Palliative chemotherapy followed by consolidation radiotherapy in patients with advanced and metastatic non-small cell lung cancer not suitable for radical treatment

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SUMMARY

Background: *This is a retrospective study to assess the effectiveness of consolidation radiotherapy (CRT) following palliative chemotherapy in patients with metastatic or locally advanced non-small cell lung cancer (NSCLC) who are not suitable for radical treatment.*

Methods: *This study involved retrospective analysis of a prospective database of Northampton Oncology Center from January 2005 through December 2010, 63 patients with advanced / metastatic NSCLC treated at the oncology center were enrolled. Patients were either treated with high dose (39/36 Gy /13-12 fractions, group 1) or low dose (20 Gy /5 fractions, group 2) CRT or there were those who were not offered any CRT (group 3).*

Results: *There was no significant difference between the three groups as regard age, sex, performance status, co-morbidities or chemotherapy given. However, there was a statistically significant difference as regard the stage P = 0.009 with more stage IV patients at group II and III compared to group I. The mean survival for the three groups was 27m, 14m & 15m respectively.There was a statistically significant improvement of survival in patients treated with high dose palliative CRT compared to the other two groups (P = 0.006). In multivariate analysis only the radiotherapy dose remains as the only statistical significant factor affecting the survival with hazard ratio 0.372 and confidence interval (0.147-0.726).*

Conclusion: *Despite the limitation of our retrospective study, it is worth considering CRT approach for patients with advanced and metastatic NSCLC – not suitable for radical treatment – who have not progressed on chemotherapy.*

Key words: *Carcinoma, Non-Small-Cell Lung; Radiotherapy; Radiotherapy Dosage; Antineoplastic Agents; Treatment Outcome*

INTRODUCTION

Lung cancer is the leading cause of cancer related deaths in Western countries, with non-small cell lung cancer (NSCLC) accounting for more than 85% of primary lung cancers (1).

A minority of patients with unresectable non-small cell lung cancer whose lesions are confined to the thorax are selected for immediate, radical radiotherapy aimed at a cure or prolonging survival. For the remainder, however, advanced disease within the chest, the presence of distant metastases, or poor performance status preclude such potentially curative treatment (2).

Many patients with metastatic lung cancer (LC), and selected patients with locally advanced disease, are routinely treated with thoracic radiotherapy with palliative intent to relieve tumor-related symptoms (haemoptysis, bronchial obstruction, cough, shortness of breath, and chest pain) and to improve health-related quality of life (3).

Patients who usually require palliative radiotherapy upfront are suffering from symptoms that need faster radiotherapy intervention rather than waiting to see a response with palliative chemotherapy. Cytotoxic chemotherapy is the mainstay of management in advanced NSCLC with response rates of 20-40% and a median survival time of 7-10 months (4). For patients with advanced NSCLC, we have moved from a situation of one size fits all to the dawn of individualized cancer therapy (5).

Despite the increased research in use of new chemotherapy drugs as well as biological agents, little has been done to explore the position of palliative radiotherapy in the management plan for those patients, especially the concept of consolidation radiotherapy following chemotherapy.

In our work we looked at retrospective groups of patients who had been treated with palliative radiotherapy immediately after the end of chemotherapy treatment and compared different fractionated regimens and also compared these to those patients who have been offered delayed radiotherapy.

PATIENTS AND METHODS

This study involved retrospective analysis of a prospective database of Northampton Oncology Center from January 2005 through December 2010, 63 patients with advanced / metastatic NSCLC treated at the oncology center were enrolled. The selected patients for analysis fulfilled the following criteria:

1. Patients are not candidates for radical treatment.
2. At least one cycle of palliative chemotherapy was administered with either stable disease or partial response.
3. No radiotherapy given prior to chemotherapy.

Patients were categorized into three groups:

Group I: Patients who were offered high dose (39/36 Gy /13-12 fractions) consolidation radiotherapy (radiotherapy given straight after the last cycle of chemotherapy)

Group II: Patients who were offered low dose (20 Gy /5 fractions) consolidation radiotherapy

Group III: Patients who were not offered any consolidation radiotherapy.
The decision to offer patients consolidation radiotherapy was mainly consultant driven as one oncologist adopts this approach; the other two consultants in the center did not use it. All the patients' and tumors' characteristics were extracted and analyzed.

