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Palliative hypofractionated radiotherapy in south Egyptian patients with stage iii and iv non-small cell lung cancer

Abstract

Background: In patients with advanced non-small cell lung cancer the priority should be given to controlling symptoms of the disease and thoracic radiotherapy remains an important treatment modality for these patients. The use of shorter radiotherapy schedules has an economic and logistic advantage for radiotherapy departments, as well as a high degree of patient convenience. However there is still no consensus on which fractionation scheme should be used. The aim of the study is to evaluate the effect of hypofractionated regimen (36Gy/12 fractions versus 17Gy/2 weekly fractions regimen) on symptoms relief, assessment of treatment related toxicity and its impact on overall survival (OS) in patients with locally advanced stage III and stage IV non-small cell lung cancer (NSCLC).

Patients and methods: Patients were randomly assigned into two treatment groups: 1, receive 36 Gy per 12 fractions and group 2, receive 17 Gy per two fractions. Assessments by clinician for improvement of symptoms and toxicity were done weekly during radiotherapy, one month, 3 months and every 3 months thereafter. Symptomatic response was assessed by comparing the initial score for each symptom with the best score during follow-up period. A total symptom score (TSS) was produced for each patient, by adding the scores of each individual symptom.

Results: The total symptom scores before radiotherapy was significantly higher to that after radiotherapy (Wilcoxon signed-rank test Z=-6.434, *P*=.0001). The degree and duration of symptom relief were equivalent in the treatment groups. There were no reported cases of grade 3 or 4 esophagitis or pulmonary toxicity. Grade 2 acute esophagitis was greater among patients received 36 Gy/ 12 fractions compared to those received 17 Gy/ 2 fractions (26.3% vs 14%, *P* = .177) but did not reach statistical significance. Two patients (3.5%) experienced grade 2 acute pneumonitis. No significant difference in survival among treatment groups was found (one year OS for group 1, was 22.3% and for group 2, was 20.4%, *P* = .434).

Conclusion: 17Gy/2 weekly fractions regimen, provide good symptomatic relief with comparable survival to 36Gy/12 fractions regimen and should be used for patients requesting a shorter treatment course especially in which palliative chemotherapy is planned.

Keywords: radiotherapy, dose fractionation, non-small cell lung cancer

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Introduction

More than two third of patients with non-small cell lung cancer (NSCLC) presented with advanced stage (III and IV).[1] The majority of patients with unresectable stage III NSCLC are unfit for radical chemoradiotherapy (CRT) either due to the presence of extensive intrathoracic disease, poor performance status or significant comorbidities. Many patients with metastatic lung cancer and locally advanced disease presented with thoracic symptoms such as, cough, dyspnea, chest pain and hemoptysis necessitating thoracic radiotherapy. Thoracic radiotherapy is effective in palliating these symptoms in about 90% of patients with advanced NSCLC.[2-4] There have been 14 published randomized clinical trials evaluating the optimal hypofractionation regimen to palliate symptoms of advanced NSCLC, which are considerably less resource and time intensive.[1,2,5–16] However there is still no consensus on which fractionation scheme should be used. If one assumes an α /β of 2 for late responding tissues, 17 Gy in 2 fractions is the radiobiologic equivalent of 45 Gy in 25 fractions or 36 Gy in 12 fractions by the linear-quadratic formula.[17] Its use in the palliative setting for patients with advanced NSCLC has compared favorably with other regimens in terms of palliation (8-10). Owing to the crowdedness and overloading at our institute, in addition to lack of an effective referral system to our center with limited facilities and services provided for the patients care, 17 Gy in 2 fractions, seems logistic , as it alleviate the crowdedness and overloading at our institute and radiotherapy machine which in turn reduce the waiting time. Therefore there was a need to assess the effect of 2 hypofractionated regimens (Group 1: 36 Gy/ 12 fractions versus Group 2: 17 Gy in 2 weekly fractions) of palliative thoracic radiotherapy on improving thoracic symptoms, evaluation of short and long term toxicities and assess the impact of these 2 hypofractionated regimens on overall survival (OS) in patients with advanced NSCLC.

