A Prospective, Randomized Study to Compare Two Palliative Radiotherapy Schedules in Advanced Non-small Cell lung Cancer (Stage IV)

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Abstract
Introduction: Lung cancer is the most commonly diagnosed cancer worldwide and causes approximately 1–2 million deaths per year. Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung cancer cases, presenting as locally advanced disease in approximately 25–30% of cases and as metastatic disease in approximately 40–50% of cases.

Aim of the work: The aims & objectives of this study was to study the improvement in Health Related Quality Of Life, treatment related side-effects and overall survival.

Patients and Methods: A prospective clinical study included 60 patients who were randomly assigned into two groups; group (A) 30 patients received RT regimen of 5 fractions of 4 Gy over 2 weeks to a total dose of 30 Gy, and group (B) 30 patients received RT regimen of two fractions of 8.5 Gy days 1 and 8 to a total dose of 17 Gy.

Results: The hypo fractionated RT regimens used in this study proved to be equally effective as the more protracted regimen in terms of treatment tolerance, HRQOL, and overall survival. This may hopefully convince at least some radiation oncologists still using more protracted regimens to adopt this simple and efficient treatment.

Introduction
Lung cancer is the most common human malignancy worldwide, accounting for 1.2 million new cases and 1.1 million deaths a year (Parkin, 2001)¹. Most patients present with inoperable tumour and the majority of disease symptoms are related to its local progression. In non-small-cell lung cancer (NSCLC) patients not suitable for surgery or radical (chemo) radiotherapy, the main aim of treatment is palliation. In these patients, palliative radiotherapy remains the main therapeutic modality. Given the short expected survival, treatment of these patients should be short and non-distressing (Durrant et al, 1971; Sundstrom et al, 2004)². Over the last 30 years, several attempts have been made to develop
treatment schedules combining effective symptom control and short treatment time. The benefits of such an approach include better comfort of patients having anyway short expected survival, and savings on the use of radiotherapy equipment, a resource still deficient in many countries. Additionally, shorter treatments generally allow hospitalisation to be avoided and enable earlier improvement of symptoms (Kowalska, 1992). The equivalence of shorter vs longer radiotherapy schemes in terms of symptom control was demonstrated in a series of randomised studies (Simpson et al, 1985; Medical Research Council Lung Cancer Working Party, 1991; Medical Research Council Lung Cancer Working Party, 1992; Abratt et al, 1995; Nestle et al, 2000; Kramer et al, 2003; Sundstrom et al, 2004). Nevertheless, doubts still exist regarding the potentially detrimental impact of shorter regimens on overall survival, particularly in patients with good performance status. In consequence, in many institutions this method has not been accepted as a standard of care. The aim of this study was to add to the evidence on the feasibility and equivalence of a 2-fraction (fr) vs commonly used 5-fraction regimen in terms of improvement of health related quality of life (HRQOL), toxicity and survival in the hope of optimizing treatment practice in our country.

In the coordinating centre, hypofractionated radiotherapy in the palliative treatment of NSCLC was introduced in 1990. In a pilot study, a dose of 24 Gy in 3 fractions delivered on days 1, 8 and 22 was used (Drozd-Lula et al, 1996). The drawback of this regimen, however, was the long overall treatment time and concern about the relatively high dose to the spinal cord. Additionally, in most patients palliative effect was already observed after two fractions, and many were spared the third fraction. The last fraction was also abandoned in patients progressing after the first two fractions (Drozd-Lula et al, 1996). As a result, experience was gained with the dose of 16 Gy in 2 fractions 1 week apart, which was then chosen as the experimental arm for the current study. The control arm (20 Gy in 5 fractions over 5 consecutive days) was the regimen of palliative lung cancer irradiation most frequently used in Poland.

**Aim of the work**

The Primary study end point was to compare the health related quality of life between two groups. Secondary end points were treatment related side-effects and overall survival.

**Materials and Methods**

Eligibility criteria included cytologically or histopathologically confirmed non-small cell lung cancer, the presence of symptoms related to chest tumour (cough, dyspnoe, chest-pain, haemoptysis), Advanced (metastatic) NSCLC (STAGE IV), Age > 18 Years, ECOG Performance score 2 or >2, No prior chemotherapy or thoracic radiotherapy, Expected survival of at least 3 months & Written & informed Consent.

Patients were randomized to receive 20 Gy in 5 fractions over five consecutive days (Arm A) & 17 Gy in two fractions 1 week apart. Randomization was conducted by means of dedicated computer program.

Baseline examinations included history and physical examination, assessment of ECOG performance score, full blood counts, CT guided or bronchoscopic biopsy, CT chest, abdomen and pelvis. Brain CT or MRI and bone scans were only performed when indicated.

