

# A Prospective Study of the Effect of Different Palliative Radiotherapy Fractionation Schedules on Tumor Response and Toxicity in Advanced Non-Small Cell Lung Cancer (NSCLC) Patients

Mohamed Lotayef<sup>1</sup>, Yaser Abd Elkader<sup>2</sup>, Amr Amin<sup>1\*</sup>, Azza Taher<sup>1</sup>, Ehab El-Kest<sup>1</sup>, Momen Abdelall<sup>1</sup>

<sup>1</sup>Radiation Oncology and Nuclear Medicine Department, National Cancer Institute, Cairo University, Giza, Egypt

<sup>2</sup>Clinical Oncology Department, Faculty of Medicine, Cairo University, Giza, Egypt

Email: \*amr.amin@nci.cu.edu.eg

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## Abstract

**Background:** The optimal dose of palliative radiotherapy (RT) in symptomatic advanced lung cancer is unclear. **Patients and methods:** Patients with advanced NSCLC who were indicated for thoracic palliative RT with age up to 65 y and Performance Status (PS) 0 - 2 and no significant cardiac or lung co-morbidities were randomized into two fractionation arms: arm A: 30 Gy/10 over 2 weeks and arm B: 27 Gy/6 over 3 weeks (2 fractions per week) using 2 anterior posterior (AP-PA) fields in both arms. Primary end points were symptomatic and radiological tumor response, respiratory functions assessment. Secondary end point was toxicity. **Results:** From December 2014 to October 2015, 40 patients were randomized, 20 patients in each arm. There was statistically insignificant higher symptomatic improvement in arm B. Four weeks after treatment, 12 out of 40 patients (30%), 6 patients in each arm, had radiological Partial Response (PR) of the primary thoracic lesion without significant difference between the two arms. There was a tendency for improvement in the post treatment mean Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) in each arm without statistical significance. There were no reported skin reactions or esophagitis in both arms up to 4 weeks after treatment. Eleven out of the 40 patients (27.5%), 6 in arm B and 5 in arm A, had radiological signs of radiation pneumonitis without significant difference between both arms. **Conclusion:** The two RT fractionation schedules showed equal efficacy in terms of symptoms relief, radiological response of the primary thoracic tumor, respiratory functions and toxicity. Thus the 27 Gy/6 fractionation arm appears preferable compared to 30 Gy/10 arm to minimize the patients' visits and load on the machines.

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## Keywords

Non-Small Cell Lung Cancer, Palliative Thoracic Radiation, Fractionation Schedules, Symptoms, Randomized Trial

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## 1. Introduction

According to World Health Organization (WHO), lung cancer is the most common cancer worldwide, accounting for 1.8 million new cases and 1.6 million deaths in 2012. In Egypt in 2013, the estimated number of lung cancer cases constituted 4.2% from total cancer cases in combined gender. In males, lung cancer cases constituted about 5.7% of total malignancies compared to 2.7% in females [1].

Primary carcinomas of the lung are traditionally classified as either Small Cell Lung Cancer (SCLC) or Non-Small Cell Lung Cancer (NSCLC). NSCLC constitutes approximately 80% of all primary lung cancers. Adenocarcinoma, Squamous Cell Carcinoma (SCC) and Large Cell Carcinoma (LCC) constitute the major histological types [2]. The primary reason that most patients with lung cancer present with advanced stage disease is that early-stage disease does not usually cause significant symptoms, especially when arising in the periphery of the lung [3].

The main goals of treatment in advanced NSCLC patients are prolongation of life, palliation of symptoms and improvement of Quality Of Life (QOL) [4]. Early initiation of palliative care for advanced or metastatic NSCLC can reduce symptoms, improve QOL, and prolong survival [5].

Treatment decisions should ideally be discussed within a multidisciplinary tumor board. Systemic therapy should be offered to all stage IV NSCLC patients with a PS 0 - 2. In any stage of NSCLC, smoking cessation should be highly encouraged because it improves the outcome [6]. Radiotherapy is often used as a palliative treatment for patients with stage IV NSCLC to relieve symptoms (*i.e.* hemoptysis, cough, chest pain, dyspnea, etc.) that are caused by loco-regional growth of primary tumor [7].