Patients and methods

Eligibility criteria

I. Patients with histologically or cytologically proven NSCLC.

II. Age ≥ 18.

III. Stage III and IV NSCLC. Among patients with stage III disease, only those who are unsuitable for CRT (disease extend, where the volume of the lung encompassed by radiotherapy plans for 60 Gy were considered unacceptable, concurrent medical illness or poor prognostic factors such as tumor diameter ≥7 cm, Karnofsky PS ≤ 70%, or weight loss ≥ 10% during the last 6 months).

The ethics committee approved the study protocol, and a written informed consent was obtained from all patients before random assignment to treatment.

Clinical examination and staging

Complete initial staging before radiotherapy was done including, clinical examination, bronchoscopy, chest computerized tomography (CT) scan, upper abdominal and brain CTs, bone scan, and laboratory tests. Patients were assessed on admission by the clinician for performance status, symptoms (dyspnea, cough, and hemoptysis, dysphagia and anorexia) and the severity of these symptoms.

Treatment

Patients were randomized into two groups:

1. Group 1: 36 Gy/ 12 fractions
2. Group 2: 17 Gy in 2 weekly fractions

Planning target volume included, the gross macroscopic disease plus 1.5-2 cm margin. An isocentric technique was used in all patients and the dose was prescribed at the isocenter. Dose specified at the midplane on the central axis. Two opposing anterior-posterior fields were used. Megavoltage radiotherapy with a 6- or 15-MV photon beam was used.

Follow up

During treatment, patients were followed up weekly, for toxicities (short term toxicity, within 90 days and long term toxicity, > 90 days) using National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0[18] and disease related symptoms. After radiotherapy, patients were followed-up 1, 3 months and every 3 months thereafter. Follow-up examinations included detailed history, clinical examination, blood tests, as well as chest radiograph. The symptoms assessed included cough, hemoptysis, dyspnea, chest pain, fatigue and anorexia; a four-degree categorical scale was used for each of the main symptoms: 0= none, 1=mild, 2=moderate, and 3=severe. Palliation of a symptom was defined as disappearance of the symptom or improvement of the initial symptom one or more categories (from mild to none, from moderate to mild or none, or from severe to moderate, mild, or none), during follow-up time. A total symptom score (TSS) was produced for each patient, by adding the scores of each individual symptom. Daily assessment of symptoms during the course of radiotherapy by the patients was not done due to poor compliance of the patients. All patients were observed until death or at the last follow-up time for symptomatic control.

Statistics

Categoric variables were analyzed using the chi-squared tests. Statistical analysis was undertaken using the Wilcoxon signed-rank test. Overall survival (OS) was calculated from randomization date to the date of death from any cause or to the date of the last follow-up using the Kaplan-Meier estimate.[19] Survival data between groups were compared with the Log rank test for univariate analysis. A two-sided $P<.05$ was considered statistically significant. All analyses performed using the Statistical Package for Social Sciences software, SPSS, version 18.0 (SPSS inc. Chicago, Illinois, USA).

Results

Between March 2013 and March 2015, 57 newly diagnosed stage III and IV NSCLC patients were treated at Radiotherapy Department, South Egypt Cancer Institute, Assiut University and Clinical Oncology Department, Assiut University, Egypt. Of the 57 patients, 31 patients (54.4%) received 36 Gy/12 fractions of radiotherapy and assigned as group 1, while 26 patients (45.6%) received 17 Gy/2 weekly fractions of radiotherapy and assigned as group 2.

