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Randomized Trial Comparing the two Different Hypofractionated Radiotherapy Schedules (20Gy in 5 Fractions versus 17Gy in 2 Fractions) in Advanced Non-small Cell lung Cancer (Stage IV)

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Abstract
*Lung cancer is a major health problem worldwide. The incidence is increasing globally at a rate of 0.5% per year. It is the leading cause of cancer mortality in most of the countries in the world[1].Non-small cell lung cancer (NSCLC) accounts for at least 85% of all lung cancer cases and presenting as metastatic disease in approximately 50-60% of cases[2].**Error! Bookmark not defined.***
Aim of the work: *The aims & objectives of this study was to investigate the effectiveness and add to the evidence on the feasibility and equivalence of a two fractions versus five fractions regimen in advanced non-small cell lung cancer in terms of: Palliation of thoracic symptoms (Cough, Dyspnoea, Hemoptysis, Chest pain), Toxicities due to treatment (Immediate as well as delayed) & 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 1 weeks to a total dose of 20 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. All patients in the study were subjected to the following; pretreatment evaluation, Radiation treatment, patient's assessment and overall survival.*
Results: *The hypofractionated RT regimens used in this study proved to be equally effective as the more protracted regimen in terms of palliation of the intrathoracic symptoms, treatment tolerance and overall survival. This may hopefully convince at some radiation oncologists still using more protracted regimens to adopt this simple and efficient treatment.*
Conclusion: *Short course hypofractionated radiotherapy is as good if not better than protracted hypofractinated radiotherapy for palliation in Stage IV Non-small cell Lung Cancer.*
Keywords: *hypofractionated, thoracic, radiotherapy, nsclc, palliation.*

Introduction

Lung cancer is a major health problem worldwide. The incidence is increasing globally at a rate of 0.5% per year. It is the leading cause of cancer mortality in most of the countries in the world[1].The worldwide incidence is 14% whereas it constitutes 6.8% of all cancers in India[3]. In Kashmir, the crude incidence rate, age

standardized (world) & truncated age adjusted (40-69years, world) incidence rates for lung cancer per lakh population were 4.01, 6.48 and 15.28 respectively[4].

Standard treatment options for stage IV non-small cell lung cancer include cytotoxic combination chemotherapy, combination chemotherapy with bevacizumab or cetuximab, EGFR tyrosine-kinase inhibitors & radiation therapy. Treatment goals are to prolong survival and control disease-related symptoms. Factors influencing treatment selection include comorbidity, performance status (PS), histology, and molecular genetic features of the cancer. Radiation therapy is generally used in selective cases for symptom palliation. Radiotherapy plays an important role in the palliation of symptomatic disease in many cancer patients.

Consequently, a shorter course of hypo-fractionated RT for palliation, if effective and unduly toxic, would be an attractive alternative to more protracted regimens, so clinical trial that is organized to ensure homogeneity in both patient characteristics and treatment interventions is needed. Shorter hypofractionated schedules require fewer trips to the RT facility for the patient, and in all likelihood, smaller directly and indirectly costs for society, especially for developing countries (like India) with limited resources[5]. To measure the effect of palliative intervention, it is recommended to use patients' self-reported assessment using validated instruments but unfortunately, most reports regarding palliative fractionation in NSCLC have used clinical assessment of palliative effect only[6].

Aim of the work

The Primary study end points were duration of relief of chest tumour related symptoms. Secondary treatment end points were treatment related side-effects and overall survival.

Patients

This was a prospective clinical study that included 60 patients, who were randomly assigned into one of two groups:

Group A: Consisted of 30 patients who received RT regimen of 5 fractions of 4 Gy over 1week to a total dose of 20 Gy.

Group B: Consisted of 30 patients who received RT regimen of two fractions of 8.5 Gy days 1 and 8 to a total dose of 17 Gy.

Patient Eligibility

1) Cytologically or Histopathologically confirmed non-small cell lung cancer
2) Advanced (metastatic) NSCLC(STAGE IV)
3) Age> 18 Years
4) ECOG Performance score 2 or >2
5) Pulmonary symptoms attributable to primary tumor
6) No prior chemotherapy or thoracic radiotherapy
7) Expected survival of at least 3 months
8) Written & informed Consent

Methods

All patients in the study were subjected to the following pretreatment evaluation:

1) History taking and physical examination.
2) Current weight, height, and detection of the weight loss in the past six months.
3) Assessment of ECOG performance status.
4) Biopsy was performed by fiber optic bronchoscopy (FOB) or CT guided biopsy.
5) Staging workup including X-ray chest, CT chest, abdomen and pelvis.
6) Brain CT or MRI and bone scans were only performed when indicated.
7) Determination of tumor measurements.
8) Routine laboratory studies.

