

ROLE OF PALLIATIVE RADIOTHERAPY AND BEST SUPPORTIVE CARE IN LOCALLY ADVANCED CARCINOMA LUNG

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ABSTRACT

BACKGROUND

Lung cancer is presently the leading cause of cancer death and most of the patients present in advanced stage where symptom palliation is the main aim. However, there is no well-defined recommendation regarding optimal dose and schedule of palliative radiotherapy. This article is a retrospective review of data from single institute to evaluate the effectiveness of palliative radiotherapy and best supportive care (BSC) in locally advanced carcinoma lung and to analyse the association between patients, and treatment related factors to the response to treatment.

MATERIALS AND METHODS

Histopathologically/Radiologically proven 191 patients with lung cancer, registered at PGIMS Rohtak, from January 2015 to June 2017 were retrospectively analysed. Treatment given was either hypo-fractionated radiation regimes with or without concurrent chemotherapy or best supportive care. The patients were divided into 4 groups based on dose schedules i.e. Group I: 8 Gy in single fraction, Group II: 20 Gy in 5 fractions over 5 days, Group III: 30 Gy in 10 fractions over 2 weeks and Group IV: best supportive care. They were compared with respect to survival, symptom palliation and quality of life. The risk factors assessed were performance status (PS), histopathology, stage and frequency and duration of smoking. Lost to follow up and time of death was taken as end point.

RESULTS

Median overall survival was 5 months. However, there were patients who survived less than 2 months, even prior to the effect of radiation. Median survival for treatment schedule groups- I to IV was 3 months, 5 months, 6 months and 2 months respectively. Out of assessable 179 patients (12 patients died or defaulted) 96 (53.6%) showed $\geq 50\%$ response in symptom palliation, although maximum palliation was achieved in Group- III. Symptomatic response evaluation was significantly associated with treatment schedule ($p=0.001$). Eastern Cooperative Oncology Group and age didn't achieve statistically significant association with symptom palliation response.

CONCLUSION

Our study concludes that all patient and treatment related parameters should be assessed prior to treatment commencement. Short course Palliative Radiotherapy is a good option in terms of symptom palliation in patients with life expectancy of more than 2 months in advanced stage disease. Best supportive care as an option should be offered to the patients/attendants who are with poor PS, but its recommendation as a guideline must be validated by randomized controlled trial.

KEYWORDS

Palliative, Thoracic, Radiotherapy.

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BACKGROUND

Lung cancer is the most common cancer seen among all cancers (11.6%) and it is the leading cause of death due to

cancer (18.4% of the total cancer deaths).¹ In India, lung cancer constitutes 6.9% of all new cancer cases and 9.3% of all cancer related deaths in both sexes.² Despite numerous advances in diagnostic and therapeutic modalities, the outcome is mainly dismal due to advanced stage at presentation.

Radiotherapy, chemotherapy and targeted therapy are the mainstay of treatment in carcinoma lung and as large number of patients present with advanced stage, radiation is a very effective strategy as palliative approach. Palliative thoracic radiotherapy (PTR) improves quality of life in approximately one third of all patients.³ Various radiotherapy treatment schedules have been used till date e.g. 30 Gy in

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10 fractions, 8 Gy in single fraction or sometimes two fractions with once weekly schedule or 20 Gy in 5 fractions over 5 days etc. trying to achieve better and prolonged symptom palliation. Performance status, symptoms severity, co morbidities, life expectancy patients' preference/compliance are the factors which help in deciding the treatment.

In this retrospective study, we investigated data for effectiveness of various radiotherapy schedules and best supportive care and aimed to find association between patient and treatment related factors to the response to treatment.

MATERIALS AND METHODS

Retrospective analysis of histopathologically/radiologically proven 191 lung cancer patients, registered at PGIMS Rohtak, from January 2015 to June 2017, was done from the database. Various demographic characteristic was looked into. Inclusion criteria was advanced stage (stage- III/IV; American Joint Committee on Cancer, 7th edition) and histopathologically confirmed carcinoma of lung except in superior vena cava syndrome.⁴ Patients with early stage of disease and treated with radical intent were excluded.