A comprehensive review involving 14 randomized clinical trials, all related to different dose schedules to palliate the symptomatic primary lung cancer, was performed by the Cochrane Collaboration [8]. In general, the results of those trials suggest that there are no significant differences among short compared to long radiotherapy regimens in terms of palliation, but higher-dose regimens were associated with mild increase in acute toxicity, particularly esophagitis. However, the studies were not homogeneous with different assessment end points and the reviewers did not make a clear conclusion on the ideal regimen of palliative radiation treatment. In fact, in clinical practice, depending on the institution, different doses and fractionations regimens are being used for similar clinical situations [9].

## Aim of the Study

This study is a prospective randomized study to compare the effect of two RT schedules

for thoracic palliation in advanced NSCLC patients (30 Gy in 10 fractions over two weeks and 27 Gy in 6 fractions over three weeks, 2 fractions per week) on improvement of pulmonary symptoms, respiratory functions, radiological response of the primary thoracic tumor and toxicity.

## **2. Patients and Methods**

### **2.1. Patients**

Patients with advanced NSCLC who presented to radiation oncology department, National Cancer Institute, Cairo University for palliative irradiation to the lung From December 2014 to October 2015 were studied for eligibility. Patients younger than 65 years with World Health Organization (WHO) PS up to 2 and expected survival of at least 3 months were eligible. Patients with significant cardiac disease, pleural effusion and known asthmatic patients or those with history of previous radiotherapy to chest region were excluded.

### **2.2. Methods**

#### **2.2.1. Randomization**

Eligible patients were randomized into two fractionation arms: 30 Gy in 10 fractions over two weeks and 27 Gy in 6 fractions over three weeks (two fractions per week).

#### **2.2.2. Assessment**

Was done pretreatment and 4 weeks after end of RT in the form of:

1) Full history taking and complete physical examination. Symptomatic assessment according to a 4-point scale (none, mild, moderate, severe). Palliation of a symptom was defined as disappearance or improvement of the initial symptom one or more degree along the scale. Acute Toxicity (esophagitis and skin reaction) assessment according to Radiotherapy Oncology Group (RTOG) Acute Radiation Morbidity.

2) Complete blood count (CBC).

3) Respiratory function testing: FVC and FEV<sub>1</sub>.

4) CT chest with contrast: to assess radiological tumor extent initially and response to RT (*longest diameter was recorded*) and radiation pneumonitis. Assessment of tumor response was done according to: New Response Evaluation Criteria In Solid Tumors: Revised (RECIST) guideline version 1.1 [10].

#### **2.2.3. RT Technique**

The patients in both arms were simulated in the supine position with arms up. Geeral Electric computerized tomography simulator (CT-simulator) light speed 1017CT02 was used for the simulation. All patients were treated with 2 dimensional (2D) RT technique with two parallel opposing (AP-PA) iso-centric fields. The treatment portals were extended 2 cm around the gross disease.

#### **2.2.4. Several End Points Were Assessed**

Primary end points encompassing palliation of chest tumor related symptoms, respira-

tory functions: FVC and FEV1 and radiological response of the primary thoracic tumor. Whereas the secondary end point aimed at comparing the treatment side effects relative to each fractionation arm.

### 2.2.5. Statistical Methods

The continuous variables were summarized by descriptive data (*i.e.*, mean, standard deviation (SD), frequencies). Mean values were compared using simple t test. Percentages were compared using Chi-square test. *P* value less than 0.05 was considered statistically significant.

## 3. Results

This study included forty Patients with advanced NSCLC who presented to the radiation oncology department, National Cancer Institute, Cairo University-from December 2014 to October 2015 for palliative irradiation to the lung. The patients were randomized into two fractionation arms 20 patients in each arm: 30 Gy in 10 fractions over two weeks (arm A) and 27 Gy in 6 fractions over three weeks, two fractions per week (arm B).

### 3.1. Patients Criteria

Both arms were well balanced regarding age, sex, smoking habit, co morbidity, weight loss before radiation, HB level and PS (**Table 1**).

#### Clinical Presentation

Cough was the most common complaint (90%) followed by pain (85%), dyspnea (60%) and haemoptysis (50%). There was no significant difference between the two treatment arms in the incidence or the degree of thoracic symptoms (**Table 2** and **Table 3**).

### 3.2. Disease Criteria

Both arms were well balanced regarding pathology, stage and the field size.

#### 3.2.1. Pathology

Adenocarcinoma was the most common pathology type, followed by SCC and lastly large cell carcinoma (**Figure 1**). There was no significant difference between the two treatment arms in pathological types (*P* value = 0.80).

