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Single Institution Prospective Randomized Trial of Radiation as a Sole Modality in Palliation of Advanced Non-small Cell Lung Cancer-an International Atomic Energy Agency Study

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Abstract

Introduction: There has been no consensus on the optimal treatment schedule for palliation of symptoms in advanced non-small cell lung cancer (NSCLC) despite the large number of studies reported from Europe, USA, and Asia.

Material and methods: Patients with advanced incurable stage III/IV disease with a confirmed histological diagnosis of NSCLC (Squamous, adenocarcinoma or mixed squamous-adenocarcinoma), Karnofsky Performance Status (KPS) ≤ 60%, any TNM status, no prior chemotherapy or radiation therapy, estimated life expectancy of at least 12 weeks. Sixty patients were randomized to one of the 3 treatment arms; Arm-1: 20 Gy in 5 fractions within one week, Arm-2: 17 Gy in 2 fractions with a one week interval and Arm-3: 10 Gy in 1 fraction. The purpose of the study was to find the most effective and shorter schedule for palliation of symptoms.

Results: A symptomatic improvement was noted in the majority of patients with cough, hemoptysis chest pain and dyspnea with no significant differences between different schedules. Treatment related toxicity was noted in 34 of 60 (57%) patients. Twenty-four (71%) of 34 patients had grade 2 dyspnea as the main toxicity with 5 (25%), 10 (50%) and 9 (45%) with 5 fractions, 2 fractions and 1 fraction respectively. Overall there was no impact of fractionation on acute toxicity (p=0.81).The overall survival was 11% at 1 year with a median survival of 3 months. A median survival of 5 months, 3 months and 2 months was noted in patients receiving 5 fractions, 2 fractions and 1 fraction respectively (p=0.08). Patients younger than 60 years had significantly higher survival than more than 60 years (p=0.03) on multivariate analysis.

Conclusion: No significant difference was noted between the treatment arms for the palliation of major symptoms. Patients younger than 60 years had higher 1 year survival.

Keywords: Squamous-adenocarcinoma; Dyspnea; Chemotherapy; Chest pain; Dysphagia

Introduction

Carcinoma of the lung forms 5.6% of patients presenting with cancer at the Tata Memorial hospital in India and 65% of these have advanced stages of disease [1]. Seventy percent of the patients receiving radiation therapy have stage III or IV disease. Treatment with radiotherapy alone has an extremely poor outlook in patients with lung cancer, with only 5% of patients surviving for 5 years [2-4].

A number of randomized clinical trials have compared different fractionation schedules in the palliation of thoracic symptoms [5 -14]. Only one of these studies [9] compared single fraction radiotherapy of 10 Gy with two fractions of 8.5 Gy each one week apart. Five studies have compared two fractions of 8.5 Gy radiotherapy with more protracted schedules (30 Gy in 10 fractions or 27 Gy in 6 fractions [8], 36 or 39 Gy in 12 or 13 fractions [10] and 22.5 Gy in 5 fractions [11], 21.5 Gy in 5 fractions of 4.25 Gy given over 2 days [15] and 42 Gy in 15 fractions daily as well as 50 Gy in 25 fractions daily [16]. The most commonly used regimen in the USA for palliative treatment has been 30 Gy in 10 fractions within 2-3 weeks.

The effectiveness of radiotherapy in palliating pulmonary symptoms due to non-small cell lung cancer (NSCLC) ranges from 50-90% [6-11,15,17-19]. In general, hemoptysis has the highest response rate (76-95%), followed by chest pain (50-80%), cough (50-65%) and dysphagia (37-60%). The optimal schedule for palliation of these symptoms has not been determined.

The final choice of dose and fractionation are often influenced by the physician's perception of the patient's prognosis and survival, availability of resources and differences in the approach to the terminal care of the cancer patient. A shorter fractionation schedule requires fewer trips to the radiotherapy facility for the patients, and in all likelihood, smaller direct or indirect costs for society [20]. Erridge et al. [21] reported on the results of 149 patients with NSCLC treated with either 30 Gy in 10 fractions or 10 Gy in 1 fraction and suggested that further investigation of palliative radiotherapy schedules in NSCLC is necessary to define the best dose and fractionation.

Hoskin [22] has noted in his editorial that the situation is becoming increasingly confusing in the group of patients who are seen with performance status 0 or 1 who have extensive tumor beyond that considered appropriate for radical treatment.

