Original Article

Palliative Hypofractionated Radiotherapy For Non–small–cell Lung Cancer (NSCLC) Patients Previously Treated By Induction Chemotherapy

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ABSTRACT

Aim: To investigate the effectiveness and toxicity of radiotherapy (RT) given as 17 Gy in 2 fractions, in patients with locally advanced non-small-cell lung cancer (NSCLC) previously treated by platinum-based chemotherapy (CHT) and the impact of total tumor volume (TTV) on symptoms control

Materials and methods: Patients with inoperable NSCLC resistant to induction platinum-based CHT, who developed symptoms during or just after radiotherapy, were treated by 17 Gy in two fractions one week apart. In 12/28 patients a minimal response (up to 20% of TTV) and in 16/28 a stable or locally progressive disease had been recorded after induction CHT. In 26/28 patients, symptoms were present during-after CHT and before RT. The prognostic significance of pre-RT TTV on symptoms control and patients survival was also examined.

Results: We report on 28 patients. Response rates for the four main symptoms were: cough 13/19 (68%), haemoptysis 9/10 (90%), pain 8/14 (57%) and dyspnoea 5/13 (38%). Hematologic and local-thoracic toxicities were minimal. The median survival from the beginning of RT, for the whole group of patients was 9 months (95% CI:3.7-14.3), while for those patients with TTV<120 cc it was 12 months, and for those with TTV 120cc, it was 5.2 months. TTV was not suggested to influence symptoms control rate.

Conclusion: The two-fraction radiotherapy course is safe and effective in palliation of symptomatic non-small-cell lung cancer patients non-responding to induction CHT. Present data suggests that the TTV may influence survival time.

KeyWords: Non-small-cell lung cancer, chemotherapy, radiotherapy, palliation, and fractionation

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Introduction

Patients with non-small cell lung cancer (NSCLC) can be divided into three groups (1). Those with good performance status and a small/localised tumour, who are candidates for radical treatment; those with poor PS and advanced or metastatic tumour for whom simple palliative measures only are appropriate; and a middle group of patients (who are the majority) with (Karnofsky Performance Status) KPS equal or higher than 70 and locally advanced (stage III) disease. Within this last group, the borders between treatment with radical and palliative intent are ill defined and the treatment of these people remains controversial. Radiotherapy (RT) and chemotherapy (CHT) have been used in various combinations (concurrently, sequentially etc) for this group of patients (2). In some randomised trials such as those from Cancer and Leukemia Group B (CALGB 8433) (3) and the Radiation Therapy Oncology Group (RTOG 8808) (4) induction (neo-adjuvant) chemotherapy has been used for these patients. Patients responding to initial CHT are candidates for further treatment by radical RT or concurrent RT-CHT (5). Nevertheless, as the response rates after induction CHT are approximately 30-40% (6) there is a significant amount of patients not responding or relapsing/progressing or even suffering worsening of their symptoms during or after CHT. Although second-line CHT, is gaining acceptance (7, 8), some of these patients develop serious symptomatology and worsening of their performance status and are referred for RT.

The RT schedule of 17 Gy in 2 fractions, one week apart is effective for symptoms palliation in previously untreated patients with locally advanced NSCLC (9-21). In addition, it is convenient for patients (especially those coming from remote areas with a difficult access to RT facility) and accelerates patients turnover in RT department.

We have reported our experience on palliative hypofractionated RT for previously untreated patients with locally advanced NSCLC (19). The present (not prospectively designed) study is a report on our recorded experience (from Radiotherapy Department in University Hospital of Larissa, Greece) with this RT schedule on similar patients not responding to induction CHT, who develop uncon

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trollable symptoms during or just after it. To our knowledge there is no study reporting feasibility and toxicity of this RT schedule after induction CHT.

As the tumor volume has been reported to influence prognosis in lung (21, 22) head and neck (24) and other carcinomas (25), we have attempted to investigate the prognostic impact of pre-RT tumor volume on patients' symptoms control and survival.