#### 3.2.2. Stage

Majority of patients in both arms were stage IV representing all patients in arm A compared to 18 patients (90%) in arm B while the remaining 2 patients (10%) were stage IIIB without significant difference (*P* value = 0.49) (**Figure 2**). Among the 38 patients who were stage IV, 11 (28.94%), 10 (26.31%), 7 (18.42%), 6 (15.7%), 4 (10.52%) had metastasis in bone, lung, brain, adrenal gland, and liver, respectively.

#### 3.2.3. Field Size

No significant difference was found in the mean field size between both arms (arm A:

**Table 1.** Patients criteria in both arms.

| Criteria   | No. of Patients (%) |                   |                       | P value |
|--|---------------------|-------------------|-----------------------|---------|
|  | Arm A<br>(20 pts)   | Arm B<br>(20 pts) | Total pts<br>(40 pts) |         |
| <b>Age</b>   |                     |                   |                       |         |
| Range  | 50 - 65 y           | 40 - 64 y         | 40 - 65 y             | 0.15    |
| Mean   | 59.80 y             | 57 y              | 58.40 y               |         |
| <b>Sex</b>   |                     |                   |                       |         |
| Male   | 20 (100%)           | 18 (90%)          | 38 (95%)              | 0.49    |
| Female   | 0 (0%)              | 2 (10%)           | 2 (5%)                |         |
| <b>Smoking habit</b>   |                     |                   |                       |         |
| <b>Smoker</b>  | 20 (100%)           | 18 (90%)          | 38 (95%)              | 0.49    |
| <b>Median years of smoking</b>                                 | 30 y                | 30 y              | 30 y                  | 0.61    |
| <b>Cessation of smoking</b>                                    | 19 (95%)            | 17 (94.4%)        | 36 (90%)              | 0.41    |
| <b>Diabetes Mellitus (DM)</b>                                  |                     |                   |                       |         |
| <b>DM</b>  | 2 (10%)             | 3 (15%)           | 5 (25%)               | -----   |
|  | 2 (10%)             | 3 (15%)           | 5 (12.5%)             |         |
| <b>Hypertension (HTN)</b>                                      |                     |                   |                       |         |
|  | 3 (15%)             | 4 (20%)           | 7 (17.5%)             |         |
| <b>Weight loss more than 5% before radiation</b>               |                     |                   |                       |         |
|  | 12 (60%)            | 10 (50%)          | 22 (55%)              | 0.75    |
| <b>Hemoglobin (HB)</b>   |                     |                   |                       |         |
| Range  | 9.8 - 13.7 mg/dl    | 10.3 - 13.9 mg/dl | 9.8 - 14.6 mg/dl      | 0.12    |
| Mean   | 12.3 mg/dl          | 12.7 mg/dl        | 12.52 mg/dl           |         |
| <b>World Health Organization (WHO) Performance Status (PS)</b> |                     |                   |                       |         |
| 1  | 11 (55%)            | 10 (50%)          | 21 (52.5%)            | 0.75    |
| 2  | 9 (45%)             | 10 (50%)          | 19 (47.5%)            |         |

**Table 2.** The pretreatment thoracic symptoms in both arms.

|                              |                    | Arm A         | Arm B         | Total        | P value |
|------------------------------|--------------------|---------------|---------------|--------------|---------|
|                              |                    | No. of pt (%) | No. of pt (%) | No. of pt(%) |         |
| <b>Clinical presentation</b> | <b>Cough</b>       | 17 (85%)      | 19 (95%)      | 36 (90%)     | 0.29    |
|                              | <b>Pain</b>        | 18 (90%)      | 16 (80%)      | 34 (85%)     | 0.38    |
|                              | <b>Dyspnea</b>     | 12 (60%)      | 12 (60%)      | 24 (60%)     | 1       |
|                              | <b>Haemoptysis</b> | 8 (40%)       | 12 (60%)      | 20 (50%)     | 0.21    |