Patient characteristics

Patient characteristics are summarized in Table 1. The two groups were well-matched with no statistical significance in terms of baseline characteristics. The most common presenting symptom was cough; constituted 91.2%. All patients had two or more symptoms at baseline. According to assessment of the clinician, all symptoms were significantly palliated with variable proportions in both treatment groups. The total symptom scores before radiotherapy was significantly higher to that after radiotherapy (Wilcoxon signed-rank test Z=-6.434, P=.0001). Both regimens were effective in controlling symptoms with no significant difference as regard the degree of symptoms relief (Table 2). The duration of palliation was assessed by the clinician with no significant difference in the duration of palliation of symptoms between treatment groups (Table 3).

Table 1 Patients characteristics according to assigned treatment

	Group 1 (36Gy/12Fractions) 31 (100%)	Group 2 (17Gy/2Fractions) 26 (100%)	Total 57 (100%)	*P*-value
Age				
Median	64	65	64	0.28
Range	40-76	45-77	40-77	
Sex				
Male	30 (96.8)	24 (92.3)	54 (94.7)	0.452
Female	1 (3.2)	2 (7.7)	3 (5.3)	
Karnofsky performance Status				
Median	80	70	80	
Range	50-90	40-90	40-90	0.096
Weight loss				
None	12 (38.7)	4 (15.4)	16 (28.1)	
≤ 10	9 (29)	13 (50)	22 (38.6)	0.112

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Table Continued...

	Group 1 (36Gy/12Fractions)	Group 2 (17Gy/2Fractions)	Total	*P*-value
	31 (100%)	26 (100%)	57 (100%)	
> 10	10 (32.3)	9 (34.6)	19 (33.3)	
Histology				
Squamous cell carcinoma	27 (87.1)	25 (96.2)	52 (91.2)	0.229
Adenocarcinoma	4 (12.9)	1 (3.8)	5 (8.8)	
Stage				
IIIA	1 (3.2)	3 (11.5)	4 (7)	
IIIB	8 (25.8)	6 (23.1)	14 (24.6)	0.472
IV	22 (71)	17 (65.4)	39 (68.4)	
Symptoms				
Cough				
None	3 (9.7)	2 (7.7)	5 (8.8)	
Mild	14 (45.2)	11 (42.3)	25 (43.9)	0.926
Moderate	11 (35.5)	9 (34.6)	20 (35.1)	
Sever	3 (9.7)	4 (15.4)	7 (12.3)	
Dyspnea				
None	19 (61.3)	10 (38.5)	29 (50.9)	
Mild	6 (19.4)	6 (23.1)	12 (21.1)	0.328
Moderate	4 (12.9)	6 (23.1)	10 (17.5)	
Sever	2 (6.5)	4 (15.4)	6 (10.5)	
Hemoptysis				
None	22 (71)	16 (61.5)	38 (66.7)	
Mild	5 (16.1)	5 (19.3)	10 (17.5)	0.883
Moderate	3 (9.7)	4 (15.4)	7 (12.3)	
Sever	1 (3.2)	1 (3.8)	2 (3.5)	
Chest pain				
None	8 (25.8)	6 (23.1)	14 (24.6)	
Mild	12 (38.7)	10 (38.5)	22 (38.6)	0.792
Moderate	10 (32.3)	10 (38.5)	20 (35.1)	
Sever	1 (3.2)	0	1 (1.8)	
Fatigue				
None	6 (19.4)	2 (7.7)	8 (14)	
Mild	12 (38.7)	12 (46.2)	24 (42.1)	0.591
Moderate	11 (35.5)	11 (42.3)	22 (38.6)	
Sever	2 (6.5)	1 (3.8)	3 (5.3)	
Anorexia				
None	6 (19.4)	3 (11.5)	9 (15.8)	
Mild	13 (41.9)	11 (42.3)	24 (42.1)	0.693
Moderate	12 (38.7)	12 (46.2)	24 (42.1)	
Sever	0	0	0	