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At the study center, fractionation schedules of 20 Gy in 5 fractions, 17 Gy in 2 fractions have been used for palliation of thoracic symptoms for patients with advanced inoperable NSCLC. It is because no consensus has emerged regarding the appropriate schedule, that the IAEA supported a single institution study comparing 20 Gy in 5 fractions, 17 Gy in 2 fractions and 10 Gy in a single fraction so that a short and quick palliative treatment can be chosen for treating patients with poor general condition (KPS < 60%) with NSCLC. Limited funds restricted the number of patients that could be randomized to 60 at a single institution.

Materials and Methods

The study was conducted at the Tata Memorial Hospital. Sixty patients with confirmed histological diagnosis of NSCLC with advanced unresectable stage III or IV disease and poor performance status were accrued into the study. The primary objective was to determine the role of short course palliative external beam radiation for symptoms improvement and to determine which fractionation regimen gives the best results. A secondary objective was to determine the overall survival in patients treated with this fractionation. The pretreatment evaluation included general physical examination, full blood count, biochemical screening profile, liver function test and renal function tests, chest X-ray PA and lateral and bronchoscopy with biopsy. A CT scan of the chest was done to ascertain the extent of the disease, extension to major vessels and lymph nodes spread whenever possible. The metastatic work up was extended with bone scan or CT scan of brain if symptoms demanded.

Patient characteristics

Sixty patients were randomized into 3 treatment arms. There were

Parameters		Number of Patients				p value
		Total	1 Fraction	2 Fractions	5 Fractions	
Age	< 60	37	13	13	11	0.75
	>60	23	7	7	9	
Gender	Male	53	18	18	17	0.85
	Female	7	2	2	3	
Histology	Squamous carcinoma	25 (42%)	10	6	9	0.77
	Adenocarcinoma	25 (42%)	7	10	8	
	Not specified	10 (16%)	3	4	3	
Performance status	50%	22 (37%)	9	5	8	0.39
	60%	38 (63%)	11	15	12	
Stage	III	24 (40%)	4	8	12	0.04
	IV	36 (60%)	16	12	8	
Endobronchial lesion	Present	36 (60%)	10	13	13	0.53
	Absent	24 (40%)	10	7	7	
Metastatic disease	Present	30(50%)	13	9	8	0.24
	Absent	30(50%)	7	11	12	

Table 1: Patient Characteristics.

Presenting symptoms		Number of Patients				p value
		Total	1 Fraction	2 Fractions	5 Fraction	
Cough	None	11	04	04	03	0.15
	Mild	06	00	01	05	
	Moderate	40	14	14	12	
	Severe	03	02	01	00	
Chest pain	None	14	04	06	04	0.70
	Mild	06	02	02	02	
	Moderate	31	10	08	13	
	Severe	09	04	04	01	
Dyspnea	None	18	06	09	03	0.37
	Mild	10	02	03	05	
	Moderate	22	09	06	07	
	Severe	10	03	02	05	
Hemoptysis	None	41	13	14	14	0.99
	Mild	13	05	04	04	
	Moderate	06	02	02	02	
Pyrexia	None	43	14	14	15	0.63
	Mild	16	06	06	04	
	Moderate	01	00	00	01	

Table 2: Presenting Symptoms.

53 males and 7 females. The median age of the patients was 60 years (range 37-73 years). The histology was squamous cell carcinoma in 25 (42%) patients and adenocarcinoma in 25 (42%) patients and it could not be specified in 10 (16%) patients.

Thirty patients presented with distant metastases. Eighteen (60%) of these patients presenting with distant metastases had KPS of 60%. All the patients with distant metastases had pulmonary symptoms as their main presenting symptom. All the groups were equally matched except for the stage of disease with more patients with stage III in the 5 fraction group (p=0.04) (Table 1).

Table 2 outlines the presenting symptoms which included cough 49 (82%), chest pain 46 (77%), dyspnea in 42 (76%), hemoptysis in 19 (32%) and pyrexia in 17 (28%) patients. The symptoms were graded according to criteria published by Speiser [23].

Treatment protocol

All patients were treated to the primary tumor using parallel opposed fields with megavoltage radiation using Co_{60} gamma-rays or 6/10 MV photons. Both fields were treated daily. The treatment volume included the tumor with a maximum of a 2 cm margin all around. The maximum field size did not exceed 10×10 cm in either direction. The field size was limited to 10×10 cm so as to prevent excessive treatment related toxicity because of higher doseper fraction. The dose prescription was calculated as per ICRU recommendations (midpoint of two beams). The estimated biological equivalent dose (BED) calculated for acute complications were 28 Gy_{10} for Arm 1, 31 Gy_{10} for Arm 2, and 20 Gy_{10} for Arm 3.