Radiation therapy

Radiation was given with a 2 cm margin around gross tumour on CECT Chest and 1 cm around electively treated regional lymph nodes. Ipsilateral hilum and width of mediastinum was included. During the period of radiation, patient was monitored for signs and symptoms of toxicity.

Follow up

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

Assessments of symptoms of chest tumour include cough, haemoptysis, dyspnoea, chest-pain, SVC syndrome and dysphagia were evaluated by patients and then during follow-up visits by physicians.

The grading of intensity for each symptom was performed using common terminology criteria for adverse events v3.0 (CTCAE)[7]. 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 were assessed & recorded at each follow-up visit include anorexia, nausea, vomiting, skin reaction, pneumonites, esophagites, haematological toxicity & radiation myelopathy.

Statistical Analysis of the Data

Data were analysed using SPSS software package version 18.0. Quantitative data was expressed using Range, mean & standard deviation while qualitative data were expressed in frequency & percent. Qualitative data was analysed using chi-square test. Also exact test such as Fischer test was applied to compare the two groups.

Results

Table 1: Comparison between two studied groups according to their age

	Age Group				Total
	40-50	51-60	61-70	above70	
Arm A	3	12	12	3	30
	10.0%	40.0%	40.0%	10.0%	100.0%
Arm B	2	12	12	4	30
	6.7%	40.0%	40.0%	13.3%	100.0%
Total	5	24	24	7	60
	8.3%	40.0%	40.0%	11.7%	100.0%

The mean age in ARM-A was 59.06 years & in ARM-B was 65.63 years. The difference was not significant.(p=0.952)

Table 2: Sex Distribution between the two studied groups

	Gender		Total
	Male	Female	
Arm A	26	4	30
	86.7%	13.3%	100.0%
Arm B	28	2	30
	93.3%	6.7%	100.0%
Total	54	6	60
	90.0%	10.0%	100.0%

86.7% of the patients in group A were males & 93.3% of the patients in group B were males with no significant statistical difference between the studied groups.(p=0.671)

Table 3: Comparison between two groups according to smoking habits

	SMOKING		Total
	YES	NO	
Arm A	27	3	30
	90.0%	10.0%	100.0%
Arm B	26	4	30
	86.7%	13.3%	100.0%
Total	53	7	60
	88.3%	11.7%	100.0%

27 of 30 i.e; 90% patients in ARM-A were smokers & 26 of 30 i.e; 86.7% patients in ARM-B were smokers respectively. (P=1.00)

Table 4: Performance status at presentation among the two studied groups

	ECOG PS			Total
	2	3	4	
Arm A	12	18	0	30
	40.0%	60.0%	0.0%	100.0%
Arm B	14	15	1	30
	46.7%	50.0%	3.3%	100.0%
Total	26	33	1	60
	43.3%	55.0%	1.7%	100.0%

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. (P=0.490)

Table 5: 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

Presenting symptoms: 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 6: Comparison between the two studied groups according to Histopathology

	HISTOPATHOLOGY		Total
	SQUAMOUS CELL CA.	ADENOCARCINOMA	
Arm A	27	3	30
	90.0%	10.0%	100.0%
Arm B	27	3	30
	90.0%	10.0%	100.0%
Total	54	6	60
	90.0%	10.0%	100.0%

Squamous cell carcinoma was the dominant histopathological type in both the arms. (p=1.00)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% in Group A & 23.4% in Group B) respectively.