Table 2 Response of each symptom to radiotherapy

Symptoms	Number of patients presented with symptoms	Patients in whom symptoms palliated (%)	Patients in whom symptoms disappeared (%)
Cough			
36Gy/12fr	28	22 (78.6)	14 (50)
17Gy/2fr	24	20 (83.3)	11(45.8)
Dyspnea			
36Gy/12fr	12	9 (75)	6 (50)
17Gy/2fr	16	11 (68.8)	6 (37.5)
Hemoptysis			
36Gy/12fr	9	6 (66.7)	5 (55.6)
17Gy/2fr	10	6 (60)	5 (50)
Chest pain			
36Gy/12fr	23	17 (73.9)	9 (39.1%)
17Gy/2fr	20	14 (70)	9 (45)
Fatigue			
36Gy/12fr	25	13 (52)	6 (24)
17Gy/2fr	24	14 (58.3)	11 (45.8)
Anorexia			
36Gy/12fr	25	11 (44)	11(44)
17Gy/2fr	23	13 (56.5)	7 (30.4)

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Table 3 The duration of palliation of symptoms

Variable	Median days of improvement of symptoms	Range	*P*-value
Cough			
36Gy/12 Fractions	89	31-180	0.097
17Gy/2 Fractions	78	33-167	
Dyspnea			
36Gy/12 Fractions	100	31-180	0.096
17Gy/2 Fractions	79	24-160	
Hemoptysis			
36Gy/12 Fractions	77	30-163	0.857
17Gy/2 Fractions	75	28-157	
Chest pain			
36Gy/12 Fractions	87	30-180	0.179
17Gy/2 Fractions	67.5	28-144	
Fatigue			
36Gy/12 Fractions	82	30-180	0.784
17Gy/2 Fractions	81.5	33-157	
Anorexia			
36Gy/12 Fractions	77	30-129	0.853
17Gy/2 Fractions	67	28-157	

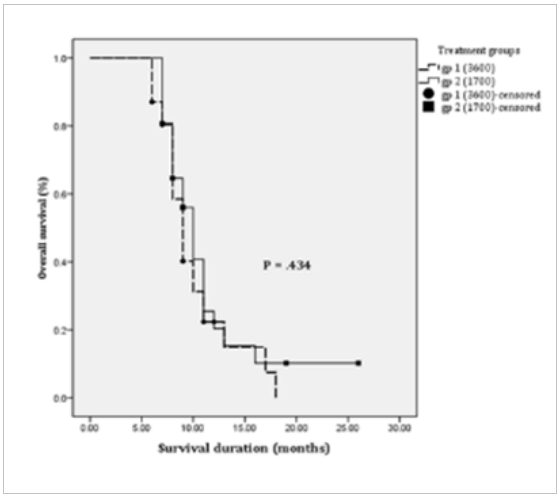

Figure 1 Kaplan-Meir analysis of overall survival per treatment groups.

Toxicity

According to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0,[19] there were no reported cases of grade 3 or 4 esophagitis or pulmonary toxicity. Regarding acute toxicity, 40.4% of patients (n=23) experienced grade 2 acute esophagitis. Although grade 2 acute esophagitis was greater among patients received 36 Gy/ 12 fractions (n=15, 26.3%) compared to those received 17 Gy/ 2 fractions (n=8, 14%), but did not reach statistical significance (*P* = .177). Two patients (3.5%) experienced grade 2 acute pneumonitis; both of them received 36 Gy/ 12 fractions. There were no reported cases of radiation myelopathy.

Survival

The median survival time was 9 months (rang, 6-26 months). There was no significant difference in survival between treatment groups; one year OS for group 1was 22.3% and for group 2 was 20.4% with *P* value of .434 (Figure 1). Other factors such as, age, sex, karnofsky performance status, tumor histology and stage were not significant prognostic factor for OS.