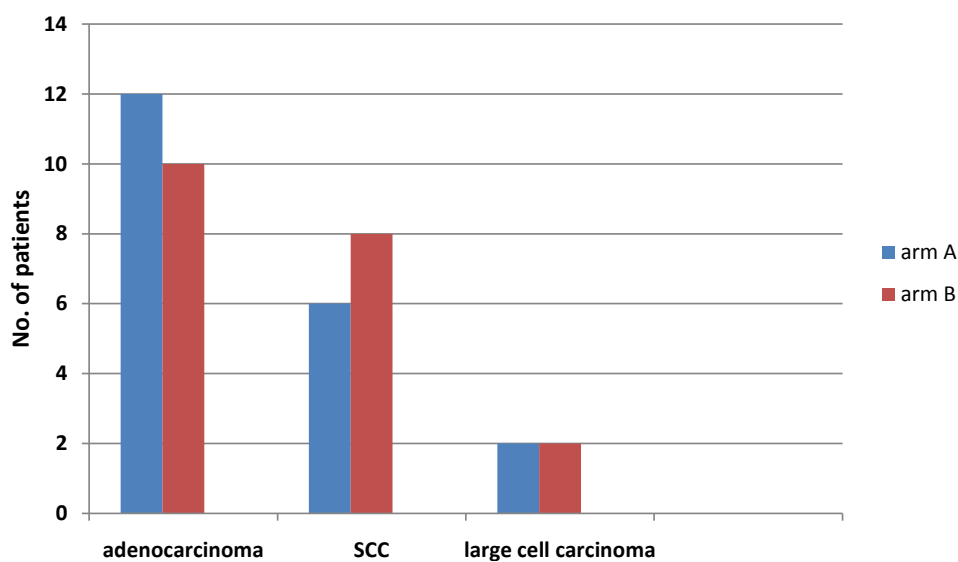
mean 148 cm<sup>2</sup>, with range 100 - 220 cm<sup>2</sup>; arm B: mean 142 cm<sup>2</sup>, with range 85 - 215 cm<sup>2</sup>; P value = 0.48).

### 3.3. Chemotherapy Criteria

The Mean number of chemotherapy cycles in each arm was 5. Platinum based regimens were the most frequent regimens, 3 patients in arm A didn't receive chemotherapy because of impaired renal functions. No significant difference was found between both

**Table 3.** The initial severity of the pretreatment thoracic symptoms in both arms.

| Symptom           | Arm A<br>No. of patients (%) | Arm B<br>No. of patients (%) | P value |
|-------------------|------------------------------|------------------------------|---------|
| <b>Cough</b>      |                              |                              |         |
| non               | 3 (15%)                      | 1 (5%)                       | 0.67    |
| mild              | 9 (45%)                      | 8 (40%)                      |         |
| moderate          | 6 (30%)                      | 8 (40%)                      |         |
| severe            | 2 (10%)                      | 3 (15%)                      |         |
| <b>Pain</b>       |                              |                              |         |
| non               | 2 (10%)                      | 4 (20%)                      | 0.76    |
| mild              | 8 (40%)                      | 6 (30%)                      |         |
| moderate          | 6 (30%)                      | 7 (35%)                      |         |
| severe            | 4 (20%)                      | 3 (15%)                      |         |
| <b>Dyspnea</b>    |                              | 8 (40%)                      |         |
| non               | 8 (40%)                      | 4 (20%)                      | 0.85    |
| mild              | 5 (25%)                      | 7 (35%)                      |         |
| moderate          | 5 (25%)                      | 1 (5%)                       |         |
| severe            | 2 (10%)                      | 1 (5%)                       |         |
| <b>Hemoptysis</b> |                              |                              |         |
| non               | 12 (60%)                     | 8 (40%)                      | 0.51    |
| mild              | 4 (20%)                      | 6 (30%)                      |         |
| moderate          | 4 (20%)                      | 5 (25%)                      |         |
| severe            | 0 (0%)                       | 1 (5%)                       |         |

**Figure 1.** Pathology in both arms.

arms regarding the response to chemotherapy (P value = 0.73) (**Table 4**).

### 3.4. The Effect of Both Fractionation Arms on Thoracic Symptoms

The number of patients achieving improvement in symptoms (namely cough chest pain, dyspnea or hemoptysis) or in performance status was higher in the arm B, but did