The patients were evaluated at least twice a week during treatment. Additional treatments such as steroids, bronchodilators, analgesics were added as and when necessary and the dose and scheduling were recorded. The patients were randomized by computer generated random number method into 3 arms.

- Arm 1: 20 Gy in 5 fractions of 4 Gy per fraction within 1 week.
- Arm 2: 17 Gy in 2 fractions of 8.5 Gy per fraction, each fraction one week apart.
- Arm 3: 10 Gy in 1 fraction in 1 day.

If the patients did well with a subjective and objective improvement in symptoms and KPS, they were given an additional boost after a period of 1 month, keeping the dose within spinal cord tolerance.

Assessment of palliation

The clinician's assessment of the patients' overall condition and severity of symptoms were recorded before the initiation of treatment, at the completion of treatment and at regular intervals of one month after treatment. Details of the management of symptoms and adverse effects of radiotherapy were recorded at each visit. A chest X-ray was taken to assess the regression of the tumor when clinically indicated.

Statistical methods

Palliation of a particular symptom was expressed as the proportion of patients with an improvement of at least one grade in the relevant scale from the pretreatment status. The proportion of patients with an improvement in each treatment arm was compared using Wilcoxon signed rank test, Matt Whitney U tests and chi-square tests. The survival was calculated from the first day of treatment to the last follow up or date of death and survival curves were plotted using Kaplan Meier method. The results were compared using the log rank test for univariate analysis and Cox regression model for the multivariate analysis.

Results

Fifty-nine of the 60 patients completed the planned course of radiation. One patient received 8.5 Gy and could not receive the second fraction due to deteriorating general condition. All patients entered were included for an intention to treat analysis.

Symptom improvement

Overall improvement of symptoms was noted in 65.4% with cough improvement in 75%, chest pain relief in 69%, dyspnea improvement in 52%, relief of hemoptysis in 84% and pyrexia in 47% (Table 3). All the symptoms improved significantly after the treatment with cough ($p<0.0001$), pain ($p<0.0001$), breathlessness ($p<0.0001$), haemoptysis ($p=0.001$) and pyrexia ($p=0.013$) as compared to the pretreatment levels using the 3 treatment arms. Dyspnea did not improve significantly with two fraction regimen ($p=0.15$) when analyzed individually. In most cases symptom improvement was maintained until death.

There was no impact of the different fractionation schedules on improvement of symptoms of cough ($p=0.25$), chest pain ($p=0.61$), dyspnea ($p=0.33$), hemoptysis ($p=0.99$) and pyrexia ($p=0.66$) as seen in table 3.

Sex had significant impact on symptom improvement with males

Presenting symptoms	Number improved/ Number with symptom (%)				p value
	Total	1 Fraction	2 Fractions	5 Fractions	
Cough	37/49(75)	14/16(87.5)	10/16(62.5)	13/17(76.5)	0.25
Chest pain	32/46(70)	11/16(69)	09/14(64)	12/16(75)	0.61
Dyspnea	22/42(52)	07/14 (50)	04/11(36)	11/17(65)	0.33
Hemoptysis	16/19(84)	06/07(86)	05/06(83)	05/06(83)	0.99
Pyrexia	08/17(47)	02/06(33)	03/06(50)	03/05(60)	0.66

Table 3: Symptom Improvement.

Toxicity	Total	1fraction	2fractions	5fractions
Nil	26	8	6	12
Breathlessness	24	9	10	5
Cough	4	1	1	2
Chest pain	2	0	1	1
hiccups	2	1	1	0
Generalized weakness	2	1	1	0

Table 4: Fractionation versus toxicity.

showing improvement in cough (p=0.03), pain (p=0.04), dyspnea (p=0.01) and hemoptysis (p=0.02) as compared to females. Pain relief was significantly better (p=0.02) for patients with KPS of 60%. However, age, stage of disease, presence or absence of endobronchial lesions, presence or absence of metastatic disease at presentation did not have any impact on symptom improvement.

Partial responses (>50% regression) were recorded in 11 (18%) patients as evaluated clinically as well as on chest X-rays. There was a significant improvement in chest pain (p=0.04), dyspnea (p=0.04) and pyrexia (p=0.04) and a trend towards improvement in cough (p=0.07) in patients who achieved a partial response as compared to the group that did not. Eight of the 11 patients with partial response received boost doses of radiation with 20 Gy in10 fractions using localized off-cord fields. There was no significant difference in the prior treatment for the patient's receiving boost (p=0.80). The delivery of boost radiation did not add further to the improvement in symptoms. Another 12 (20%) patients showed less than 50% regression on chest X-ray but had good symptom relief.