Material and methods

Patient population

Patients with locally advanced, inoperable, stage IIIA-B NSCLC, were treated by platinum-based induction chemotherapy with the intend to be treated by concurrent RT-CHT or radical RT-alone, thereafter. Patients were evaluated after 3 cycles of CHT. Evaluation was based on clinical picture and chest CT scan. Those with a response to the initial 3 cycles of chemotherapy, were planned to receive 3 more cycles aiming at maximal tumor response. Patients who developed at least one of the following during or just after the completion of CHT, were referred for RT: locally progressive or non-responding disease (see below on how response was assessed), progressive symptomatology, lowering of KPS, weight loss of >10% in the past 3 months, presence of symptomatic pleural effusion. Symptoms included at least one of the following: chest pain, dyspnoea-wheezing, cough and haemoptysis. Patients with superior vena cava obstruction were not included in this group of patients as they were treated by more protracted RT schedules, such as 20 Gy in 4 fractions or 30 Gy in 10 fractions.
All patients had histologically or cytologically confirmed NSCLC and complete initial (before CHT) staging with clinical examination, bronchoscopy, thoracic, upper abdominal and brain CTs, bone scan, and laboratory tests. Before starting RT, a chest CT scan was requested; restaging was carried out in case of clinical suspicion for metastatic disease.

Treatment

Radiotherapy was given in a median time of 5 weeks after the last cycle of chemotherapy. All patients underwent conventional simulation before treatment. The RT portals were delineated to encompass the GTV (Gross Tumour Volume) with 1-2 cm margin to all directions. An AP/PA parallel pair of fields was employed in the most of the patients (25/28). In 3/28 of the patients, opposed oblique fields were used. Field sizes varied between 8x7 to 13x13 cm^2 (median field surface 120 cm^2). A spinal cord block 2.5 cm in width was added to the posterior field of the second fraction. With this technique we had not observed any radiation myelitis in the past (26). RT consisted of 17 Gy in two fractions one week apart. An isocentric technique (with lung correction) was used in all patients and the dose was prescribed at the isocenter. Filter compensators were used if needed to maintain the calculated dose within 7% of the prescribed dose. Linear accelerator delivering 6 MV photons was used.

Evaluation of the patients

Palliation of symptoms within 3 months after the end of RT, and toxicity were recorded. The patients were followed-up 1 and 3 months after RT and every 3 months thereafter. Follow-up examinations included detailed history, clinical examination, blood tests, as well as a check for metastatic disease, if clinically indicated. Chest radiograph was obtained at 3 months after RT. Questionnaires for the assessment of quality of life were not used due to poor patients' compliance in fulfilling the forms (19).

The symptoms assessed included cough, dyspnoea, chest pain and haemoptysis; a four-degree categorical scale was used for each of the main symptoms: none 0, mild 1, moderate 2, and severe 3. Especially for dyspnoea the scale was as follows: 0: walks without dyspnoea, 1: walks with mild dyspnoea, 2: dyspnoea on walking a short distance and 3: dyspnoea with mild exertion (19).

Symptoms palliation and treatment-related toxicity were assessed and recorded by the radiation oncologists who scored symptoms relief according to patient's statement. Symptoms were graded and recorded at the first day of RT 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 3 months of follow-up. An improvement of one grade or higher was considered as response. A total symptom score (TSS) was produced for each patient, by adding the scores of each individual symptom. All patients were able to visit hospital at one and 3 months for follow-up evaluation.

Toxicities assessed and recorded at each follow-up visit, included: anorexia/nausea-vomiting, skin reaction, pneumonitis, esophagitis, hematological toxicity and radiation myelopathy. Because of the preceding cytotoxic chemotherapy, all patients were surveyed closely and were advised either to visit us or to telephone in case of serious toxicity in the meantime between their prebooked attendances. For the grading of toxicity the RTOG acute/late radiation morbidity scoring was used.

CT evaluation–volumetry

The pre-CHT and pre-RT CT scans were reviewed. Examinations were obtained with various CT machines. All imaging studies were performed with IV injection of contrast medium. A slice thickness of 5-10 mm was used in all cases. Soft tissue windows were used for defining mediastinal masses and lung windows were used for lesions surrounded by lung parenchyma.

To determine tumour volume, the primary tumour and enlarged (>1.5 cm) lymph nodes were outlined on each CT slice that contained tumour. Tumour outlines were then transferred into a treatment-planning computer using a digitiser. After accounting for the magnification factor and CT slice thickness, the computer gen

erated a tumour volume measured in cubic centimetres. The total tumour volume was registered for each patient: primary tumour plus enlarged lymph nodes.

Patients were evaluated after CHT according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria (27). According to RECIST criteria partial response is defined as a decrease of at least 65% in tumor volume. The response after CHT was evaluated by the ratio (R) of volumes:

$$R = \frac{\text{pre-Chemotherapy-TTV}}{\text{TTV-after-chemotherapy}}$$

Stable disease was characterized in case of R=1 (0.05); "minimal response" if R >1.05, and progressive disease if R<0.95 (please note that the TTV as measured just after chemotherapy is actually assigned as pre-RT TTV).