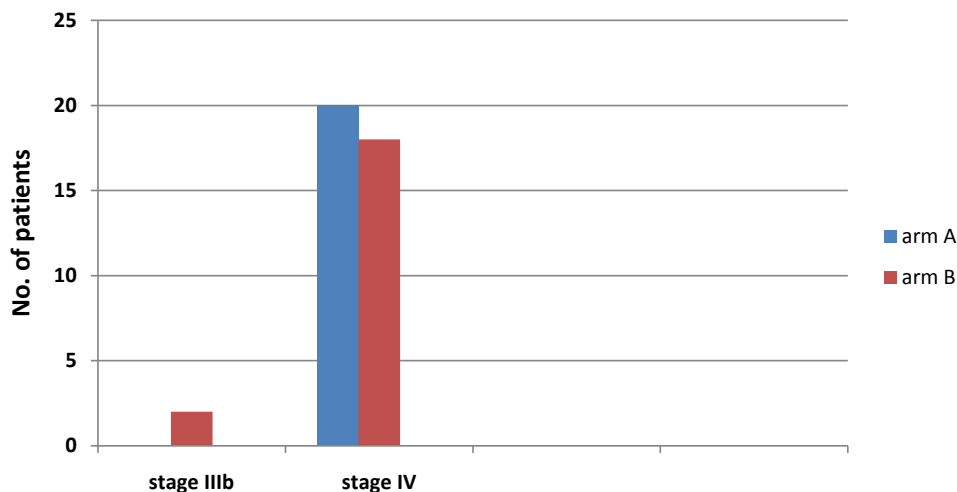


Figure 2. Stage of patients in both arms.

Table 4. Chemotherapy criteria in both arms.

| Criteria                        | Arm A<br>No. of pts (%) | Arm B<br>No. of pts (%) | Total pts<br>No. of pts (%) | P value |
|---------------------------------|-------------------------|-------------------------|-----------------------------|---------|
| <b>Chemotherapy given</b>       | 17 (85%)                | 20 (100%)               | 37 (92.5%)                  | 0.072   |
| <b>Response to chemotherapy</b> |                         |                         |                             |         |
| Progressive Disease (PD)        | 11 (64.7%)              | 14 (70%)                | 25 (67.5%)                  | 0.73    |
| Stable Disease (SD)             | 6 (35.2%)               | 6 (30%)                 | 12 (32.5%)                  |         |

not reach statistical significance for any symptom (Table 5).

### 3.5. The Effect of Both Fractionation Arms on Radiological Response of Chest Tumor

The mean longest tumor diameter recorded in pre treatment CT was 7.12 cm in arm A compared to 7.45 cm in arm B without significant difference (P value = 0.68).

Four weeks after treatment, no significant difference was found between both arms in radiological response of the primary thoracic tumor (P value = 0.64) (Table 6).

### 3.6. The Effect of Both Fractionation Arms on Respiratory Functions

FVC and FEV1 were presented as percentage (%) of actual from predicted value (actual/predicted).

At base line, patients in both arms had comparable mean FVC and FEV1 (Table 7).

Four weeks after treatment, there was a tendency for improvement in the mean of FVC and FEV1 compared to the pre treatment mean values, however this improvement didn't reach statistical significance in each arm (Table 8). Post treatment mean values of FVC and FEV1 were higher in arm B than arm A without significant difference (Table 9).

**Table 5.** The effect of both fractionation arms on thoracic symptoms and PS.

|                                | Arm A<br>No. of pts (%) | Arm B<br>No. of pts (%) | P value |
|--------------------------------|-------------------------|-------------------------|---------|
| <b>Cough</b>                   |                         |                         |         |
| Improvement                    | 10/17 (58.82%)          | 13/19 (68.42%)          | 0.41    |
| Progression                    | 4/17 (23.5%)            | 3/19 (15.7%)            |         |
| SD                             | 3/17 (17.6%)            | 3/19 (15.7%)            |         |
| <b>Pain</b>                    |                         |                         |         |
| Improvement                    | 13/18 (72.2%)           | 15/16 (93.75%)          | 0.27    |
| Progression                    | 3/18 (16.6%)            | 1/16 (6.2%)             |         |
| SD                             | 2/18 (11.11%)           | 0/16 (0.0%)             |         |
| <b>Dyspnea</b>                 |                         |                         |         |
| Improvement                    | 5/12 (41.66%)           | 6/12 (50%)              | 0.57    |
| Progression                    | 4/12 (33.33%)           | 3/12 (25%)              |         |
| SD                             | 3/12 (25%)              | 3/12 (25%)              |         |
| <b>Haemoptysis</b>             |                         |                         |         |
| Improvement                    | 6/8 (75%)               | 10/12 (83.33%)          | 0.81    |
| Progression                    | 1/8 (12.5%)             | 0/12 (0.0%)             |         |
| SD                             | 1/8 (12.5%)             | 2/12 (16.66%)           |         |
| <b>Performance Status (PS)</b> |                         |                         |         |
| Improvement                    | 10/20 (50%)             | 12/20 (60%)             | 0.75    |
| Stable                         | 10/20 (50%)             | 8/20 (40%)              |         |