Eight patients received palliative radiation therapy for metastatic disease (5 lung, 1 each for bone, brain and supraclavicular area) at a later date. Three patients received chemotherapy only for metastatic disease in the lungs.

Toxicity

All the acute toxicities recorded were grade 2 according to the common toxicity criteria [24]. Treatment related toxicity was noted in 34 of 60 (57%) patients. Twenty-four (71%) of 34 patients had grade 2 dyspnea as the main toxicity with 5 (25%), 10 (50%) and 9 (45%) with 5 fractions, 2 fractions and 1 fraction respectively (p=0.22). Eleven of 24 patients had other side effects in addition to dyspnea (I patient each with cough and loose motions in the 1 fraction group; 3 patients had fever, 2 gastritis, 1hiccup, 1 hoarseness and 1 weakness in 2 fraction group and 1 had cough in the 5 fraction group). Of the 10 remaining patients with toxicity, 4 (6.6%) developed moderate cough, 2 (3.3%) patients each had chest pain, hiccups and generalized weakness which were equally distributed in 3 arms. Overall there was no impact of fractionation on acute toxicity (p=0.81) (Table 4). All acute toxicities were successfully managed with symptomatic treatment. None of the patients developed late toxicity related to the treatment.

Survival

An overall survival of 11.6% at 1 year was noted and the median survival for the whole group was 3 months. The 1 year survival and median survival was 20% and 5 months with 5 fractions, 0% and 3 months with 2 fractions and 5% and 2 months with 1 fraction respectively (p=0.08) (Figure 1). The median survival was longer for patients who had symptom improvement as compared to those with no improvement with respect to all the symptoms (p=0.02).

Age group, Karnofsky performance status, stage of disease, sex, histology, presence or absence of metastatic disease as well as the presence of an end bronchial lesion did not have an impact on survival on univariate analysis. A comparison of the fractionation schedules showed a significant survival benefit with the 5 fraction schedule as compared to 2 fraction schedule (p=0.03) but no difference when compared to 1 fraction schedule (p=0.1). The multivariate analysis using Cox regression model showed a significant impact of age group and fractionation schedule on survival, with a trend towards significance for males and KPS of 60% (Table 5). Although sub group analysis

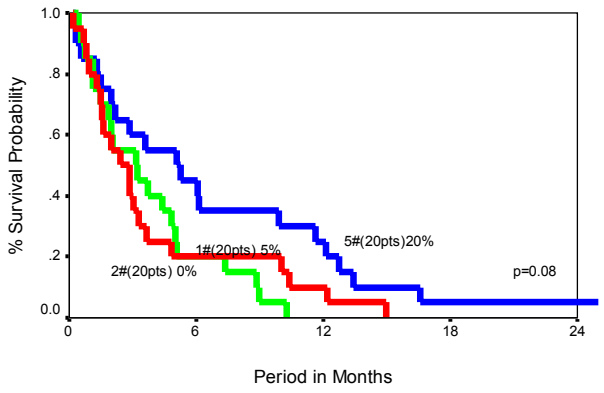

Figure 1: Overall Survival (1 year) by Fractionation Whole Group = 60 pts.

(Table 6) showed a significant benefit for squamous cell histology (p=0.01) and trend towards significance for males (p=0.07), KPS of 60% (p=0.09) and patients with no endobronchial lesion (p=0.07) when treated with 5 fractions, the patient groups were not stratified prior to randomization. There was a survival benefit for patients with metastatic disease (p=0.01) but it was confined to the group receiving additional treatment (p=0.05).

Patients with partial responses who received boost radiation had a higher median survival of 9 months in comparison to 3 months in those not receiving a boost (p=0.006).

Discussion

Thoracic radiation remains an important treatment modality for patients who have symptoms from intra-thoracic disease. This is despite the greater use and increasing efficacy of palliative chemotherapy during the past 10-15 years [25].

The treatment is palliative in nature and this group of patients has a poor median survival of between 2-9 months. Thus shorter hypo-fractionated schedules may use less of this limited survival period and allow patients more time to benefit from the palliation provided that quality of palliation is equivalent and morbidity is not increased [21]. Shorter fractionation regimens are likely to be activated more speedily than those of longer duration. This is an important advantage in a group of patients who have a short median survival.

Various groups have included patients into their studies with either poor performance alone [9,20,26], good performance alone [16,27] or a combination of good and poor performance [8,11,12,15,28]. The present study had patients with Karnofsky performance status of ≤ 60%.

The presenting symptoms in our group of patients were similar to that reported by others [5,7-9,29-31].