Discussion

Thoracic radiotherapy 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. A variety of fractionation schedules, ranging from 10 Gy per one fraction to 60 Gy per 30 fractions, are used in clinical practice.20 However, there is a debate about the optimal fractionation scheme to be used; some randomized studies favor a hypofractionation treatment policy,[6–8,10] others do not recommend hypofractionation because of the increased toxicity and/or reduced survival.[5,6,11,13] In the present study, as recorded by clinicians, there was similar degree of palliation of all symptoms in the two treatment groups with disappearance of symptoms in substantial proportions of patients. Similary, a Cochrane analysis19 of 10 randomized palliative radiotherapy trials indicated that the degree of symptom relief was equivalent regardless of the total radiotherapy dose. In contrast, a study conducted by the National Cancer Institute of Canada,[13] found that patients treated with fractionated radiotherapy (20 Gy), had greater improvement in symptoms, ability to carry out normal activities, and better global quality of life than patients treated with single fraction of 10 Gy. Bezjak et al.[13] and Erridge et al.[15] reported better palliation with higher dose and more fractionated regimen.

The median duration of palliation reported by our study, was slightly longer in patients received higher dose regimen although did not reach a statistical significance. In the 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.[15] 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,[6] 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.[10] noted that only one symptom (hemoptysis), was improved in more than 50% of patients at eighth weeks with no difference in degree and duration of

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relief of other symptoms. A consistent finding in the studies is that higher equivalent doses of radiotherapy are associated with more acute side effects.[1,6,7,9] Our study revealed similar results; the two-fraction regimen was associated with dysphagia due to esophagitis. Grade 2 acute esophagitis was greater among patients received 36 Gy/ 12 fractions (n=15, 26.3%) compared to those received 17 Gy/ 2 fractions (n=8, 14%), but did not reach statistical significance (P = .177). Two patients (3.5%) developed grade 2 pnumonitis and both of them received 36Gy/12 fractions. In the MRC trial 1991,[6] dysphagia reported by the clinicians occurred in 25% of patients received 17Gy in 2 weekly fractions regimen and 17% of single fraction group since the pretreatment assessment. Sundstrom 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 2 fractions regimen. In our study, there was no reported cases of radiation myelitis following the use of both regimens. In contrast, MRC trials, 1991, 1992, and 1996,[6,7,9] reported radiation myelitis following the use of 17Gy/2 fractions and 39Gy/13 fractions. Sundstrom et al.1 reported one case of radiation myelitis following the use of 50Gy/25F.

In our study, the median survival was 9 months and one year overall survival for group 1 was 22.3% and for group 2 was 20.4%. There was no significant difference in one year OS between both groups (P = .434). Similar finding was reported by Abratt et al.[8] MRC 19969 and Simpson et al.2 they reported median survival of 6.[3–9] months.[20] Macbeth & Stephens[21] grouped 13 of 14 trials based on the radiobiological equivalency (RBE). Patients were stratified into 3 groups, 1) RBE-equivalent regimens in all groups of patients, 2) RBE-equivalent regimens in patients with poor performance status and 3) RBE-differing regimens in better performance status patients. For group 1, they found similar efficacy and survival irrespective of radiation regimen. For group 2, they concluded that a single 10-Gy fraction is an effective treatment although, for group 3, they found 2 trials[9,11] with significantly better survival for high dose (30-Gy/10-fraction equivalent or greater) radiation regimens. A study conducted by Sundstrøm et al.[1] revealed no significant survival difference among the treatment groups (P = .83). In contrast, Fairchild et al.[22] 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, 36-45Gy/12-15 fractions, or 50-60 Gy/25-30 fractions).

Conclusion

Hypofractionated regimen of 17Gy/2 weekly fractions is as effective at providing symptomatic relief and yield equivalent survival as 36Gy/12 fractions. Therefore, based on the promising results of our study, we recommend treatment of patients with advanced non-small cell lung cancer and thoracic symptoms, with short courses of palliative hypofractionated regimen as it has the advantage of fewer visits to hospital and reduced workload for radiotherapy department. In addition, shorter fractionation schedules will be more easily integrated between chemotherapy cycles for patients with thoracic symptoms.

Author contributions

AM Attia: design and planning the research article, interpreting the data, writing and critical revision of the article.

MI Abdelgwad: contribute in the design of the research article and revision of the article.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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