Radiation was given with a 2 cm margin around gross tumour on CECT Chest and 1 cm around electively treated regional lymph nodes. Dose of radiotherapy were prescribed to mid-point. No spinal shielding was used.

**Follow Up**

Patients were followed two weeks after completion of radiotherapy. Then monthly in 1st year & bimonthly thereafter. Chest x-ray was repeated bimonthly or when clinically indicated.

Quality-of-life was assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire.
(lung cancer–specific module QLQ-LC13). Symptoms were graded & recorded at the first day of radiotherapy and at every patient’s visit during follow-up time. Symptomatic response was assessed by comparing the initial score for each symptom with the best score during the first three months of follow-up. An improvement one grade or higher was considered as response. Toxicities was assessed & recorded at each follow-up visit include anorexia, nausea, vomiting, skin reaction, pneumonites, esophagites, haematological toxicity & radiation myelopathy.

Results
Clinico-pathological Features
1. Age: The study population characteristics were homogenous between the two study groups with no statistically significant differences. The mean age was 60.93 and 59.33 years for the group (A) and the group (B) respectively.
2. Gender: The majority of patients in both groups were males (80% in group A and 93.3% in group B respectively).
3. Smoking history and frequency: 90% patients in ARM-A & 86.7% patients in ARM-B were smokers respectively with no significant statistical difference.
4. Performance status (P.S): ECOG score in most patients was 3; 60% in ARM-A & 50% in ARM-B. 40% patients in ARM-A & 46.7% patients in ARM-B had ECOG performance score of 2. Only 1 patient in ARM-B had ECOG of 4(Fig.).
5. Presenting symptoms: According to CTCAE. In group A the frequency of symptoms were cough (83.3%), dyspnea(83.3), chest pain(53.3%) & hemoptysis (33.3%), whereas in group B the symptoms were also cough, dyspnea, hemoptysis and chest pain with a frequency of 73%, 73.3%, 22% and 53.3%, respectively (Table 1).
6. Tumor characteristics: All patients incorporated in this study were stage IV. Bone metastasis were present in 23.3% in Group A & 56.7% in Group B, adrenal metastasis (3.3% in Group A & 0.00% in Group B), Brain metastasis (53.3% in Group A & 33.3% in Group B & Liver metastasis (26.7% & 23.4%) respectively.
7. Methods of obtaining biopsy: Most of the patients in both groups were diagnosed through FOB biopsy.
8. Histopathological type: Squamous cell carcinoma was the commonest pathological type in both groups and represented 90% in both groups.(Fig. 2).

Table 01: Presenting symptoms among the two studied groups

| symptom     | Group A(20Gy/5#) | Group B(17Gy/2#) | Test of significance |
|-------------|------------------|------------------|----------------------|
|             | No.   | %       | No.   | %       |         |
| Cough       | 25    | 83.3%   | 22    | 73.3%   | P=0.347 |
| Dyspnoea    | 25    | 83.3%   | 22    | 73.3%   | P=0.347 |
| Chest Pain  | 20    | 66.7%   | 16    | 53.3%   | P=0.292 |
| Hemoptysis  | 10    | 33.3%   | 12    | 40%     | P=0.592 |
| Weight Loss | 15    | 50%     | 17    | 56.7%   | P=0.796 |

Table 02: Comparison between mean scores of cough between two studied groups (reported by patients) as assessed by EORTC Quality Of Life Questionnaire (Lung cancer specific module QLQ-LC13)

|               | Mean±SD | RANDOMIZATION (PRE-TREATMENT) | IST FOLLOW-UP | 2ND FOLLOW-UP |
|---------------|---------|--------------------------------|----------------|---------------|
| Arm A         | 68.19±33.67 | 54.2±21.11                  | 47.39±16.83   |
| Arm B         | 65.31±31.58 | 55.17±23.22                 | 44.2±14.88    |
| P-VALUE       |         |                               |               | 0.309         |

Mean scores of cough decreased more in ARM-A than ARM-B after radiotherapy with no significant statistical difference between the two studied arms.
Table 03 Comparison between mean scores of hemoptysis between two studied groups (reported by patients) as assessed by EORTC Quality Of Life Questionnaire (Lung cancer specific module QLQ-LC13).

|          | RANDOMIZATION (PRE-TREATMENT) | IST FOLLOW-UP | 2ND FOLLOW-UP |
|----------|------------------------------|---------------|---------------|
| Arm A    | 55.79±20.19                  | 20.31±8.73    | 14.11±7.68    |
| Arm B    | 57.55±22.66                  | 17.22±9.41    | 11.53±6.94    |
| P-VALUE  |                              |               | 0.414         |

Mean scores of hemoptysis decreased more in ARM-B than ARM-A after radiotherapy with no significant statistical difference between two arms.