**Table 6.** The effect of both fractionation arms on radiological response of chest tumor.

|   |    | Arm                     |                            | Total<br>No. of pts<br>(%)<br>No. of pts<br>(%) | P<br>value |
|---|----|-------------------------|----------------------------|---|------------|
|   |    | Arm A<br>No. of pts (%) | Arm B<br>No. of pts<br>(%) |   |            |
| <b>Radiological response of chest tumor 4 weeks after treatment</b> | PR | 6 (30%)                 | 6 (30%)                    | 12 (30%)  | 0.64       |
|   | SD | 12 (60%)                | 14 (70%)                   | 26 (65%)  |            |
|   | PD | 2 (10%)                 | 0 (0.0%)                   | 2 (5%)  |            |

**Table 7.** Pretreatment FEV1 and FVC in both arms.

|         | Pre treatment FVC (%) |       |         | Pre treatment FEV1 (%) |       |         |
|---------|-----------------------|-------|---------|------------------------|-------|---------|
|         | Arm A                 | Arm B | P value | Arm A                  | Arm B | P value |
| Mean    | 56.80                 | 56.60 | 0.96    | 53.90                  | 54.40 | 0.95    |
| Minimum | 33                    | 30    |         | 32                     | 30    |         |
| Maximum | 89                    | 92    |         | 92                     | 86    |         |



**Table 8.** The effect of both arms on FVC and FEV1 four weeks after treatment.

|       | Pretreatment Mean FVC (%) | Post treatment Mean FVC (%) | p value | Pretreatment Mean FEV1 (%) | Post treatment Mean FEV1 (%) | P value |
|-------|---------------------------|-----------------------------|---------|----------------------------|------------------------------|---------|
| Arm A | 56.80                     | 59.45                       | 0.24    | 53.90                      | 56.10                        | 0.23    |
| Arm B | 56.60                     | 61.45                       | 0.11    | 54.40                      | 56.40                        | 0.09    |

**Table 9.** Post treatment FEV1 and FVC in both arms.

|         | Post treatment FVC (%) |       |         | Post treatment FEV1 (%) |       |         |
|---------|------------------------|-------|---------|-------------------------|-------|---------|
|         | Arm A                  | Arm B | P value | Arm A                   | Arm B | P value |
| Mean    | 59.45                  | 61.45 | 0.73    | 56.10                   | 56.40 | 0.79    |
| Minimum | 33                     | 30    |         | 32                      | 30    |         |
| Maximum | 89                     | 92    |         | 92                      | 86    |         |

### 3.7. The Effect of Both Fractionation Arms on the Treatment Side Effects

Treatment was generally well tolerated in the two treatment arms. According to RTOG Acute Radiation Morbidity, no reported cases of skin reaction or esophagitis were recorded in both arms up to 4 weeks after treatment. Four weeks after treatment, 11 patients out of 40 (27.5%) had radiological signs of radiation pneumonitis through CT chest. Five patients (25%) in arm A had radiological signs of radiation pneumonitis compared to 6 patients (30%) in arm B without significant difference (P value = 0.68). The radiological finding was a diffuse haziness or fuzziness in areas of the irradiated lung.

## 4. Discussion

The issue of optimal palliative irradiation schedule in advanced symptomatic NSCLC has been a subject of numerous randomized studies (Table 10). There is a debate about the optimal fractionation scheme to be used; some randomized studies favor a hypo fractionation treatment policy [11]. Others do not recommend hypo fractionation because of the increased toxicity and/or reduced survival [12].

In our study the fractionation in arm B 27 Gy/6 over 3 weeks was not used in previous randomized trials and the long overall treatment time was intended to minimize toxicity of short fractionation schedules and it proved same palliation.

In our study, we restricted ECOG PS up to 2 and age up to 65 y. This facilitated respiratory function assessment. In many similar studies patients of any age or PS were included however Simpson *et al.* [15] excluded patients above 75 years. Although age has not been shown to be an independent prognostic factor, it may reflect co-morbidity and give information about case selection [20].