Therapeutically patients were divided into four groups i.e. Group -I: 8 Gy in single fraction, Group-II: 20Gy in 5 fractions over 5 days and Group -III: 30 Gy in 10 fractions over 2 weeks and Group- IV: best supportive care. The schedule was decided mostly based on general condition of patients, age, comorbidities and departmental logistics e.g. Patients with poor general condition but with poor compliance were chosen for 8 Gy in single fraction and even worse general condition and unwilling for any intervention were chosen for best supportive care. Radiation treatment was commenced on Telecobalt machine by conventional two-dimensional radiotherapy in supine position to the chest. Performance status and stage at presentation were analysed by the clinician with clinical and radiological examination. Data on various parameters like symptomatic relief of chest pain, breathlessness, cough, smoking history were recorded in database as brief questionnaire to the patients and post treatment they were assessed immediately after treatment and monthly thereafter in group I to III and twice weekly for group IV. They were asked to score the response from 0 to 100% in term of relief in symptoms. Visual Analog Scale was also used for the same. Supportive care was given with analgesics following the WHO ladder, bronchodilators with or without corticosteroids along with proton pump inhibitors. Patients were admitted and given intravenous medication, nebulization with bronchodilators and/or corticosteroids, intermittent oxygen inhalation wherever needed. Moreover, psychosocial support was also given. Smoking cessation measures were taken. Chest physiotherapy was also a part of BSC. BSC was given to patients who couldn't withstand even palliative thoracic irradiation or didn't give consent for active radiation/chemotherapy/targeted therapy. Lost to follow up and time of death was taken as end point.

Smoking index (SI) was done for quantification of smoking which was defined as the number of bidis + cigarettes smoked/day multiplied by a number of years smoked. Patients were categorized accordingly into four SI-based groups: never smokers (SI - 0), light smokers (SI – 1 to 100), moderate smokers (SI – 101 to 300), and heavy smokers (SI- ≥ 301).^{5,6}

Statistical Analysis

Data entered was analysed using SPSS (Statistical Package for Social Sciences) version 16.0 for Windows. Quantitative data presented as mean and standard deviation (SD). Qualitative data presented as ratio and percentage. Qualitative data were compared using Chi-square test. Normally distributed Qualitative data was analysed using t-test. For statistical significance p value <0.05 was taken as point of clinical significance.

RESULTS

Analysis of 191 patients of carcinoma lung for clinical presentation, histopathology, staging, treatment intervention, symptom palliation and survival outcome was carried out. Patients were in the age between 34 to 78 years, with a mean age of 58 years and median age was 60 years (Figure 1). Out of 191 patients 170 were male and the remaining 21 were female. Smoking habit was seen in 93.7% of total patients; however only two male patients were non-smokers and only 11 female cases were smokers. Patients distribution as per Smoking Index (SI) was SI 0- 12 cases, SI 1 to 100 -15 cases, SI 101 to 300- 25 cases, SI >300 – 139 cases. Performance status was decided as per Eastern Cooperative Oncology Group (ECOG) and no patients were with ECOG 0 & 1 and 5 cases with ECOG -2, 95 cases with ECOG-3, 82 cases with ECOG-4 and rest of 9 patients were with ECOG-5. Histopathology wise maximum patients were with Squamous Cell Carcinoma (94) followed by Adenocarcinoma (28), Small cell carcinoma (21), Poorly differentiated carcinoma (20), Large cell carcinoma (5), Non-small cell carcinoma (not specified) (11), SVC syndrome (10) and others (2). Maximum patients i.e. 82 out of 191 were seen in stage- IV and 41 cases with stage-IIIA, 60 cases with stage IIIB, and 8 cases were with unspecified stages. Patient's distribution as per treatment (RT) regimens used was 21 cases in Group-I, 72 cases in Group-II, 77 cases in Group-III and 21 cases in Group-IV.