Table 04 Comparison between mean scores of dyspnoea between two studied groups (reported by patients) as assessed by EORTC Quality Of Life Questionnaire (Lung cancer specific module QLQ-LC13).

|          | RANDOMIZATION (PRE-TREATMENT) | IST FOLLOW-UP | 2ND FOLLOW-UP |
|----------|------------------------------|---------------|---------------|
| Arm A    | 66.59±27.16                  | 50.37±18.49   | 49.03±17.66   |
| Arm B    | 58.24±21.39                  | 44.59±15.84   | 42.77±15.0    |
| P-VALUE  |                              |               | 0.283         |

Mean scores of dyspnoea decreased more in ARM-B than Arm-A after radiotherapy with no significant statistical difference between two arms.

Table 05 Comparison between mean scores of chest pain in two studied groups (reported by patients) as assessed by EORTC Quality Of Life Questionnaire (Lung cancer specific module QLQ-LC13).

|          | RANDOMIZATION (PRE-TREATMENT) | IST FOLLOW-UP | 2ND FOLLOW-UP |
|----------|------------------------------|---------------|---------------|
| Arm A    | 60.88±25.11                  | 43.77±21.10   | 41.13±19.44   |
| Arm B    | 64.15±26.83                  | 48.19±18.64   | 45.68±16.73   |
| P-VALUE  |                              |               | 0.331         |

Mean scores of chest pain decreased more in ARM-A than ARM-B after radiotherapy with no significant statistical difference between two arms.

Table 06: Numbers of patients reporting esophagites after Radiotherapy

| TREATMENT | ESOPHAGITES | Total |
|-----------|-------------|-------|
|           | No | Yes |       |
| Arm A     | 22 | 8   | 30    |
| Arm B     | 23 | 7   | 30    |
| Total     | 45 | 15  | 60    |

26.7% patients in Arm A & 23.3% patients in Arm B suffered from esophagites after radiotherapy with no significant statistical difference between the two studied groups.

Table 07 Comparison between the two studied groups according to their survival (in months)

| Regime | N  | Mean | Median | Std. Deviation | Minimum | Maximum |
|--------|----|------|--------|----------------|---------|---------|
| Arm A  | 30 | 5.20 | 5.00   | 1.424          | 4       | 12      |
| Arm B  | 30 | 5.33 | 5.00   | .606           | 5       | 7       |
| Total  | 60 | 5.27 | 5.00   | 1.087          | 4       | 12      |
| p-value|    | 0.648|        |                |         |         |