**Table 10.** Some randomized trials of different fractionations used in thoracic palliation of advanced lung cancer.

| Reference                               | No. of pts | Stage or selection criteria                       | Dose (Gy) | No. of fractions and overall treatment period |
|---|------------|---|-----------|---|
| Macbeth <i>et al.</i> 2004 [13]         | 509        | Inoperable non metastatic                         | 17        | 2F in 8 days (1 week apart)                   |
|   |            |   | 39        | 13F over 2 weeks and half                     |
| Sundstorm <i>et al.</i> 2004 [14]       | 421        | Stage III-IV                                      | 17        | 2F in 8 days (1 week apart)                   |
|   |            |   | 42        | 15F over 3 weeks                              |
|   |            |   | 50        | 25F over 5 weeks                              |
| Simpson <i>et al.</i> 1985 [15]         | 409        | Inoperable stage III B                            | 30        | 10F over 2 weeks                              |
|   |            |   | 40        | 20F over 4 weeks                              |
| MRC. 1991 [16]                          | 369        | Inoperable including Metastases-ECOG PS up to 2   | 17        | 2F in 8 days (1 week apart)                   |
|   |            |   | 27        | 6F in 8 days                                  |
|   |            |   | 30        | 10 F in 2 weeks                               |
| Kramer <i>et al.</i> 2005 [7]           | 297        | Stage III-IV                                      | 16        | 2F (1 week apart)                             |
|   |            |   | 30        | 10F over 2 weeks                              |
| MRC. 1992 [17]                          | 235        | Locally advanced including Metastases-PS $\geq 2$ | 17        | 2F (1 week apart)                             |
|   |            |   | 10        | 1F  |
| Besjak <i>et al.</i> 2002 [18]          | 230        | Locally advanced including metastases             | 10        | 1F  |
|   |            |   | 20        | 5F over 1 week                                |
| Rees <i>et al.</i> 1997 [11]            | 216        | Locally advanced including metastases             | 17        | 2F in 8 days (1 week apart)                   |
|   |            |   | 22.5      | 5F over 1 week                                |
| Senkus-Konfeica <i>et al.</i> 2005 [19] | 100        | Locally advanced including metastases             | 20        | 5F over 1 week                                |
|   |            |   | 16        | 2F (1 week apart)                             |

MRC: Medical Research Council. F: fraction(s).

#### 4.1. Radiotherapy Technique

Like most of the previous similar studies, we used relatively simple treatment planning using two AP-PA parallel-opposed fields.

#### 4.2. Symptomatic Assessment

Many studies emphasized the importance of relying (as we did) more on patient self-assessment than on physicians' evaluation, as major differences are observed between results of both these judgments [14] [21].

In the current study, 4 weeks after treatment, pain, hemoptysis, cough and dyspnea

had improved in 82.3%, 80%, 61.1%, 45.8%, of patients, respectively. The number of patients achieving symptomatic improvement was higher in the arm B, but did not reach statistical significance for any symptom. This was similar to other authors [11] [14] [15] [21] [22] who found that the most effectively palliated symptoms were chest pain and haemoptysis. Dyspnea was the least effectively palliated symptom in our study and this is similar to [15] [22] due to irreversible lung damage caused by pulmonary collapse or consolidation. This is in contrast to Attia and Abdelgawad [23] who reported that the most effectively palliated symptoms were dyspnea and cough.

Sundström *et al.* [14] reported equality of 3 arms in thoracic palliation of lung cancer. The arms were: A, 17 Gy in 2 fractions, day 1 and 8 (n = 146); B, 42 Gy in 15 fractions in 3 weeks (n = 145); and C, 50 Gy in 25 fractions in 5 weeks (n = 130). In contrast of our study, there was no limitation of age and PS was 0 - 3. Clinicians' assessments of symptom improvement were at 2, 6, and 14 weeks after completion of treatment. Also Macbeth *et al.* [13] reported that no strong evidence for the superiority of any particular regimen in spite of differences in the radiotherapy regimens, patient characteristics and outcome measures. Senkus-Konefka, *et al.* [19] randomized 100 patients into 2 arms: 20 Gy in 5 daily fractions (arm A: 55 patients) or 16 Gy in 2 fractions, day 1 and 8 (arm B: 45 patients). The grading of symptom intensity was performed using a 4-point scale (none, mild, moderate, severe). No significant differences between study arms were observed.

This idea of non superiority of any particular regimen in thoracic palliation of advanced lung cancer was confirmed by a Cochrane analysis of 10 randomized palliative radiotherapy trials indicated that symptomatic relief was equivalent regardless of the total radiotherapy dose [8].

Van den Hout *et al.* [24] compared two fractionation arms (30 Gy in 10 fraction in 2 weeks and 17 Gy in 2 fractions 1week apart) and reported that arms were equally effective regarding palliation. This is similar to Rees *et al.* [11] who also found that 17 Gy in 2 fractions, day 1 and 8 or 22.5 Gy in five daily fractions had no clinically important differences in efficacy between the two regimens. Similarly, Sourav *et al.* [25] randomly assigned patients to three treatments arms: 1) 17 Gy in 2 fractions, day 1 and 8; 2) 20 Gy in five fractions in one week and 3) 30 Gy in 10 fractions in two weeks. Symptomatic relief was equivalent in all the three arms.

