Optimization of dose and fractionation of endobronchial brachytherapy with or without external radiation in the palliative management of non-small cell lung cancer: A prospective randomized study

ABSTRACT

Aims: Endobronchial brachytherapy (EBBT) is an established modality for the palliation in advanced non-small cell lung cancer. We compared three different schedules using EBBT with or without external radiation (XRT) in this setting.

Materials and Methods: Forty-five patients were randomized to three treatment arms. Arm A received XRT to a dose of 30 Gy/ 10 fr/ 2 weeks and two sessions of EBBT 8 Gy each. Arm B received the same XRT and a single session of EBBT 10 Gy at 1 cm. Arm C received only a single fraction of brachytherapy to a dose of 15 Gy at 1 cm without XRT. Symptomatic response rates, duration of symptom palliation, obstruction scores, quality of life outcomes and complications were assessed and compared.

Results: The overall symptomatic response rates were 91% for dyspnea, 84% for cough, 94% for hemoptysis and 83% for obstructive pneumonia. There was no significant difference between the arms. The median time to symptom relapse was 4-8 months for all symptoms and the median time to symptom progression was 6-11 months. The results were comparable between groups except for hemoptysis, where a shorter palliation was seen in Arm C that achieved statistical significance ($P < 0.01$). Quality of life showed significant improvement, with maximum benefit in Arm A. Complication rates were low. Only one patient died of fatal hemoptysis.

Conclusion: EBBT is thus a safe and effective palliative tool in advanced non-small cell lung cancer, either alone or in conjunction with XRT. The difference between the treatment arms were not statistically significant in most categories, but patients treated with XRT and two endobronchial sessions of 8 Gy had the most consistent benefit in terms of all the parameters studied.

KEY WORDS: Brachytherapy, endobronchial lung cancer, palliation, quality of life, radiotherapy, randomized controlled trial

I Mallick, SC Sharma,
D Behera*, S Ghoshal,
AS Oinam

Departments of
Radiotherapy and
*Pulmonary Medicine,
Post-graduate Institute
of Medical Education
and Research,
Chandigarh, India

For correspondence:
Dr. Indranil Mallick,
Department of
Radiotherapy, PGIMER,
Chandigarh -160 012,
India.
E-mail:
imallick@gmail.com

INTRODUCTION

Lung cancer is the commonest cause of cancer death worldwide.[1] The majority of patients present with unresectable disease that results in a 1-year survival of 20-50% even with the best of nonsurgical modalities.[2] Symptoms of endobronchial disease are extremely common with local progression. These include cough, hemoptysis, dyspnea and post-obstructive pneumonia. Endobronchial occlusion is common, even at initial diagnosis and many lung neoplasms present with atelectasis and pneumonia. The palliation of these symptoms is an important goal and could lead to an improved quality of life in these patients.

Various modalities have been used in palliation of symptoms in unresectable non-small cell lung cancer (NSCLC). Endobronchial brachytherapy (EBBT) has been one of most successful in endobronchial symptom relief. Numerous reports over the last two decades have firmly established the efficacy of High Dose Rate (HDR) endobronchial brachytherapy as a safe, convenient and effective tool for symptom palliation in NSCLC. However, the optimal dose and fractionation schedule for endobronchial brachytherapy is still not established, nor is the way in which it should be combined with external radiation (XRT), if at all. The published literature has largely reported the treatment of a heterogeneous group of patients with both primary carcinoma and carcinoma that is recurrent after prior XRT. Many different treatment schedules have been used.[3-7] External radiation has been used concurrently in some groups but not in others. No study so far has prospectively compared different regimens in the palliative setting. The duration of symptomatic improvement has not been consistently assessed.

The impact on quality of life with endobronchial brachytherapy has also not been evaluated using validated questionnaires.

Our study was designed to compare the subjective and objective responses to three such commonly used regimens, for subjective and objective response rates, response duration, quality of life outcomes and complications. This would serve as a guide to better palliation of endobronchial symptoms in inoperable NSCLC.