Statistical analysis

Descriptive statistics and simple proportions were used to present the data. The two patients with stage IIB were grouped in IIIA stage for the purpose of analysis. Statistical analysis was undertaken using the Wilcoxon signed-rank test and chi-squared non-parametric tests. Correlations were studied by Pearson correlation coefficient. Overall survival was estimated, from the date of starting RT, by the Kaplan-Meier method. Patients alive at the last follow-up were censored. The prognostic cut-off point in TTV was searched for the value that would yield the best discrimination between the two Kaplan-Meier survival curves, as assessed by the repeated application of the Log-rank test. We used the correction as proposed by Altman et al (28), and give both values. Univariate survival analysis was performed using the log-rank test. The parameters examined (given the small number of patients in the study) were: KPS as a binary variable (>70 vs. 70), total tumor volume (TTV) as both continuous and binary (<120 vs. >120 cc) variable and response to chemotherapy as a binary variable (minimal response vs. no response or progressive disease). The impact of factors on patients survival was studied with the Cox proportional hazards model (backward stepwise selection routine) (29).

Results

Patients and treatment

Although our study is not prospectively designed, it includes patients treated according to a particular radiotherapy clinical protocol. Between March 2003 and November 2004, 28 patients were treated. Their characteristics are shown in table 1. Four patients had received 4 cycles of docetaxel as a second-line CHT, before RT. There were also patients with symptoms worsening after 1-2 cycles and they were also re

Table 1
Patients, disease and treatment characteristics. (+) as evaluated on CT just after chemotherapy and before initiation of radiotherapy.

Characteristic	N (%)
Gender	
Male	28 (100)
Female	0 (0)
Age (y)	
Median	70
Range	55-79
Karnofsky Performance Status	
Median	80
Range	60-90
Histology	
Squamous	17 (60.7)
Adenocarcinoma	6 (21.4)
Other NSCLC*	5 (17.9)
Hemoglobin (g/dl)	
12	15 (53.6)
<12	13 (46.4)
T stage	
T2	3 (10.7)
T3	12 (42.9)
T4	13 (46.4)
N stage	
N0	8 (28.6)
N1	3 (10.7)
N2	14 (50)
N3	3 (10.7)
Stage	
IIb	2 (7)
IIIA	12 (43)
IIIB	14 (50)
Tumour volume before radiotherapy (cm^3)	
Mean	130.5
Median	129.85
Range	7.5-321
Patients with symptomatology (Grade 1/2/3)	
Cough	19(9/9/1)
Dyspnoea	13(6/6/1)
Hemoptysis	10(8/2/0)
Chest pain	14(5/4/5)
Volume greater than 120 cm3	15 (53.6)
Weight loss of >10%	7 (25%)
Response to chemotherapy (+)	
Minimal response (volume reduction ~up to 20%)	12 (43%)
Stable disease	8 (29%)
Locally progressive disease	8 (29%)

NSCLC: Non–small cell lung cancer

Table 2 Symptoms response (of at least 1 grade) to RT, 1 month after RT

	Response of symptoms to RT (%)	**Complete resolution of symptoms (%)**
Cough	13/19 (68)	8/19 (42)
Hemoptysis	9/10 (90)	9/10 (90)
Pain	8/14 (57)	3/14 (21)
Dyspnoea	5/13 (38)	3/13 (23)

ferred for RT. Two patients declined further chemotherapy; they both had stable disease after 3 cycles of CHT.

In detail, induction chemotherapy consisted of one of the following combinations: 3 cycles of paclitaxel+carboplatin (n=4), 3 cycles of paclitaxel+carboplatin followed by docetaxel (n=4), 1 cycle of gemsitabine+carboplatin (n=2), 3 cycles of gemsitabine+carboplatin (n=4), 6 cycles of gemsitabine+carboplatin (n=4), 3 cycles of gemsitabine+cisplatin (n=2), 6 cycles of gemsitabine+cisplatin (n=4), 2 cycles of paclitaxel-cisplatin (n=2). One patient received 3 cycles of cisplatin+vinorelbine and one 3 cycles of taxotere+vinorelbine.

Symptoms control and survival

According to RECIST criteria (27) all of our patients were non-responders to chemotherapy. Eight patients had stable disease, 8 had progressive disease and, 12 had "minimal response" (~15-20% decrease in tumor volume). The response of each symptom to RT is presented in table 2.