Statistical analysis

Life tables and the log rank (Kaplan Meier) test were used to test for significance of difference in survival in different treatment groups. Cox regression was used to test the effect of other risk factors on survival. Using backward stepwise Cox regression, only consolidation therapy remains in the last step model. Using forward stepwise Cox regression, only a number of fractions were accepted in the significant model. As the number of fractions is parallel to consolidation therapy, it was excluded from other risk factors included in the Cox regression model using the enter method. The P value was considered significant if less than 0.05. These tests were run on an IBM compatible personal computer using the Statistical Package for Social Scientists (SPSS) for Windows version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

Twenty-two patients were in group I, while group II included 19 patients and group III had 22 patients. Patients' and tumors' characteristics are presented in Table 1.

Table 1. Patients' and tumors' characteristics

	Group I	Group II	Group III
Age	61	61	60
Males/females	15/7	12/7	10/12
PS			
0	6	3	4
1	8	10	15
2	8	6	3
Co-morbidities			
1	13	7	14
2	6	8	5
3	3	4	3
Stage			
II	1	0	0
IIIA	5	0	1
IIIB	9	4	3
IV	7	15	18
Histology			
Adenocarcinoma	7	7	11
Squamous CC	9	4	10
Non-specified NSCLC	6	8	1
Chemotherapy			
Received 1st line	22	19	22
Received 2nd line	7	4	8
Received 3rd line	1	1	1

In group I, 6 patients received 39 Gy /13 fractions and 16 patients received 36 Gy /12 fractions, while in group II all patients received 20 Gy /5 fractions. Patients in all groups received 4 cycles of palliative chemotherapy on average.
There was no significant difference between the three groups as regard age, sex, performance status, co-morbidities or chemotherapy given. However, there was a statistically significant difference as regard to the stage (P = 0.009) with more stage IV patients at groups II and III compared to group I. The mean survival for the three groups was 27m, 14m & 15m respectively, while the median survival was 21m, 12m & 14m respectively. Survival curves are shown in Figure 1.

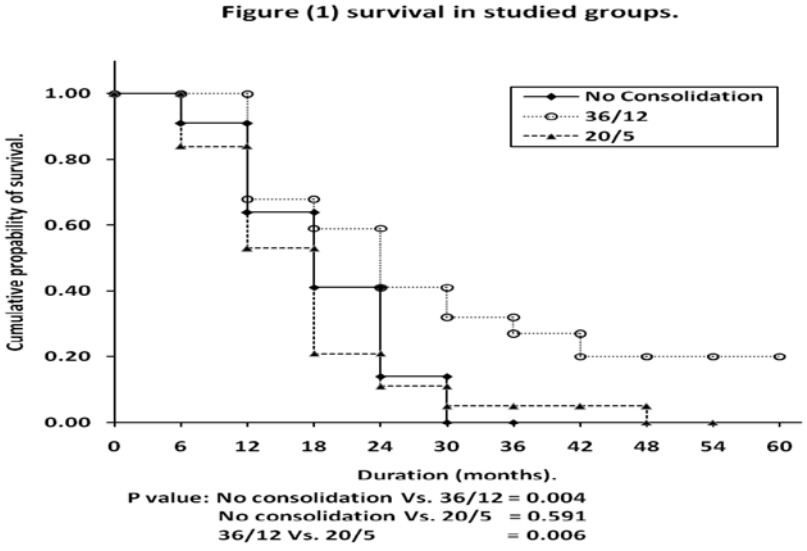

Figure 1. Survival in studied groups

There was a statistically significant improvement of survival in patients treated with high dose palliative consolidation radiotherapy compared to the other two groups (P = 0.006).
In multivariate analysis, only the radiotherapy dose remains as the only statistical significant factor affecting the survival with hazard ratio 0.372 and confidence interval (0.147-0.726) (Table 2). There was not enough data on the database to comment on the quality of life in the three groups.

Table 2. Multivariate Cox regression of survival on consolidation therapy and different risk factors

	Partial R	S.E. of partial R	Wald χ^2	P.	Hazard ratio	95.0% CI for Hazard ratio	
						Lower	Upper
Consolidation			10.379	.006			
Consolidation (36/12)	-1.118	.407	7.553	.006	.327	.147	.726
Consolidation (20/5)	.122	.359	.116	.733	1.130	.559	2.283
Sex (Male)	-.007	.290	.001	.980	.993	.563	1.752
PS	.126	.196	.411	.521	1.134	.772	1.666
Histology			.401	.818			
Histology (Scc)	-.028	.423	.005	.946	.972	.424	2.227
Histology (Adeno)	-.214	.388	.306	.580	.807	.378	1.725
Stage	-.246	.234	1.109	.292	.782	.494	1.236
Comorbidities			1.363	.506			
Comorbidities (Average/mild)	.391	.335	1.362	.243	1.478	.767	2.849
Comorbidities (Moderate)	.172	.404	.181	.671	1.187	.538	2.623

S.E.: standard error, R: regression coefficient

DISCUSSION

In lung cancer, the most commonly accepted symptomatic treatment consisted of palliative radiotherapy. With palliation as the aim, most patients should be treated with short courses of one or two fractions (6). Various randomized trials and meta-analysis has extensively addressed the issue of radiotherapy dose and fractionation (6-20).