MATERIALS AND METHODS

Forty-five patients with previously untreated, inoperable, locally advanced non-small cell lung cancer were recruited into this prospective phase II randomized study between May 2003 and February 2005. All patients had endoscopically proven endobronchial disease and one or more symptoms of endobronchial disease (dyspnea, cough, hemoptysis or obstructive pneumonia). A KPS score of 60 to 80 was required for eligibility into a palliative protocol. Previously treated patients and those with metastatic disease who would require primary chemotherapy were not considered eligible.

All patients were randomized to one of three treatment arms. In Arm A, all patients received external radiation to the dose of 30 Gy in 10 fractions over 2 weeks. Endobronchial application and brachytherapy was carried out at the end of the first and second weeks on days 6 and 13. XRT was not given simultaneously with EBBT on the same day. The dose of EBBT was 8 Gy at 1 cm from the source axis on each of these applications. In Arm B, the same schedule for external radiation was used. Endobronchial application and brachytherapy was carried out at the end of the second week on day 13 with a single fraction of 10 Gy at 1 cm. In Arm C, patients did not receive external radiation. They were treated with a single fraction of EBBT to a dose of 15 Gy at 1 cm.

External radiation was delivered with megavoltage photon beams of Co^{60} or a 6-MV Linear accelerator using (antero-posterior) AP-PA parallel-opposed fields. The clinical target volume (CTV) included the gross tumor and mediastinal nodes with a 2 cm margin based on simulator images.

Endobronchial brachytherapy was performed as an outpatient procedure. Trans-nasal fiber-optic bronchoscopy was performed to define the location and extent of the endobronchial involvement. A polythene catheter of diameter 6 Fr (1.9 mm) and length 100 cm was introduced through the working channel of the bronchoscope and then pushed to at least 2 cm beyond the distal end of the endobronchial lesion. The bronchoscope was then withdrawn while maintaining the catheter in place.

The position of the catheter was verified under fluoroscopy using dummy sources. The total length of the endobronchial component plus a clear margin of 2 cm both proximally and

distally was treated. Treatment planning was done with the help of a Nucletron® PLATO treatment planning system using orthogonal films. A Nucletron HDR Microselectron® with an Ir-192 source was used for treatment. A step size of 5 mm was used. Dose was prescribed at 1 cm from the central axis of the source.

Each patient was monitored twice a week during treatment by external radiotherapy to look for any acute toxicity. After 1 month of completion of treatment, patients were examined by repeat bronchoscopy for evaluation of endobronchial response. The extent of obstruction using radiological and endoscopic criteria before and after treatment was scored using the obstruction score [Table 1]. Symptoms were recorded and scored before treatment and at monthly intervals after treatment completion using the Speiser symptom score[8] [Table 1]. Chest X-rays were done at monthly intervals to follow the radiological response to treatment. A quality of life assessment using the EORTC QLQ-C30 and LC-13 version 3 questionnaires was done before treatment and at the end of 1 month following treatment.[9,10] Acute and late

Table 1: Symptom and obstruction scores of speiser[8]

Symptom index scores of speiser

Score	Definition
Dyspnea	
0	None
1	Dyspnea on moderate exertion.
2	Dyspnea with normal activity, walking on level ground.
3	Dyspnea at rest.
4	Requires supplemental oxygen.
Cough	
0	None
1	Intermittent, no medication required.
2	Intermittent, non narcotic medication.
3	Constant or requiring narcotic medication.
4	Constant, requiring narcotic medication but without relief.
Hemoptysis	
0	None
1	Less than 2 per week
2	Less than daily but greater than 2 per week
3	Daily, bright red blood or clots
4	Decrease of Hemoglobin and/or hematocrit >10% , greater than 150 cm, requiring hospitalization or transfusion.
Pneumonia or elevated temperature	
0	Normal temperature, no infiltrates, white blood count <10,000
1	Temperature > 38.5 C and infiltrate. WBC < 10,000.
2	Temperature > 38.5 C and infiltrate and/or WBC >10,000
3	Lobar consolidation on radiograph
4	Pneumonia or elevated temperature requiring hospitalization