Lester et al. [32] suggested that patients with significant thoracic symptoms at presentation should be treated with palliative radiation, the dose of which will mainly be decided by the patient's performance status. Large fractions of palliative radiotherapy are safe and effective for these patients, and although some may report acute chest pain, fevers and rigors, these are transient.

Symptom improvement depending on different dose schedules by various groups as outlined in table 7 suggests that relief of cough ranged from 20-82% [5,8,9,15,20,29,30]. In the present study, however a single

Parameters		Number	1 year survival (%)	Multivariate
Age group	≤ 60	37	11	0.03
	60	23	8	
KPS	50	22	4.5	0.09
	60	38	10	
Fraction	1#	20	5	0.01
	2#	20	0	
	5#	20	20	
Stage	III	24	8	0.57
	IV	36	5	
Metastases	Present	30	13	0.98
	absent	30	7	
Endo-bronchial lesion	Present	36	8	0.84
	absent	24	8	
Sex	Male	53	5	0.08
	female	7	0	
Histology	Squamous	25	12	0.18
	Adeno	25	8	
	Not specified	10	0	

Table 5: Parameters versus survival.

Parameters	1 yr. Survival (%)			Univariate P value
	1 Fraction	2 Fractions	5 Fractions	
KPS 50 60	 0 9	 0 0	 12.5 25	 0.73 0.09
Stage III IV	 25 0	 0 0	 17 25	 0.51 0.11
Metastases Present absent	 0 14	 0 0	 37.5 8	 0.01 0.29
Endo-bronchiallesion Present absent	 0 0	 0 0	 8(13mths) 14	 0.29 0.07
Sex Male female	 5.5 0	 0 0	 23 0	 0.07 0.82

Table 6: Prognostic factors versus fractionation.

fraction of 10 Gy provided relief in 87.5% patients as against 62.5% noted by two fractions of 8.5 Gy each one week apart. This contrasts with Rees et al. [11] who concluded from their study that the palliation of cough with radiation was poor.

Relief in chest pain was reported by various groups [5,8,9,26,29,30] ranging from 44-83%. Seventy–five percent of patients had pain relief with five fractions of 4 Gy each delivered daily in comparison to 64% patients with two fractions of 8.5 Gy each one week apart in the present series. The relief was significantly higher for patients who had at least a partial response but the addition of boost radiation in the present study did not improve pain relief further as has been reported by Donato et al. [31]. The10 fraction schedule reported by Erridge et al. [21] resulted in significant reduction of chest pain (p=0.004) in comparison to a single fraction of 10 Gy in a study of 149 patients.

Dyspnea improvement was noted in 30-97% patients depending on different schedules [5,8,13,20,29,31]. In the present study, dyspnea improved in 36-65% of patients. The 10 fraction schedule reported by Erridge et al. [21] resulted in better palliation of dyspnea than single fraction.

Most studies have reported relief of hemoptysis ranging from 60-100% using different radiation regimens [5, 8,9,15,20,26]. In the present study, 83-86% of patients had relief of hemoptysis when treated with 3 dose schedules. Rees et al. [11] have reported a higher rate of relief of hemoptysis in comparison to other symptoms.

Teo et al. [7] have noted significantly better palliation of 71% with 45 Gy in 18 fractions as compared to 51% with 31.2 Gy in 4 fractions given once weekly (p=0.02). Bezjek et al. [28] have reported the results of multi-institutional trial comparing 10 Gy single fraction radiotherapy with 20 Gy in 5 fractions in the palliation of thoracic symptoms from lung cancer. The fractionated radiotherapy group had a greater overall improvement in symptoms related to lung cancer (p=0.009) and pain (p=0.0008). There was no difference between symptom relief in the 3 arms in our study and similar results have also been reported by three MRC trials [8-10].

The rates of palliation for hemoptysis, chest pain, cough and dyspnea reported from studies wi th short regimen (8.5 Gy × 2) are comparable to those of other trials that used more protracted palliative treatment. The biological effect of radiation on tumours is increased as the overall treatment is shortened [33].