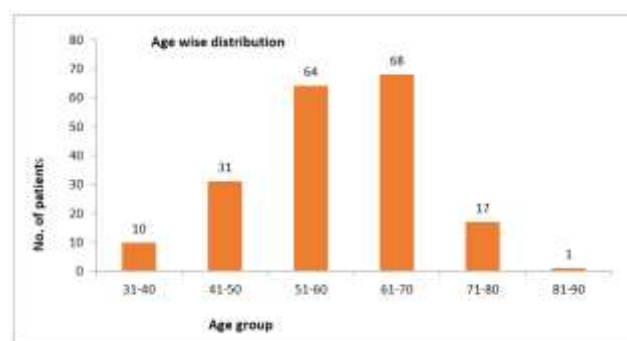


Figure 1. Age-Wise Distribution of Cases

Evaluation of Symptom palliation was done only in 179 patients as 2 patients died, 5 patients discontinued treatment and 5 lost to follow up. On the contrary, the results were dismal with maximum survival of three months and mean response of 30% in symptoms palliation with best supportive care in 21 patients of group IV. Mean response rate was 37%, 49% and 53% in group I, II and III respectively i.e. best in group III using 30 Gy in 10 fractions and maximum survival was up to 24 months.

Characteristics		Response Number of Patients (Percentage)		Statistical Significance
		<50%	≥ 50%	
ECOG *	< 3	0 (0%)	5 (100%)	p value=0.254
	≥ 3	83 (45.7%)	91 (54.3%)	
Age	<60	43 (49.4%)	44 (50.6%)	p value=0.425
	≥60	40 (43.5%)	52 (56.5%)	
Groups	1 8 Gy/1 #	12 (70.6%)	5 (29.4%)	
	2 20 Gy/5#	30 (46.9%)	34 (53.1%)	p value=0.001
	3 30 Gy/10#	20 (26%)	57 (74%)	
	4 BSC†	21 (100%)	0 (0%)	

Table 1. Association Analysis between Response to Different Hypofractionation Regimen and Best Supportive Care with Patient, Tumour and Treatment Related Factors

*Eastern Cooperative Oncology Group.

† Best Supportive Care.

The association between performance status, age and treatment schedule with the response was also analysed (Table-1). Out of 179 patients 96 (53.6%) showed ≥ 50% response in symptom palliation (Figure-2). Only treatment schedule had significant association ($p=0.001$). Median survival was 5 months and subgroup analysis showed median survival of 3 months, 5 months, 6 months and 2 months for group 1, 2, 3, and 4 respectively.

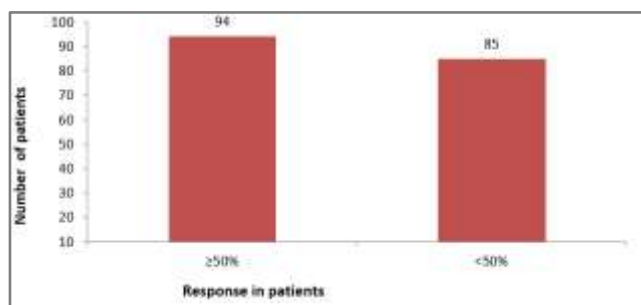


Figure 2. Response in 179 Carcinoma Lung Patients After Radiation Treatment, Intervention or Best Supportive Care

DISCUSSION

Carcinoma lung is one of the deadly diseases with very high mortality rate, constitute 18.4% of all cancer related deaths.¹ It is the leading cause of death amongst males and in India most of the patients present in advance stage, thus the prognosis is dismal despite all measures. Many a times the diagnosis is delayed due to masking of symptoms by

other common diseases like tuberculosis. Bidi smoking is promulgated as the most common type of smoking product in India and similar scenario was observed in lung cancer patients seen at our center. Heavy smoking has already been strongly associated with advanced stage, which justifies 139 out of 191 patients as heavy smokers in our study.⁷