Table 7: Comparison of both arms with respect to symptom control

SYMPTOMS	GROUP	START	1st F/U	2nd F/U	3rd F/U	OVERALL IMPROVEMENT
COUGH	A	25/30(83.3%)	18/30(46.7%)	13/30	12/30	35/60(58.3%)
	B	22/30(73.3%)	15/30(50%)	14/30	13/30	
HAEMOPTYSIS	A	10/30(33.3%)	02/30	022/30	02/30	55/60(91.7%)
	B	12/30(40%)	03/30	02/30	03/30	
DYSPNOEA	A	25/30(83.3%)	12/30	11/30	10/30	39/60(65.0%)
	B	22/30(73.3%)	13/30	12/30	11/30	
CHEST-PAIN	A	20/30(66.7%)	05/30	04/30	04/30	51/60((85.0)
	B	16/30(53.3%)	07/30	05/30	05/30	

Hemoptysis had the highest improvement rate 100% in bothgroups which is noted at the first week after RT and seemedto last throughout the planned follow up period. Dyspneawas palliated in 10 (66.7%) out of 15 patients with significant dyspnea in group A. Specifically, dyspnea improved in 9 patientsat the first week after RT and in I patient at the sixthweek; while 9 (64.3%) out of 14 patients with significant dyspnea in group B were palliated, 6 of them at the first week after RT and 3 at the sixth week. Cough was improved in 9 (60%) out of 15 patients with significant cough in group A, 8 of them were improved at first week after RT and only I patient at the sixth week; while 10 (66.7%) out of 15 patients with significant cough in group B were palliated, all of them at the first week after RT. As regards patients with significant chest pain, in group A 5 (71.4%) out of 7 patients were palliated, all

at the first week after RT; while in group B 7 (70%) out of 10 patients with significant chest pain were improved, all of them at the first week after RT.

Table 8: Numbers of patients reporting esophagites after Radiotherapy.

TREATMENT	ESOPHAGITES		Total
	No	Yes	
Arm A	22	8	30
	73.3%	26.7%	100.0%
Arm B	23	7	30
	76.7%	23.3%	100.0%
Total	45	15	60
	75.0%	25.0%	100.0%

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. (p=0.766)

Table 9: Comparison between the two studied groups according to their survival (in months).

Regimne	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

Although the effect of chemotherapy in advanced NSCLC in the 1980s was proven superior to the best supportive care with respect to survival, quality of life and symptom relief and there has been an expanded use and increasing efficacy of novel chemotherapy regimens for this disease during recent years[8]. Still, thoracic RT remains an important treatment modality for patients with symptoms from intrathoracic disease.

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). This was close to the mean age of the patients randomized in the medical research council (MRC) I study[9]which was 65 years, and that of the Norwegian study[10]which was 68 years.

The majority of patients in both groups were males 80% in group A and 93.3% in group B. This male predominance is found in almost all the previously listed studies except in the American study[11] in which females were 61% of the study population. All cases were histopathologically proved to be NSCLC. Squamous cell carcinoma (SCC) was the most common pathological subtype in both groups followed by large cell carcinoma and adenocarcinoma, this is against the international incidence in which adenocarcinoma is the most common histopathological type of NSCLC and this could be attributed to the small number of patients in this study which may not be representative of the real incidence in the community. Moreover, most of the patients were males who smoke bad quality of cigarettes with high tar content. However, this is matching with the MRC I, the Norwegian and the Polish[9,10] studies, population in which SCC was also the predominate subtype.

All patients incorporated in this study were stage IV disease. In our study, only patients with poor prognostic factors in stage IIIA who were not considered as candidates for any curative treatment were eligible, and those were only 13.3% of patients in both groups.

Considering the poor prognosis for the patients in this study, the primary end point was the relief of symptoms caused by the intra-thoracic disease, which were dyspnea, cough, hemoptysis, and chest pain. The results of our study showed that

there was a significant palliation of these symptoms following RT as reported by patients and also assessed clinically with no statistically significant difference among both groups. 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). Such a comprehensive assessment is particularly important in the setting of lung cancer, a tumor typically accompanied by multiple symptoms. The efficacy of palliative RT depends on the type of predominant symptom. Several studies demonstrated that the most effectively palliated symptoms include hemoptysis and chest pain[11]. In some studies, including the present study, RT also resulted in effective relief of cough and dyspnea[9,10].

According to the patient reported symptom control, hemoptysis had the highest improvement rate of 100% in both groups which was noted at the first week after RT and seemed to last throughout the planned follow up period as noted by the significant improvement of the mean scores of hemoptysis throughout the follow up period. Patients reported improvement in chest pain by 71.4% and 70% in group A and B respectively but for a shorter period of time as noted by the increased mean scores of chest pain at week 16 after RT. Cough was improved in 66.7% and 73.3% of patients in group A and group B respectively while dyspnea was palliated in 73.3% and 60% of patients in group A and group B respectively. The palliation for both dyspnea and cough was of longer duration than that of chest pain and continued till week 16 after RT. There was no statistically significant difference in the palliation rate or degree of all symptoms among both groups.