Hemoptysis was the symptom with the most remarkable response rate after RT (9/10 patients, 90%). The TSS before RT was significantly higher to that after RT (Wilcoxon signed-rank test Z=-2.894, p=0.004) (fig.1). After RT the TSS was lower (improvement) in 19 patients (68%), stable in 6 (21%), and higher in 3 (11%) patients. KPS was stable in 17 patients, lower in 7 and higher in 4 patients (Wilcoxon signed-rank test Z=-1.182, p=0.237). The rates of complete symptoms resolution were: cough 8/19 (42%), hemoptysis 9/10 (90%), dyspnoea 3/13 (23%), chest pain 3/14 (21%).

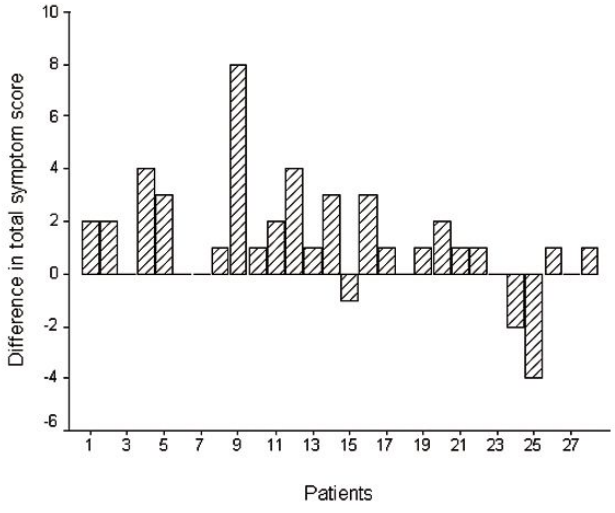

Fig. 1 Bars illustrating the difference in Total Symptom Score: (TSS before RT)–(TSS after RT). TSS>0 means improvement in symptoms

From the beginning of RT the median survival time for the whole group of patients was 9 months (95% CI: 3,7-14.3) and one-year survival rate was 29.8% (SE: 0,956) (fig. 2).

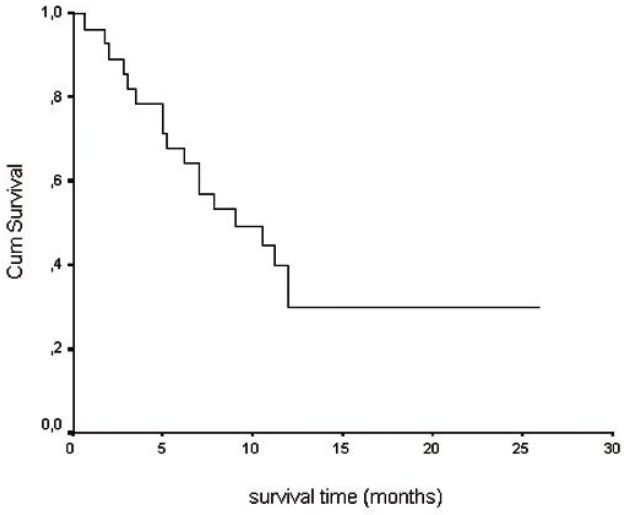

Fig. 2 Actuarial survival from the beginning of radiotherapy, for the whole group of patients

Volumes and correlations

The median and mean tumor volumes were 129.9 and 131.5 cm^3 respectively. Patients with tumor volume 120 cm^3 had a median survival of 5.2 months (95% CI: 2.6-7.7), while those with tumor volume <120 cm^3 had a median survival of 12 months (95% CI: 10.7-13.3) (log-rank test, p=0.02 and after correction (28) pcorr=0.09) (fig. 3). Tumor volume has shown no association with the parameter "difference in TSS" (before and after RT), (Pearson correlation coefficient, p=0.7) i.e. the degree of palliation could not be related with tumor volume, in the present material.

Prognostic factors for survival

Parameters significant for survival in univariate analysis were: tumor volume as a binary variable more or less than 120 cm^3 (see above), response to chemotherapy (minimal vs. all others) (p=0.03) and KPS as a binary variable (p=0.048). In Cox regression analysis important variables were: tumor volume as a dichotomous variable