Obstruction definition and scores

Location	>50% obstruction	< 50% obstruction	<10% obstruction
Trachea	10	5	2
Main bronchus	6	3	1
Lobar bronchus	2	1	

Atalectasis or pneumonia: An additional 2 points per lobe

pulmonary and esophageal toxicity were recorded based on RTOG morbidity scoring criteria.[11]

Symptom response was defined as a reduction of the severity of the symptom characterized by a fall in the symptom score. For time-based analysis, the 'time to relapse' was defined as the time for which the symptom severity remained lesser than at presentation. The 'time to progression' was defined as the time for which the symptoms did not show progression to a higher grade of severity than at presentation.

Symptomatic response rates were measured for the four symptoms assessed and compared between groups using the Chi-square test. Actuarial time-based analyses for relapse and progression of symptoms were done using the Kaplan Meier method. Objective response rates were compared using the Kruskall Wallis test. The quality of life before and after treatment was compared using nonparametric statistics using the Wilcoxon signed-rank test. All analyses were performed using the statistical software SPSS® version 10. Differences were considered significant with a *P* value of <0.05.

RESULTS

The patients in the three arms in this study were well matched with respect to age, sex, histology and stage of disease [Table 2]. The mean age was 65 years (range 35 to 75 years). The subjects were predominantly male (96%). Squamous cell carcinoma was the predominant histology (89%). The duration of follow-up ranged from 2 to 17 months with a median follow-up of 6 months. The CONSORT flow chart for patients in the study is provided in Figure 1.
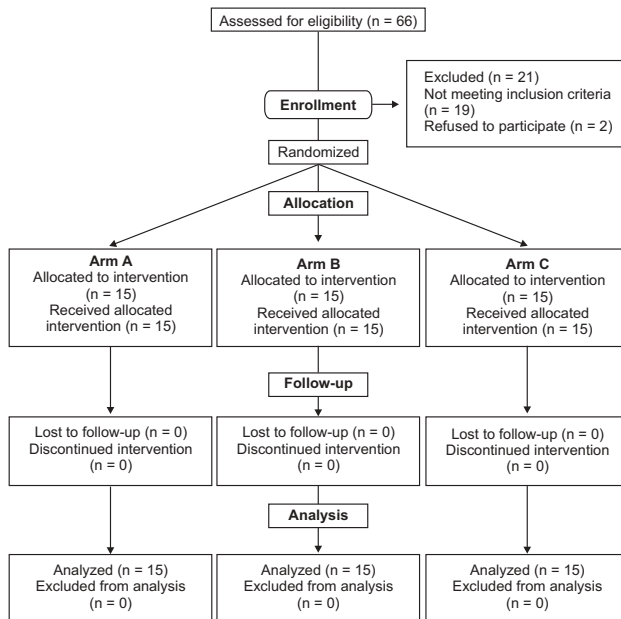
Symptomatic response
Endobronchial symptoms were common at presentation. Dyspnea was present in 95.6% of the patients, cough in 100%, hemoptysis in 75.6% and fever in 64.4%.

There was a significant improvement in all the four symptoms

Figure 1: CONSORT flow chart for patients in the study

assessed. The overall response rate for dyspnea was 90.7%; cough, 84.5%; hemoptysis, 94.1%; and obstructive pneumonia, 82.7%. The response in each study arm is depicted in Table 3. The response rates were similar between groups and there was no statistically significant difference.