Incidence of Adenocarcinoma has increased compared to squamous cell carcinoma. Now it is the most common histologic variant of lung cancer In the Western and most of the Asian countries.⁸ Contrary to this present study showed squamous cell carcinoma as most common histological variant which is in accordance to some of the Indian studies.^{9,10}

Advanced stage Carcinoma lung patients present with very devastating symptoms like cough, breathlessness, chest pain, haemoptysis requiring urgent care and management.¹¹ Palliative thoracic radiotherapy with or without chemotherapy play a pivot role especially in patients with good performance status not amenable to radical treatment. Numerous study results are available to choose the most appropriate regime of radiotherapy for palliation with doubtful results. Senkus-Konefka E et al randomized 100 patients of Non-small cell lung cancer, who were not suitable for radical treatment and had significant thoracic symptoms, into 20 Gy/5 fractions/5 days or 16 Gy/2 fractions/day 1 and 8 and assessed for symptom control and overall survival. They reported similar symptom relief but better median survival in short course arm (8 months vs. 5.3 months, $P = 0.016$).¹² It is not in accordance with our study where better median survival and symptom relief is achieved in long course arm.

Lotayef M et al also compared two schedules of 30Gy in 10 fractions and 27 Gy in 6 fractions over 3 weeks in a study of 40 patients. They assessed symptomatic, radiological Tumour response and respiratory functions.¹³ They found higher symptomatic improvement in 27 Gy in 6 fractions group but was statistically insignificant. This is in contrast to our study as we found better response in 30 Gy in 10 fractions over 2 weeks.

Comprehensive review of 14 randomized clinical trials by Cochrane Collaboration which was related to different radiotherapy dose schedules for symptom palliation found no significant differences among short and long radiotherapy regimens. But higher-dose regimens were associated with mild increase in acute toxicity, particularly oesophagitis.¹⁴ They investigated various fractionation schedules ranging from 10 Gy in 1 fraction to 60 Gy/30 fractions over six weeks, with a total of 19 regimens.¹⁵ However, they didn't make a definitive recommendation. Even large difference was not seen amongst four groups in our set of patients. However, our study also is a retrospective analysis where bias while recording can't be completely overlooked.

Median survival in our study was 5 month which is in accordance with the reported 5.8 months median survival by Van Oorschot et al in 120 Non-Small Cell Lung Cancer patients treated with 39- 45 Gy in 13 - 15 fractions of 3 Gy.¹⁶ It was their standard approach for patients requiring local radiotherapy with life expectancy between 6 and 12 months.

Multiple patient and treatment related factors will help in choosing either Palliative radiotherapy or the best supportive care as treatment schedule. In another study, Hotwani C et al, evaluated 100 patients with stages III-IV lung cancer with two different fractionation regimens of palliative thoracic radiotherapy (RT) using either protracted course of 20 Gy/5 fractions over 1 week or short course of 17 Gy/2 fractions over 8 days. They found no difference in OS at 1 year, but they found a significant relief ($\geq 50\%$) with 20 Gy/5 fractions over 1 week ($P = 0.060$) but median duration of symptoms relief was 2 months in either group.¹⁷ This study also showed significant association of symptom palliation with Radiotherapy schedule ($p=0.001$). Patients with <60 yrs. of age had median survival of 3 months which is 2 months less than overall median survival, suggesting role of age in outcome but on association analysis it was not found significant. Even in our study treatment schedule had

significant association with treatment response ($p=0.001$) (Table 1).