Overall survival for patients in the study revealed no significant difference among the two studied groups. Median survival was same 5 months in both groups but mean survival was 5.2 months in ARM-A & 5.33 months in ARM-B.
Discussion
The issue of optimal palliative irradiation schedule in symptomatic NSCLC has been a subject of numerous prospective randomised studies (Medical Research Council Lung Cancer Working Party, 1991; Medical Research Council Lung Cancer Working Party, 1992; Simpson et al, 1985; Teo et al, 1988; Abratt et al, 1995; Macbeth et al, 1996; Rees et al, 1997; Reinfuss et al, 1999; Nestle et al, 2000; Gaze et al, 2001; Bezjak et al, 2002; Kramer et al, 2003; Sundstrom et al, 2004). Although the comparison of these trials is difficult due to differences in the radiotherapy regimens, patient characteristics and outcome measures, there is no strong evidence for the superiority of any particular regimen (Hansen, 2002; Macbeth et al, 2004). Probably the most important and influential trials were those conducted consecutively in the UK by the Medical Research Council (MRC). These studies were first to demonstrate the feasibility and efficacy of very short radiotherapy regimens of two fractions of 8.5 Gy (Medical Research Council Lung Cancer Working Party, 1991) or one fraction of 10 Gy (Medical Research Council Lung Cancer Working Party, 1992). The results of these studies were generally confirmed by subsequent trials (Simpson et al, 1985; Abratt et al, 1995; Macbeth et al, 1996; Rees et al, 1997; Nestle et al, 2000; Kramer et al, 2003; Sundstrom et al, 2004) and are in agreement with the results of our study. Importantly, like all these studies, we used relatively simple treatment planning system rather than sophisticated three-dimensional methods used in protracted radiotherapy regimens. Indeed, these easy to administer and nontoxic regimens resulted in effective and durable palliation of main symptoms (Medical Research Council Lung Cancer Working Party, 1991; Medical Research Council Lung Cancer Working Party, 1992; Sundstrom et al, 2004). These results, however, were challenged by a few studies, which demonstrated better palliation in patients given higher radiation doses (Teo et al, 1988; Gaze et al, 2001; Bezjak et al, 2002). These discrepancies can at least partially be explained by various end points and differences in evaluation tools used in particular studies (Bezjak et al, 2002). In particular, many studies emphasised 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 (Macbeth et al, 1996; Stout et al, 2000; Sundstrom et al, 2004). The major concern related to the use of hypofractionated treatment schedules is their potential inferiority in terms of overall survival (Macbeth et al, 1996; Bezjak et al, 2002). However, our study had demonstrated almost equal survival in both survival in both groups. Median survival was same in both groups but mean survival was 5.2 months in Group-A & 5.3 months in Group-B with no significant statistical difference between the two groups. Apart from purely medical factors, such an approach has obvious logistic and economical benefits, which is of particular importance in countries with limited health care resources. Commonly used treatment schedules are still, however, more often based on tradition than on clinical research results (Macbeth et al, 2004). In particular countries treatment policy is a subject of different societal, cultural, attitudinal and health service delivery influences (Bezjak et al, 2002). The sources of reluctance toward hypofractionated regimens include the lack of experience with large single fraction, concerns about its acute toxicity and uncertainty about the appropriate patient selection for hypofractionated therapy (Bezjak et al, 2002). The main rationale for the use of larger radiotherapy doses and longer fractionation schemes is improvement in local control leading to better quality of life (Macbeth et al, 1996). Indeed, in some studies during long follow-up, better palliative effect was observed in patients applied protracted schedules (Macbeth et al, 1996). On the other hand, short regimens allow for more rapid symptom control (Macbeth et al, 1996). As one of the aims of palliative radiotherapy is psychological support, another worry related to the use of very short fractionation
regimens is their potentially negative effect on patients’ psychological functions, such as levels of anxiety or depression\textsuperscript{13} (Falk et al, 2002). In one study, increased anxiety was observed in patients treated with one fraction, compared to those administered 10 fractions\textsuperscript{8} (Gaze et al, 2001). The efficacy of palliative radiotherapy depends on the type of predominant symptom. Several studies, including the present one, demonstrated that the most effectively palliated symptoms include haemoptysis and chest pain (Simpson et al, 1985; Macbeth et al, 1996; Rees et al, 1997; Cross et al, 2004; Sundstrom et al, 2004). In some studies, irradiation also resulted in effective relief of cough – the symptom least effectively palliated in our series, as well as in the recently reported Norwegian study\textsuperscript{14} (Rees et al, 1997; Sundstrom et al, 2004. The modern definition of palliation (as recommended by the MRC Cancer Trials Office) encompasses symptom improvement (reduction of existing moderate or severe symptoms), control (no deterioration in mild symptoms) and prevention (no deterioration in those with no symptoms)\textsuperscript{15}. Nevertheless (although not planned in the study protocol), the evaluation of the mean score of symptom intensity encompassed also the development of new symptoms and allowed for some estimate of the efficacy of compared treatments in their control and prevention. An unanswered question remains the optimal management of asymptomatic or minimally symptomatic NSCLC patients not suitable for radical treatment, in whom one of the options is watchful waiting. The argument for early treatment in these patients is that enhanced local control may prolong survival and improve quality of life by delaying development of thoracic symptoms (Falk et al, 2002). The results of randomised studies testing early vs delayed or ‘as required’ radiotherapy in this group of patients are contradictory\textsuperscript{16} (Roswit et al, 1968; Durrant et al, 1971; Reinfuss et al, 1999; Falk et al, 2002). A Polish study demonstrated a major difference in overall survival in favour of early treatment (Reinfuss et al, 1999), whereas in the recent MRC trial no differences in main outcome measures, including overall survival, were observed (except for a delay in the development of severe or moderate symptoms in the early treatment group) (Falk et al, 2002). Importantly, 58% of patients in the ‘delayed treatment’ group never needed thoracic radiotherapy (Falk et al, 2002; Hansen, 2002). Furthermore, obviously not all symptoms were present in all patients, making statistical analysis more difficult (Bezjak et al, 2002). In future studies, this problems can perhaps be overcome by the assessment of ‘index symptom’, that is, the single most troublesome symptom in each patient, constituting the primary indication for palliative radiotherapy. It may also be valuable to derive some aggregated variable lumping scores of key symptoms. In the current study, however, no difference was observed between treatment arms in terms of health related quality of life, treatment tolerance and survival after radiotherapy. To conclude, our study confirmed the equal efficacy of shorter vs longer palliative lung cancer radiotherapy schedules in terms of palliative effect and treatment tolerance. This may hopefully convince at least some radiation oncologists still using more protracted regimens to adopt this simple and efficient treatment.

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