They all concluded that no significant differences were observed for specific symptom-control endpoints across all of the trials comparing low versus high radiotherapy, although improvement in survival favored high dose regimens.

Other six single-arm studies have confirmed symptom palliation after hypo-fractionated radiotherapy in patients with non-small cell lung cancer (21-26).

Our study has targeted selected groups of patients who have received at least more than one cycle of chemotherapy – without evidence of progression – followed by either consolidation radiotherapy in different fractionations or delayed radiotherapy on progression. This means that patients in our study were not suffering from significant local chest symptoms that necessitated upfront palliative radiotherapy and neither did they present with known brain metastasis.

The Norwegian Lung Cancer Study Group (27) in their randomized trail has concluded that non-symptomatic patients had significantly more favorable survival when compared to symptomatic patients with a median survival of 11.8 versus 6.0 months ($P<0.0001$), respectively.

In our study, there was no survival benefit from consolidation radiotherapy with radiation dose 20 Gy /5 fractions, which highlights the importance of radiation dose in consolidation.

There is established evidence of survival benefit of a higher dose (HD) of radiotherapy as highlighted by the systematic review carried out by Fairchild et al, where in the 13 analyzed trials, a statistically significant survival advantage was found for HD palliative radiotherapy, with 26.5% (420 of 1,586) alive versus 21.7% (350 of 1,613) at 2 years (*P* 0.002) (7). Sensitivity analysis suggests this survival improvement was seen with 35 Gy_{10} BED schedules compared with LDs. Overall survival at 2 years was reported by 10 trials, comprising 1,376 HD patients and 1,409 LD patients. A total of 8.1% were alive at 2 years after being treated with HD RT versus 6.7% treated with LD, with an OR of 0.82 (95% CI, 0.63 to 1.07; *P* 0.84).

The Cochrane review in 2005 and 2009 has also addressed the radiation dose and fractionation questions with similar outcomes and acknowledged that in the future, large trials comparing different RT regimens may be difficult to set up because of the increasing use of systemic chemotherapy. The reviewer also recommended that trials looking at how best to integrate these two modalities, particularly in good PS patients, need to be carried out (28).

The National Institute has issued guidance in 2005 and 2011 recommending that a high dose should be offered where the aim is to substantially reduce the size of the cancer (29).

The recent ASTRO guidelines has also advised that patients with good performance status may benefit from higher-dose/fractionation EBRT palliation (30-Gy/10-fraction equivalent or greater) (30).

The other question that also has been addressed before, but without much in the context of randomized control trial, is the timing of palliative radiotherapy in relation to chemotherapy. In the MRC trial, addressing immediate versus delayed palliative thoracic radiotherapy in patients with unresectable locally advanced nonsmall cell lung cancer and minimal thoracic symptoms (31), they found that no persuasive evidence was found to indicate that giving immediate palliative thoracic radiotherapy improves symptom control, quality of life, or survival when compared with delaying until symptoms require treatment.

However, in this trial only short courses of radiotherapy were allowed (17 Gy /2 fractions or 10 Gy single). It also has to be noted that none of those patients had been offered upfront chemotherapy.

We knew that response to first line chemotherapy is an important prognostic factor in this group of patients (32) and this is why we only offered consolidation radiotherapy to those who achieved at least, stable disease following chemotherapy.

In our study we endorsed the consolidation radiotherapy approach, which means radiotherapy given straight after the end of chemotherapy.

Recently, It has also been reported in a small trial looking at 20 patients with stage III NSCL treated with induction chemotherapy followed by radical radiotherapy that deferring radiotherapy after induction chemotherapy by more than 21 days has produced greater increases in percent volume change ($p = 0.002$) and percent diameter ($p = 0.055$) than lesser delays (33).

CONCLUSION

Despite the limitation of our retrospective small study, it is worth considering the consolidation radiotherapy approach for patients with advanced and metastatic non-small cell lung cancer – not suitable for radical treatment – who have not progressed on chemotherapy. A radiation dose of at least 36 Gy should be attempted in this group of patients. A national randomized trial is recommended.

Conflict of interest

We declare no conflicts of interest.

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