Frank MS et al did retrospective analysis of 159 patients of non-small cell lung cancer who were planned for either of the standard palliative radiotherapy schedules of 30 Gy/10 Fractions, 25 Gy/5 Fractions, 15 Gy/3 Fractions and 10 Gy/1 Fraction. They found that significant number of patients who received radiotherapy died before achieving optimal effect of the treatment. 16 patients (10%) out of 159 couldn't complete radiotherapy. However, in our study two deaths and 5 defaulters and 5 lost to follow up patients were there i.e. 12 [0.06%] out of 191 patients. They suggested that fractionated Palliative radiotherapy should be considered for patients with Performance Status 0-1. High dose single fraction only or supportive palliative care should be considered for patients with Performance Status ≥ 2 .¹⁸

Study, Year	No. of Participants	Histopathology	Intervention	Median Survival/Overall Survival	Comments
Rees et al 1997 ¹⁹	216	NSCLC [†] , SCLC [‡]	17 Gy / 2 F* / 8 days (111 patients) versus 22.5 Gy / 5 F* / 5 days (105 patients).	No significant difference in survival.	No evidence for superiority of multi-fraction regimen.
Senkus-Konefka E et al, 2005 ¹²	100	NSCLC [†]	20 Gy/5 F* / 1 week (55 patients) versus 16 Gy/2 F* / 8 days (45 patients).	8 months versus 5.3 months, $p=0.016$	No significant difference in symptom relief
Kramer et al, 2005 ²⁰	297	NSCLC [†]	30 Gy/10 F* / 2 weeks (148 patients) versus 16 Gy/2 F* / 8 days (149 patients).	1-year survival significantly better in the 10 F* arm (19.6% vs 10.9%, $p=0.03$)	No significant difference in symptom palliation or treatment-related toxicity Significantly longer palliative effect with 10 F arm ($p<0.001$)
B. Van Oorschot et al, 2014 ¹⁶	114	NSCLC [†]	Survival and prognostic variables after palliative Radiation 39 Gy - 45 Gy in 13-15 F* over 3 weeks	Median survival 5.8 months.	In the multivariate analysis, good general condition, nonmetastatic disease, and a stable or improved general condition at the end of radiotherapy were significant.
Hotwani C et al, 2017 ¹⁷	100	NSCLC [†] , SCLC [‡]	20 Gy/5 F* / 1 week (21 patients) or 17 Gy/2 F* / 8 days (79 patients)	No difference in Overall Survival at 1 year	a significant relief ($\geq 50\%$) with 20 Gy group ($P = 0.060$) but median duration of symptoms relief was 2 months in either group.
Present study	191	NSCLC [†] , SCLC [‡]	8 Gy in single session, 20 Gy/5 fractions/ 1 week, 30 Gy / 10 F* / 2 weeks, BSC [§]	Overall Median survival -5 months, on subgroup analysis- 6 months in 30 Gy group	Best symptomatic relief in 30 Gy group

Table 2. Numerous Studies Evaluating the Role of Various Palliative Treatment Schedules in Locally Advanced Carcinoma Lung Cases in Comparison to the Present Study

Abbreviations used

*-Fractions

†-Non-small cell lung cancer

‡ Small cell lung cancer

§- Best supportive care

Where the patient expected survival was <2 months, even shorter hypofractionated schedules was not of much help. However, these shorter hypofractionated schedules require fewer visits to the Radiotherapy department sparing the possible machine space and resources with the advantage of better compliance. Very short hypofractionated regimen like 8 Gy in single fraction or even best supportive care enable the patient with short expected survival time to spend more time with their family away from the hospital.

CONCLUSION

Parameters pertaining to the patient like age, performance status, comorbidities should be assessed prior to treatment commencement. Palliative Radiotherapy is a good option in terms of symptom palliation in patients with life expectancy more than 2 months. However median survival remains dismal even with palliative thoracic radiotherapy many a times due to advanced stage at presentation. Thus, best supportive care as an option should be offered to the patient/attendants especially who are with poor performance status and with suspected survival less than 2 months as it decreases the morbidity and patients and their attendants' inconvenience in term of visits and hospital stay. This observation must be validated by randomized controlled trials before accepted as a guideline.

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