Limited number of studies reported better symptom control between compared regimens. Besjak [18] compared 10 Gy single fraction with 20 Gy in 5 daily fractions and reported that highly significant improvement in symptoms control with the fractionated schedule (five fractions). Erridge *et al.* [26] reported that the 30 Gy in 10 fractions over 2 weeks regimen was significantly better at reducing chest pain and dyspnea compared to 10 Gy single fraction regimen. In addition, a significant improvement in PS with fractionated regimen.

### 4.3. Radiological Tumor Response

In our study, 12 patients (30% - 6 patients in each arm) achieved PR of the primary thoracic lesion 4 weeks after treatment on evaluation by CT chest. This was similar to

MRC. [16] in which 22% of arm A (17 Gy in 2 fractions, day 1 and 8) and 25% of arm B (30 Gy in 10 fractions in 2 weeks or 27 Gy in 6 fractions in 8 days) achieved PR without statistical significant. Senkus-Konefka *et al.* [19] also reported equality between two compared arms (20 Gy in 5 fractions in 1 week and 16 Gy in 2 fractions, day 1 and 8) regarding radiological assessment of primary thoracic lesion by chest X ray 2 weeks after treatment. In this study, 52% and 54% achieved PR in the 5 fractions regimen and the single fraction regimen respectively without significant difference.

#### 4.4. Toxicity

In our study, no dysphagia or skin reaction were reported up to 4 weeks after treatment according to RTOG Acute Radiation Morbidity. This was may be due to good PS and low biological total dose. This is similar to Bezjak [18] who reported mild esophagitis and skin reaction without significant difference between the two treatment arms. This is similar to Lupatelli *et al.* [27] study in which short course palliative radiotherapy in advanced NSCLC was carried out. The regimen was 16 Gy given in 2 fractions, day 1 and 8. Treatment was generally well tolerated, only 4 patients (5%) experienced World Health Organization grade III dysphagia. No reported cases of skin reaction. This is similar to Cross *et al.* [22] who reported no cases of radiation esophagitis or skin reaction in 16 Gy in 2 fractions, day 1 and 8 regimen.

This is in contrast to Rees *et al.* [11] who found that 50% of patients receiving two fractions (17 Gy over 2 fractions, day 1 and 8) and 38% of those having five fractions (22.5 Gy in 5 fractions in 1 week) experienced moderate or severe dysphagia at some time shortly after treatment. Two weeks after treatment, moderate or severe dysphagia was reported by 28% of those receiving two fractions and by 15% of those given five fractions. At 3 weeks after treatment, only 7% of all patients reported moderate/severe dysphagia. Also Tomasz *et al.* [28] reported 100% dysphagia and odonophagia in 125 patients with advanced NSCLC received 20 Gy in 5 fractions in one week. Radiation-induced esophagitis grade 4 was observed in 5 patients (4.0%) and these patients required enteral and parenteral support. This study included patients with poor PS (Karnofsky PS accounted 40% - 30%) and this may be the cause of high rates of morbidity.

In our study, 11 patients (27.5%) had radiological signs of radiation pneumonitis. Five patients (25%) in arm A has radiological signs of radiation pneumonitis compared to 6 patients (30%) in arm B with no significant difference. This is in contrast to Nestle *et al.* [12] study in which 152 patients were randomized to receive conventionally fractionated (arm A: 60 Gy in 30 fractions over 6 weeks, number of patients: 79) or short-term accelerated treatment (arm B: 32 Gy, 2 Gy bid in 8 days; number of patients: 73). Sixty five % of patients had clear or equivocal radiological signs of pulmonary radiation injury 6 weeks after treatment. Such a high incidence in this study can be easily linked to much higher RT doses used.

#### 5. Conclusion

Our study confirmed the equal efficacy of the two palliative lung cancer radiotherapy

schedules (30 Gy/10 fractions/2 weeks regimen and 27 Gy/6 fractions/3 weeks, 2 fractions per week regimen) in terms of palliative effect, radiological response of the primary thoracic tumor, respiratory functions and toxicity. Thus we intend to implement this regimen on a bigger number of study group patients with longer follow up to validate it to become a suitable alternative in our busy department.

### Limitations of the Study

Small number of patients in each randomization arms and short follow up.

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