The duration of response was prolonged for each symptom. The time to relapse and the time to progression for each symptom in the three arms of study are shown in Table 4. The median time to relapse of all symptoms was a minimum of 4 months in any arm. Progression of symptoms was also delayed by 6 months or more. Hemoptysis had the most sustained duration of relief. On comparison between arms, the duration of relief from hemoptysis was significantly shorter in patients in group C, who were treated with a single fraction of endobronchial brachytherapy alone. For the other symptoms, there was no statistically significant difference between groups.

Obstruction score
There was considerable improvement in the obstruction score across all patient groups. Forty-two out of 45 patients (93.3%) showed an improvement in the obstruction score. The mean initial score was 5.49 and the mean post-treatment score was 2.69. A 49% reduction in the obstruction score was seen overall. This reduction was highly significant statistically (Wilcoxon signed-rank test, *P* < 0.001). The individual reduction in arms A, B and C were 57.7, 55.8 and 44.4% respectively. The difference between groups was not statistically significant (Kruskall Wallis test, *P* = 0.54).

Radiological response
The response in lung collapse or consolidation was assessed. Twenty-nine patients initially had some features of obstructive collapse or consolidation. A favorable response was seen in 24

Table 2: Patient profile

	Overall	Arm A	Arm B	Arm C
No. of patients	45	15	15	15
Age	64.5	68.9	63.1	61.5
	(35-75 yrs)	(45-75 yrs)	(46-70 yrs)	(35-70 yrs)
Sex				
Male	43 (96)	15 (100)	14 (93)	14 (93)
Female	2 (4)	0 (0)	1 (7)	1 (7)
Histology				
SCC	40 (89)	13 (87)	13 (87)	14 (93)
Adenocarcinoma	4 (9)	1 (7)	2 (13)	1 (7)
Large cell	1 (2)	1 (7)	0 (0)	0 (0)
Stage				
IIIA	18 (40)	6 (40)	7 (47)	6 (40)
IIIB	27 (60)	9 (60)	8 (53)	9 (60)
Location				
Main bronchus	20 (44)	6 (40)	6 (40)	8 (53)
Lobar bronchus	25 (56)	9 (60)	9 (60)	7 (47)

Figures in parentheses is percentage

Table 3: Symptom incidence and response rates

	Overall	Arm A	Arm B	Arm C	*P*
Dyspnea					
Incidence	43 (96)	15 (100)	13 (87)	15 (100)	
Response (CR+PR)	39 (91)	14 (93)	12 (92)	13 (87)	*P*=0.798
Cough					
Incidence	45 (100)	15 (100)	15 (100)	15 (100)	
Response (CR+PR)	38 (84)	12 (80)	13 (87)	13 (87)	*P*=0.844
Haemoptysis					
Incidence	34 (76)	9 (60)	13 (87)	12 (80)	
Response (CR+PR)	32 (94)	9 (100)	13 (100)	10 (82)	*P*=0.143
Obstructive pneumonia					
Incidence	29 (63)	9 (60)	10 (67)	10 (67)	
Response (CR+PR)	24 (83)	9 (100)	7 (70)	8 (80)	*P*=0.216

CR: complete response; PR: partial response, Figures in parentheses is percentage

Table 4: Duration of symptom response

	Overall	Arm A	Arm B	Arm C	*P*
Dyspnea					
Median time to relapse	5	4	5	6	*P*=0.81
Median time to progression	7	7	7	6	*P*=0.07
Cough					
Median time to relapse	5	4	7	4	*P*=0.09
Median time to progression	8	7	NR	NR	*P*=0.77
Haemoptysis					
Median time to relapse	8	8	NR	5	*P*=0.01
Median time to progression	NR	11	NR	6	*P*=0.01
Obstructive pneumonia					
Median time to relapse	5	5	5	5	*P*=0.98
Median time to progression	8	8	10	NR	*P*=0.97

NR: Median not reached

out of 29 patients (82.76%). The median time to recurrence of features of collapse or consolidation on X-rays was 8 months. There was no statistically significant difference between the arms in terms of response rates or duration of response.