As regards the clinician symptom evaluation only patients with significant symptoms at baseline were analyzed, the results coincide with those reported by patients with no major discrepancy. Again hemoptysis had the highest overall improvement in 100% of patients in both groups, followed by chest pain, dyspnea and cough with overall improvement rates ranging from 60% to 71.4% with no statistically significant difference among both study arms.

These results were in agreement with the results of the prospective randomized trials of the MRC I and II[10,12]. All these studies showed a significant palliation of the intrathoracic symptoms after the hypofractionated regimen of 17 Gy in two fractions, which was equal to that achieved by more protracted regimens. The palliation rate of symptoms in these studies was reported as; hemoptysis having the highest improvement that ranged from 80% to 100%, denoting the very effective hemostatic control achieved by RT, cough palliation observed in 40–83%; dyspnea in 40–75%; and chest pain in 50–80%.

These results however were challenged by a few studies, which demonstrated better palliation in patients given higher radiation doses[13,14]. These discrepancies can at least partially be explained by different fractionation schedules, various end points and differences in evaluation tools used in particular studies[14]. In particular, many studies emphasized the importance of relying more on patient self-assessment than on physician evaluation, as major differences are observed between results of both these judgments.

Induced esophagitis was the main toxicity of treatment as reported by patients and assessed clinically as well, with no significant difference among both groups. Sixty percent of patients in both groups suffered from significant dysphasia as assessed 1 week after RT, 1patient(6.7%) in group A and 2 patients (13.3%) suffered from grade III dysphagia that required tube feeding & IV fluids. The condition then resolved rapidly and only 20% of patients in group A and 26.7% in group B had significant dysphagia at week 6 after RT, these patients were also suffering from dysphagia before the start of treatment due to the local compression of the tumor over the esophagus. Skin toxicity was detected only in 1 patient in

group A in the form of Grade I erythema which was transient and improved without treatment. Clinically vomiting after RT was transient and grade I, relieved by the routine medications. No cases of any grade of radiation induced myelopathy or pneumonitis were detected in any of the patients in both arms during the follow up times. These results are in accordance with some previous randomized trials which reported dysphagia as main toxicity of treatment with no differences among different fractionation schedules used in these trials[9,12] while other trials reported more dysphagia in the short course hypofractionated arm[15] and two trial reported more dysphagia in the more protracted regimen[16]. Spinal toxicities were reported in some studies[17] but in rare cases.

As regards the local radiographic response to RT, the overall response rate was not significantly different among both study arms (35.7% and 42.8% in group A and group B, respectively). This was close to the results of MRC I trial that showed a complete response in 7% of patients in the hypofrationated arm and 5% of the multifractionated regimen, and a partial response in 22% and 25%, respectively.

The overall survival for patients in the study revealed no significant survival difference among the two treatment groups P value = 0.550. The median survival was 5 and 6 months in group A and B respectively. This short overall survival is not surprising given the overall poor PS of the patients, as well as that more than half of them were metastatic at treatment and about two thirds had received previous chemotherapy and progressed on it.

Survival analysis of this study is in accordance to that of the majority of the RCTs which showed no significant differences between the hypofractionated and higher dose multifractionated regimens in terms of survival[18]. The major concern related to the use of hypo fractionated treatment schedules is their potential inferiority in terms of overall survival as shown in three RCTs[15]. Some evidence exists that higher RT doses result in a modest increase in survival, although at the expense of higher acute toxicity[16]. The effect of RT dose and regimen on overall survival if any was in all instances limited to patients with good PS and/or relatively non advanced disease, i.e. those most likely to benefit from improved local control[16]. In contrast to these results, the polish study[12] demonstrated improved survival in the shorter treatment arm. This intriguing result should howeverbe interpreted with caution due to a relatively small number of patients in that study. Although in two other studies a trend toward improved survival in the lower dose group was observed in a subset analysis[19]. It seems reassuring that such a short treatment is at least not inferior in terms of survival compared to a standard schedule.

Apart from purely medical factors such an approach has obvious logistic and economic 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[14]. 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 RT[14].

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