social and symptom scales, i.e., fatigue, nausea/vomiting, and pain. The QLQ-LC13 module contains items for measuring dyspnea, cough, hemoptysis, mucositis, dysphagia, peripheral neuropathy, alopecia, pain, and analgesic consumption or effect.

The scales and items were linearly transformed to a scale from 0 to 100, with a higher score on functional scales indicating a high degree of function, and a higher score on the symptom scales indicating a high degree of symptoms.\textsuperscript{[13]} For QOL assessments, the EORTC QLQ-C30 and the lung cancer-specific module QLQ-LC13 were used. The patients completed the first questionnaire before RT. Later questionnaires were completed by the patients at 2, 5, 12, and 24 weeks from the start of treatment.

**Examination and follow-up**

At baseline, symptoms such as cough, hemoptysis, and dyspnea were categorized by the responsible clinicians according to a four-point verbal rating scale, ranging from none to severe. Dyspnea was categorized in a six-point scale: able to climb hills or stairs without dyspnea, walk any distance on flat without dyspnea, walk more than 100 m without dyspnea, dyspnea from walking 100 m or less, dyspnea from mild exertion (e.g. undressing), and dyspnea at rest. Patients were scheduled for a clinical examination, including systematic assessment of the symptom scales and a chest X-ray, at 2, 6, and 14 weeks after treatment. A clinically significant change was defined as at least a one-step change on the scales. Clinical follow-up beyond week 14 was optional according to individual patient need and follow-up policy at the institution. Subsequent palliative treatment such as chemotherapy and RT was allowed. All patients were observed until death or a minimum of
2 years. By the time of death or at the last follow-up time close to 23 months, assessment of symptomatic control within the RT field was performed on the basis of available clinical information for each patient.

**Statistical analysis**

Stratification was done for the absence (symptom-preventive treatment) or presence (symptomatic treatment) of symptoms at the time of inclusion. The primary outcome of the study was patient-reported dyspnea (using the QLQ-C30), cough, and hemoptysis (using the QLQ-LC13 module).

The log-rank test was applied for comparison of survival. The effect of treatment at each assessment time was evaluated using the nonparametric Mann–Whitney U-test for comparing two samples and the Kruskal–Wallis test for comparing three or more samples. The significance level was set at 0.05, using a two-sided test. Differences in HRQOL were calculated using group scores for the mean value of each variable and differences were tested using the Wilcoxon rank-sum test. A difference in mean score – 10 points was considered clinically significant, whereas a difference <10 points was considered as a moderate change and of uncertain clinical relevance.

**RESULTS**

Sixty-six out of 75 (88%) patients were male. Majority of patients presented in the fifth and sixth decade of their lives, the mean age of presentation was 58.87 (range 31–80). Majority (69%) of patients had presented with poor KPS <70. Only advanced stage patients were included in this study of the patients 24 (32%) were Stage III A, 25 patients (33%) were Stage IIIB, and 26 patients (35%) were Stage IV [Table 1]. Most common presenting symptom [Table 2] in this study was cough with expectoration (74.66%), followed by loss of weight (61.33%) and hemoptysis (61.33%); however, there was a considerable overlap of symptoms (patients presenting with two or more symptoms). We observed that the incidence of radiation-induced pneumonitis was maximum between 1 month and 5 months after completion of radiation. It was observed to be maximum with high-dose single-fraction radiation schedule; however, the difference between arms did not reach statistical significance (we described radiation-induced pneumonitis as dyspnea worse after radiation which responded to oral steroids).

The primary study end points were the patient’s symptom control cough, hemoptysis, and dyspnea. Among the entire group of patients, there were no differences among the treatment arms with respect to dyspnea, cough, and hemoptysis. Moreover, subset analysis according to the patients with symptoms at baseline (n = 75) also showed similar data across the treatment. Among the patients with symptoms at baseline (Score = 2), 36% reported reduced cough, 44% reported reduced dyspnea, 57% reported reduced pain, and 90% reported reduced hemoptysis within 20 weeks from treatment start, with no statistical difference among the groups. According to the clinicians’ symptom evaluation, dyspnea and cough were improved in approximately 40%–55% of patients, whereas hemoptysis was palliated in 80%–90% of patients. Only patients with symptoms at baseline were analyzed. Except for improved hemoptysis at week 5 in arm A (P = 0.02), there was no difference among the groups. Furthermore, the palliative effect of symptoms

| Table 1: Studies comparing hypofractionated radiotherapy in locally advanced nonsmall cell lung cancer |
| Study | Patient number (n) | Inclusion criteria | Dose | Fraction | Survival (months) | Palliative effect |
|-------|-------------------|-------------------|------|----------|-------------------|------------------|
| MRC et al., 1992 | 235 | Inoperable/poor performance | 17 | 2 | 9 | 48%-75% |
| Rees et al.[9] | 216 | Poor performance | 17 | 2 | 6 | No difference between treatment arms |
| Sundstrom et al.[1] | 421 | Stage III, IV/mostly KPS 70-80 | 17 | 2 | 8.2 | No difference in symptom response or toxicity |
| Kramer et al.[22] | 297 | Stage IIIA, IIIB, IV/mostly ECOG 3-4 | 16 | 2 | 10.9 | 30 Gy in 10 fractions/better 22 week Posttreatment |
| Macbeth FR, 1996 | 509 | Nonmetastatic locally advanced cases | 17 | 2 | 7 | Rapid palliative effect in 17 gray in two-fraction arm |
| Senkus-Konefka et al | 100 | Inoperable/median ECOG of 2 | 20 | 5 | 5.3 | No difference in symptom control |

KPS: Karnofsky Performance Scale, ECOG: Eastern Cooperative Oncology Group, MRC: Medical Research Council
seemed to last throughout the planned follow-up period (6 months).