Quality of life

The QLQ scores are depicted in Table 5. There was improvement in all categories that had impaired initial scores. The global health status was significantly improved. Overall scores show a statistically significant improvement in the symptom scales of dyspnea, cough, hemoptysis and fatigue; nearly all the functional scales also showed significant improvement. Other parameters that were initially normal were maintained.

When each group was separately assessed, patients in Arm A showed a statistically significant improvement in 10 variables.

Table 5: Quality of life outcomes

	Overall		Arm A		Arm B		Arm C	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
QLQ-C30								
Global health status (QOL)	35	67*	37	75*	35	63*	34	62*
Functional Scales								
Physical functioning	67	85*	71	90*	74	85*	56	78*
Role functioning	61	83*	64	89*	71	84*	49	78*
Emotional functioning	69	77*	71	81*	71	74	64	76
Cognitive functioning	90	93	96	96	88	92	87	91
Social functioning	79	86*	88	96*	80	80	68	82
Symptom scales								
Fatigue	48	31*	50	23*	42	36	50	33*
Dyspnea	55	21*	62	20*	45	24*	58	22*
Appetite loss	30	19	29	16	20	16	40	23*
Nausea and vomiting, pain, insomnia, constipation, diarrhea, financial	<20	<20	<20	<20	<20	<20	<20	<20
QLQ-LC13								
Symptom scales								
Dyspnea	30	10*	33	4*	25	13*	33	13*
Cough	62	33*	67	40*	65	36*	56	22*
Haemoptysis	31	6*	20	0*	47	9*	27	9
Sore mouth, dysphagia, peripheral neuropathy, alopecia,chest pain, arm-shoulder pain, other pain	<20	<20	<20	<20	<20	<20	<20	<20

*Denotes a statistically significant difference by the Wilcoxon sign-rank test, QOL: Quality of life

Though similar improvements were seen in the other two groups, some did not reach statistical significance. Significant improvement was seen in 7 variables in Arm B and 8 in Arm C. In the absence of clear guidelines on comparison of QLQ scores between groups, a formal statistical test of comparison was not performed.

Complications

The treatment-related morbidity was low. On the basis of the RTOG acute morbidity criteria, acute grade I odynophagia was seen in 14 of the 45 patients (31.1%). All occurred during the first month and resolved spontaneously within a few weeks. A transient increase in cough was seen in 12 patients (26.7%) immediately after the bronchoscopy procedure; it resolved by 72 h. All were self-limiting. No grade II-grade IV acute complications were noted.

One patient in Arm C died of fatal hemoptysis at 7 months. He had significant residual disease endoscopically at follow-up bronchoscopy after treatment completion and had progressive disease with pleural effusion.

Three out of the 45 patients developed features of post-radiation fibrosis without evidence of disease progression. Only 1 of these patients is symptomatic for fibrosis.

DISCUSSION

Palliation of symptoms in locally advanced NSCLC is a very important objective of treatment, given the poor prognosis of patients and short life expectancy. Endobronchial brachytherapy has established itself as a safe and extremely effective modality for palliation of endobronchial symptoms. Initially used mainly for recurrent endobronchial lesions, it soon found a place as a part of the primary palliative treatment with or without the simultaneous use of external radiation. Over the last three decades, numerous publications have highlighted excellent rates of palliation of endobronchial symptoms using EBBT, either alone or with external radiation.

The proper optimization of treatment using EBBT however suffers from a lack of uniformity in the treatment schedules used and in the type of patients treated. Most publications have retrospectively reported results of treatment of a mixed group of patients - recurrent, progressive and previously untreated. The treatment schedules used were also different in different studies. Some studies have used smaller fraction sizes (4-10 Gy) and three or more fractions.[3-5,7] Others have used higher doses 15-20 Gy, treated with a single fraction only.[6] External radiation has been used in some studies in addition to EBBT, but not used in some others.