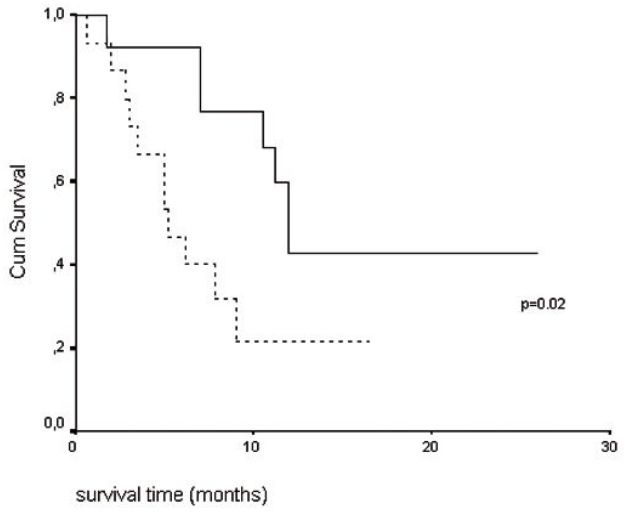

Fig. 3 Actuarial survival for the patients with tumors <120cc (solid line) and > 120 cc (dashed line)

(Hazard Ratio, HR:0.23, 95% CI:0.075-0.7, p=0.007), and response to chemotherapy (HR:0.24, 95%CI: 0.08-0.75, p=0.008).

Toxicity

Esophagitis toxicity Grade 3-4 was not seen; seven patients had a Grade 2 and 8 patients a Grade 1 esophagitis. Radiation pneumonitis occurred in 2 patients and subsided promptly (within 7-10 days) after dexamethazone administration. Dyspnoea was recorded as "worse" after RT for these patients. Fatigue was reported in 11/28 (39%) and nausea/vomiting in 6/28 (21%) during the first week after RT. No radiation myelitis was recorded up to the end of the follow-up time. The four patients treated with second-line CHT before RT did not develop excessive side effects.

Discussion

After the publication of the MRC (Medical Research Council) studies in the UK (9,10) on hypofractionated RT in locally advanced NSCLC, many centers around the world have adopted it (11-15, 17-21), while others have criticized hypofractionation with 1-2 fractions (30). The criticism for this hypofractionation is two-fold: firstly it is focused on the issue that higher-dose regimens would probably offer an increase in survival or a more durable response and, secondly there is concern about the potential toxicity of large dose per fraction. In the USA although hypofractionated RT schemes have been used from time to time, radiation oncologists are generally reluctant to prescribe such a hypofractionated treatment for lung cancer. A recent study of a 2 x 8.5 Gy RT course, from Boston (12) has been terminated after an accrual of only 23 patients in a time interval of 7 years, because the doctors "did not want to deny fit patients potentially curative treatment or treatment that might give a more durable response". They only treated patients, with ECOG Performance Sstatus of 2 or worse or those that could not tolerate a more aggressive treatment course. However, their clinical results were comparable to those reported by other similar studies.

A randomised MRC trial (31) offers a strong evidence of a modest increase in survival (5% at 1 year and 3% at 2 years) in patients with better PS, who were treated by 12-13 fractions of 3 Gy. Other studies have also favored more protracted RT schedules (14, 16, 18). However in the most recent randomised study (with 421 patients) from Norway (13) it was shown that protracted palliative RT of 42 Gy in 15 fractions or 20 Gy in 25 fractions were not superior to the 17 Gy in 2 fractions regimen, in terms of symptoms control and survival.

Toy et. al. in an interesting review of the literature, have concluded that symptomatic patients with NSCLC can be treated safely and effectively with regimens of RT of one or two fractions. Nevertheless selected patients with good PS could be considered for higher-dose regimens if the chance of modest improvement in survival and palliation is considered worth the additional inconvenience and toxicity (21).

In the present study the median survival from the beginning of RT was higher (9 months) from that reported by hypofractionated RT-alone studies, probably due to both patients selection before CHT and a likely additive effect of CHT and RT (1).

The finding that the patients with total tumour volume (after CHT) of less than 120 cc had a median survival of 12 months, while those with TTV>120 cc had a median overall survival of only 5.2 months (log-rank, p=0.02), might be of importance.

In a report by Willner et al. (22) from the University of Wü rzburg the authors concluded that tumors 100 cm^3 were unlikely to be controlled long term, but tumor volume was not significant for survival in their study. A similar cut-off value for tumor control has been reported in a series of 22 patients with NSCLC (23). Impact of TTV and its reduction during or after RT has been examined by some recent studies (32-34).

The RT schedule of 17 Gy in 2 fractions seems to be safe and it offers a reasonable palliation rate of symptoms for patients previously treated by platinum-based CHT. Although initial tumor volume was not suggested to affect the rate of symptoms palliation, could be a criterion for patients stratification in future studies.

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