Authors/Institution	Dose Schedule	Cough %	Hemoptysis %	Chest pain %	Dyspnea %
RTOG 1985	4x5-2wks-4x5=40Gy 3x10=30Gy 2x20= 40Gy	56 55 53	77 74 73	44 51 56	30 43 40
MRC 1991	3 x10=30Gy 4.5 x 6=27Gy 8.5x2=17Gy(weekly)	56 65	86 81	80 75	NA
MRC 1992	8.5x2=17Gy(weekly) 10x1 =10Gy	48 56	75 72	59 72	NA
Scolario 1995	10x1=10Gy	46	75	83	69
Vyas1998	8.5x2=17Gy(weekly)	60	90	70	50
Donato1999	4x5=20Gy	82	80	NA	97
Bhatt2000	4x5=20Gy(weekly)	68	77	77	59
Nestle 2000	2x30=60 Gy 2x16(bid)=32 Gy	71 64	89 89	72 80	76 93
Plataniotis 2002	8.5x2=17Gy(weekly) 4.25x5=21.25Gy(2 days)	24 20	60 67	57 64	55 45
Cross 2004	8.5x2=17Gy(weekly)	60	100	NA	30
Erridge2005	10 x 1=10Gy 3x10=30Gy	51 58	88 97	50 84	45 68
Present study	4 x 5=20Gy 8.5x2=17Gy(weekly) 10 x 1= 10 Gy	76.5 62.5 87.5	83 83 86	75 64 69	65 36 50

Table 7: Dose Schedule versus Symptom Improvement- Literature Review.

Authors/Institution	Patient Number	Dose Schedule	Median Survival (months)
MRC 1991	349Good PS	3 x10=30Gy 4.5 x 6=27Gy 8.5x2=17Gy(weekly)	6
MRC 1992	235Poor PS	8.5x2=17Gy(weekly) 10 x 1 =10Gy	4
Steven1995	38 Good PS	8.5x2=17Gy	9
MRC 1996	509 Good PS	8.5x2=17Gy(weekly) 3x 13=39 Gy	7 9
Rees 1997	216Good/Poor PS	8.5x2=17Gy(weekly) 4.5 x 5 =22.5 Gy	6
Lupattelli 2000	91Poor PS	8x2=16Gy(weekly)	5
Plataniotis 2002	92Good/Poor PS	8.5x2=17Gy(weekly) 4.25x5=21.25Gy(2 days)	6
Bezjak 2002	230Good/Poor PS	4x5=20Gy 10 x 1=10 Gy	6 4.2
Cross 2004	23Poor PS	8.5x2=17Gy(weekly)	4
Sundstrom2004	421 Good PS	8.5x2=17Gy(weekly 2.8 x15=42Gy 2 x25=50Gy	8.2 7.0 6. 8
Present Study	60Poor PS	4 x 5=20Gy 8.5x2=17Gy(weekly) 10 x 1= 10 Gy	5 3.0 2.0

Table 8: Dose Schedule versus Median Survival -Literature Review.

Fairchild et al. [34] did not find significant differences for specific symptom control end points, although suggested that improvement in survival favour high dose radiation. For symptom control in assessable patients, lower dose (LD) RT was comparable with higher dose (HD) except for total Symptom Score (TSS): 65.4% of LD and 77.1% of HD patients had improved TSS (p=0.003).

Macbeth et al. [35] report from the review of literature that patients with poor PS (WHO PS 2 or 3) should be treated with 10Gy in a single fraction and patients with good performance and thoracic symptoms should receive 16-17 Gy in 2 fractions.

Treatment related toxicity was noted in 34 of 60 (57%) patients. Twenty-four patients (71%) had grade 2 dyspnea with 3 patients (5%) having radiological changes suggestive of pneumonitis on X-rays,4 (6.6%) developed moderate cough, 2 (3.3%) patients each had chest pain, hiccups and generalized weakness in the present study. The side effects observed were in 14 (70%) patients with 2 fractions schedule as compared to 12 (60%) receiving 1 fraction schedule and in 8 (40%) patients treated to 5 fraction schedule. Lupattelli et al. [36] have reported grade 3 esophagitis in 5% patients. Scolaro et al. [30] have reported nausea in 17%, vomiting in 5% and grade II dysphagia in 10% patients. There is a concern among some radiation oncologists that higher single fraction doses of 10 Gy may have a higher incidence of acute complications [37] but our study did not confirm it. In the MRC

trials, 2 patients treated with 17 Gy in 2 fractions developed a radiation myelopathy [8,9]. The authors suggest that this high incidence may be related to the use of larger field sizes. Bezjek et al. [28] did not report any treatment related toxicity. There was no patient reported to have radiation myelopathy in the present series as well as in studies by Cross et al. [20] and Steven and Begbie [27].The acceptability of this regimen to patients is therefore an important finding as no significant toxicity was encountered in all 3 treatment arms in the present study

The median survival of patients following various fractionation schedules (randomized or non-randomized) is shown in table 8. The median survival noted in the present study was 5 months with 5 fractions of 4 Gy each in comparison to 2 months with single fraction of 10 Gy. The survivals reported by other groups were similar in the range of 4 months [9,20,28]. Some authors [12,31] have reported a higher overall survival for patients with good performance status patients when the studies included both good and poor performance patients. Our study confirmed that patients with KPS of 60 did better than those with KPS of 50.