Overall survival (OS) for all patients \( n = 67 \) revealed no significant survival difference among the treatment groups \( (P = 0.2) \). The median survival was 6.2, 6.7, and 6.8 months in arm 1, 2, and 3, respectively.

**Discussion**

Radiation remains an effective and a commonly used local therapy to relieve thoracic symptoms for lung cancers of all stages.\(^{[17]}\) RT remains an important treatment modality for patients with symptoms from intrathoracic disease, either after disease progression during chemotherapy or in patients with poor general conditions, who are not candidates for or decline chemotherapy. Data from various trails cannot be compared due to heterogeneity in patient population (range of PS, age, inclusion of small cell lung cancer, methods of symptom assessment, and measured outcomes). However, the meta-analysis by Fairchild et al.\(^{[18]}\) suggests that a selected group of patients can be considered for higher total doses of RT to derive more durable palliation and improved OS. The number of patients who may benefit most from a protracted course of radiotherapy is essential in population who often have poor performance status or significant comorbidities. A variety of fractionation schedules, ranging from 10 Gy/one fraction to 60 Gy/30 fractions, are used in clinical practice.\(^{[19,20]}\) However, there is a debate about the optimal fractionation scheme to be used; some randomized studies favor a hypofractionation treatment policy\(^{[6,7]}\) others do not recommend hypofractionation because of the increased toxicity and/or reduced survival.

In the present study, there was a similar degree of palliation of all symptoms in the treatment groups with disappearance of symptoms in substantial proportions of patients. Similarly, an analysis\(^{[20]}\) of ten randomized palliative RT trials indicated that the degree of symptom relief was equivalent regardless of the total RT dose. In contrast, a study conducted by the National Cancer Institute of Canada, found that patients treated with fractionated RT (20 Gy), had greater improvement in symptoms, ability to carry out normal activities, and better global QOL than patients treated with single fraction of 10 Gy. Bezjak et al and Erridge et al.\(^{[21]}\) reported better palliation with higher dose and more fractionated regimen. Rates of palliation by symptom type were as follows: dyspnea, 40%–97%; hemoptysis, 77%–92%; cough, 60%–91%; and pain, 70%–78%. The reported duration of symptom relief was up to 50% of remaining the survival time.

The median duration of palliation reported by our study, was slightly longer in patients received high-dose regimen although did not reach a statistical
significance. In the Medical Research Council (MRC) 1996,[9] shorter regimen of 2 fractions, have more rapid onset of palliating symptoms than higher dose of 13 fractions, although the differences in the proportion of patients who were palliated were not significant. Kramer et al.[21] showed that both regimens of 30 Gy/10 fractions and 16 Gy/2 fractions were effective in controlling symptoms, but the duration of palliative effect was significantly longer with 30 Gy/10 fractions compared to 16 Gy/2 fractions. MRC 1991[23] found that the median duration of palliation was similar in the two treatment groups; it ranged from 46 to 73 days in the two-fraction group and from 45 to 101 days in the single-fraction group and palliation of symptoms last for at least 50% of survival time. In contrast, Rees et al.[6] noted that only one symptom (hemoptysis) was improved in more than 50% of patients at 8th weeks with no difference in degree and duration of relief of other symptoms.

A consistent finding in the studies is that higher equivalent doses of RT are associated with more acute side effects.[1,9,23] Our study had similar results; the two-fraction regimen was associated with dysphagia due to esophagitis. Grade 2 acute esophagitis was greater among patients received 39 Gy/13 fractions (n = 25, 26.3%) compared to those received 17 Gy/2 fractions (n = 25, 14%) but did not reach statistical significance. Two patients (3.5%) developed Grade 2 pneumonitis and both of them received 39 Gy/13 fractions. In the MRC trial 1991[21] dysphagia reported by the clinicians occurred in 25% of patients received 17 Gy in 2 weekly fractions regimen and 17% of single fraction group since the pretreatment assessment. Sundström et al.[1] reported earlier dysphagia with the two shorter treatment regimens. MRC 1996[9] showed that higher dose of 13 fractions regimen caused more tiredness and anorexia than the two fraction regimens. In our study, there were no reported cases of radiation myelitis following the use of both regimens. In contrast, MRC trials, 1991 and 1996[8,23] reported radiation myelitis following the use of 17 Gy/2 fractions and 39 Gy/13 fractions. Sundstrom et al.[1] reported one case of radiation myelitis following the use of 50 Gy/25F.

In our study, the median survival was 6.6 months. There was no significant difference in OS between the groups. Similar findings were reported by Abratt et al.[7] MRC 1996[9] and Simpson et al.,[3] they reported median survival of 6.3–9 months.[24] A study conducted by Sundstrøm et al.[1] revealed no significant survival difference among the treatment groups (P = 0.83). In contrast, Fairchild et al.[18] reported a statistically higher survival and lower total symptom score with the higher dose regimens (30 Gy/10 fractions equivalent or higher, e.g., 30–35 Gy/10 fractions, 36–45 Gy/12–15 fractions, or 50–60 Gy/25–30 fractions).

**Conclusion**

Hypofractionated regimen of 17 Gy/2 weekly fractions is at least as effective at providing symptomatic relief and yield equivalent survival as 30 Gy/10 and 36 Gy/13 fractions. Therefore, based on the results of our study, we recommend short courses of palliative hypofractionated regimen as treatment of patients with advanced NSCLC and thoracic symptoms, as it has the advantage of fewer visits to hospital and nondistressing treatment.

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**Conflicts of interest**

There are no conflicts of interest.

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