The third MRC trial [10] showed an improved survival with 39 Gy in 13 fractions. In our study, there was a trend towards improved survival in the group that received 20 Gy in 5 fractions compared to the shorter fractionation schedules. However, Sundstrom et al. [16] have reported equivalent median survivals of 8.2, 7.0 and 6.8 months in a randomized trial of 421 patients treated with 3 different regimens of 17 Gy in 2 fractions 1 week apart, 42 Gy in 15 fractions daily and 50 Gy in 25 fractions daily respectively. Nestle et al. [13] reported similar survivals with 60 Gy in 30 fractions as compared to 32 Gy in 16 fractions.

Donato et al. [31] have reported an overall survival of 52% at 1 year in patients receiving boost radiation and a survival of 33% at 1 year in patients receiving no boost. The median survival of patients receiving a boost was 9 months in comparison to 3 months for patients who did not receive a boost in the present study.

Conclusion

No differences were noted between treatment arms in any of the major symptoms palliated, there was a non-significant improved survival with 20 Gy in 5 fractions in comparison to 17 Gy in two fractions separated by 1 week and a single fraction of 10 Gy.

Confirmation of the results of this study would have clear benefits for the developing countries with limited resources.

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References

1. Dinshaw KA, Rao DN, Shroff PD (1998) Hospital Cancer Registry, Annual Report 1995, Mumbai: Tata Memorial Hospital.
2. Hoffman PC, Mauer AM, Vokes EE (2000) Lung Cancer. Lancet 355: 479-485.
3. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR (1996) Improved survival in Stage III Non-Small-Cell Lung Cancer: seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial. J Natl Cancer Inst 88: 1210-1215.
4. Le Chevalier T, Arriagada R, Quoix E, Ruffle P, Martin M, et al. (1991) Radiotherapy alone versus combined chemotherapy and radiotherapy in Nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst 83: 417-423.
5. Simpson JR, Francis ME, Perez-Tamayo R, Marks RD, Rao DV (1985) Palliative radiotherapy for inoperable carcinoma of the lung: Final report of a RTOG multi-institutional trial. Int J Radiat Oncol Biol Phys 11: 751–758.
6. Salazar OM, Slawson RG, Rosillo HP, Amin PP, Sewchand W, et al. (1986) A prospective randomized trial comparing once-a-week vs daily radiation therapy for locally-advanced, non-metastatic, lung cancer: A preliminary report. Int J Radiat Oncol Biol Phys 12: 779–787.
7. Teo P, Tai TH, Choy D, Tsui KH (1988) A randomized study on palliative radiation therapy for inoperable non small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 14: 867–871.
8. Medical Research Council (1991) Inoperable non-small-cell lung cancer (NSCLC): A Medical Research Council randomized trial of palliative radiotherapy with two fractions or ten fractions. Report to the Medical Research Council by its Lung Cancer Working Party. Br J Cancer 63: 265–270.
9. Medical Research Council Lung Cancer Working Party (1992) A Medical Research Council (MRC) randomized trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Br J Cancer 65: 934–941.
10. Macbeth FR, Bolger JJ, Hopwood P, Bleehen NM, Cartmell J, et al. (1996) Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Clin Oncol 8: 167–175.
11. Rees GJ, Devrell CE, Barley VL, Newman HF (1997) Palliative radiotherapy for lung cancer: Two versus five fractions. Clin Oncol (R Coll Radiol) 9: 90-95.
12. Abratt RP, Shepherd LJ, Salton DG (1995) Palliative radiation for stage 3 non-small cell lung cancer--a prospective study of two moderately high dose regimens. Lung Cancer 13: 137-143.
13. Nestle U, Nieder C, Walter K, Abel U, Ukena D, et al. (2000) A Palliative Accelerated irradiation regimen for advanced non-small-cell lung cancer vs. conventionally fractionated 60 Gy: results of a randomized equivalence study. Int J Radiat Oncol Biol Phys 48: 95-103.
14. Reinfuss M, Glinski B, Kowalska T, Kulpa J, Zawila K (1999) Radiotherapy for stage III, inoperable, asymptomatic small cell lung cancer. Final results of a prospective randomized study (240 patients). Cancer Radiother 3: 475-479.
15. Plataniotis GA, Kouvaris JR, Dardoufas C, Kouloulias V, Theofanopoulou MA, et al. (2002) A short radiotherapy course for locally advanced non-small cell lung cancer (NSCLC). Effective palliation and patients' convenience. Lung Cancer 35: 203-207.
16. Sundstrom S, Bremnes R, Aasebø U, Aamdal S, Hatlevoll R, et al. (2004) Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. J Clin Oncol 22: 801-810.
17. Baldini EH (1997) Palliative radiation therapy for non-small cell lung cancer. Hematol Oncol Clin North Am 11: 303–319.
18. Collins TM, Ash DV, Close HJ, Thorogood J (1988) An evaluation of the palliative role of radiotherapy in inoperable carcinoma of the bronchus. Clin Radiol 39: 284–286.
19. Appold S, Baumann M, Neidt F, Herrmann T (1999) Results of irradiation of inoperable stage III non-small cell lung cancer with 25Gy in 5 fractions. Strahlenther Onkol 175: 267-270.
20. Cross CK, Berman S, Buswell L, Johnson B, Baldini EH (2004) Prospective study of palliative hypofractionated radiotherapy (8.5 Gy x 2) for patients with symptomatic non-small-cell Lung Cancer. Int J Radiat Oncol Biol Phys 58: 1098-1105.
21. Erridge SC, Gaze MN, Price A, Kelly CG, Kerr GR, et al. (2005) Symptom control and quality of life in people with lung cancer: A randomised trial of two palliative radiotherapy fractionation schedules. Clin Oncol (R Coll Radiol) 17: 61-67.
22. Hoskin PJ (2005) Palliative radiotherapy for non-small-cell lung cancer: which dose? Clin Oncol (R Coll Radiol) 17: 59-60.
23. Speiser BL (1990) Protocol for local control of endobronchial carcinoma using remote afterloading HDR brachytherapy. Activity: SelectronBrachytherJ: 16-19.
24. Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, et al. (2000) Common Toxicity Criteria: version 2.0. An improved reference for grading the acute effects of

cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 47: 13-47.

25. Shepherd FA (1999) Chemotherapy for non-small cell lung cancer: Have we reached a new plateau? Semin Oncol 26: 3-11.

26. Vyas RK, Suryanarayana U, Dixit S, Singhal S, Bhavsar DC, et al. (1998) Inoperable non-small cell lung cancer: Palliative radiotherapy with two weekly fractions. Indian J Chest Dis Allied Sci 40: 171–174.

27. Stevens MJ, Begbie SD (1995) Hypofractionated irradiation for inoperable non-small cell lung cancer. Australas Radiol 39: 265-270.

28. Bezjak A, Dixon P, Brundage M, Tu D, Palmer MJ, et al. (2002) Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). Int J Radiat Oncol Biol Phys 54: 719-728.

29. Bhatt M L, Mohani BK, Kumar L, Chawla S, Sharma DN, et al. (2000) Palliative treatment of advanced non small cell lung cancer treated with weekly fraction radiotherapy. Indian J Cancer 37:148-152.

30. Scolaro T, Bacigalupo A, Giudici S, Guenzi M, Vitale V (1995) Single-dose palliative radiotherapy in inoperable non-small-cell lung carcinoma. Radiol Med 90: 808-811.

31. Donato V, Zurlo A, Bonfili P, Petrongari M, Santarelli M, et al. (1999) Hypofractionated radiation therapy for inoperable advanced stage non-small cell lung cancer. Tumori 85: 174-176.

32. Lester JF, MacBeth F, Toy E, Coles B (2006) Palliative radiotherapy regimens for non-small cell lung cancer. Cochrane Database Syst Rev Issue 4.

33. Beli I, Koukourakis G, Platoni K, Tolia M, Kelekis N, et al. (2010) Hypofractionated radiotherapy in non small cell lung cancer: A review of the current literature. Rev Recent Clin Trials 5: 103-111.

34. Fairchild A, Harris K, Barnes E, Wong R, Lutz S, et al. (2008) Palliative thoracic radiotherapy for lung cancer: A systematic review. J Clin Oncol 26: 4001-4011.

35. Macbeth FR, Abratt RP, Cho KH, Stephens RJ, Jeremic B (2007) Lung cancer management in limited resource settings: Guidelines for appropriate good care. Radiotherapy and Oncology 82: 123-131.

36. Lupattelli M, Maranzano E, Bellavita R, Chionne F, Darwish S, et al. (2000) Short-course palliative radiotherapy in non-small-cell lung cancer: Results of a prospective study. Am J Clin Oncol 23: 89-93.

37. Macbeth FR, Bolger J (1991) Palliative radiotherapy for bronchial carcinoma: Science or Art? Clin Oncol (R Coll Radiol) 3: 245-246.