There are no prospective randomized comparisons of different treatment schedules using endobronchial brachytherapy in the palliative setting. Guidelines have been based on consensus rather than prospective data.[12] It needs to be determined whether a single fraction of endobronchial brachytherapy would be as good as two or more fractions and whether external radiation needs to be used in conjunction with EBBT. A shorter or a more cost-effective schedule, if equally effective, would make the procedure much more acceptable to patients and caregivers.

The patients enrolled in the study were representative of the population of untreated NSCLC patients registered in our department. The patients were predominantly male, with squamous cell carcinomas and in their 5th-7th decade of life. Squamous cell carcinomas are the commonest histology in India and other developing countries.[13] These are also centrally located tumors, in contrast to adenocarcinomas and large cell carcinomas, and therefore more likely to cause an endobronchial growth or obstruction at proximal sites like the main or lobar bronchi.

Treatment in each of the three study arms resulted in excellent response rates. The overall response rates were similar to larger published retrospective series, as shown in Table 6. Hemoptysis had the best response rates with nearly all cases showing a complete response. But dyspnea, cough and obstructive pneumonia also responded in more than 80% of cases.

There was no significant difference between the treatment groups in the response rates to any of the symptoms. Most

Table 6: Comparison of symptom response and complications with published series

Study	n	Treatment EBBT ± XRT schedule (s)	Symptom control				Fatal haemoptysis %
			Dyspnea %	Cough %	Hemoptysis %	Obstructive pneumonia %	
Bedwinek[3]	38	(post-XRT 50 Gy) EBBT: 6 Gy x 3#	71	81	81	71	32
Speiser[4]	362	EBBT 10Gy x 3# ± XRT 60Gy; EBBT 10Gy x 3# ± XRT 37.5Gy; EBBT 7.5Gy x 3#	86	85	99	99	7.3
Chang[5]	76	EBBT 7Gy x 3# ± XRT 60-70 Gy	87	79	95	88	4
Gollins[6]	406	EBBT 15-20Gy x 1#	60	60	88	50	7.9
Muto[7]	320	EBBT 5Gy x 3# or 7 Gy x 2# or 10Gy x 1# + XRT 60Gy	90	82	99	90	7
Present series	45	EBBT 8Gy x 2# + XRT 30Gy/10# EBBT 10Gy x 1# + XRT 30Gy/10# EBBT 15Gy x 1#	91	84	94	83	2

EBBT: endobronchial brachytherapy; XRT: external radiation; #: fractions

results were nearly equal in the three radiation schedules. The rate of control of hemoptysis was low in Arm C compared to the other two arms but the difference was not statistically significant, probably owing to the limited number of patients in the study.

The duration of symptom palliation is a very important issue and has not been addressed adequately in published literature. Only two studies have specifically addressed the issue. Bedwinek *et al*[3] reported a median duration of 5 months and Sharma *et al*[14] reported that the addition of EBBT to XRT increased the duration of response from 4.4 to 6 months. In this study, the Kaplan Meier method was used to calculate the time to relapse and time to progression of each of the four symptoms individually. It was found that the palliation was durable for each of the symptoms studied. Both relapse and progression were delayed for a duration which was comparable to the life-expectancy of stage III patients with poor KPS. On comparison of the groups by the log rank test, there was no significant difference in duration of palliation of dyspnea, cough and obstructive pneumonia. But the duration of hemoptysis palliation was significantly shorter in Arm C compared to the other arms, both for relapse and progression.

Thus, though the overall symptomatic response rates are comparable in the three treatment schedules, there appears to be a significantly shorter duration of palliation of hemoptysis when endobronchial brachytherapy is used alone. The response rate for hemoptysis is also lower, though not statistically significant. The explanation for this could be that the biological equivalent dose (BED) of the schedule involving only endobronchial brachytherapy (Arm C) was lower than the BED in the other two schedules. The addition of external radiation in the other two schedules may also have led to a better control of the extra-bronchial component of disease and delayed overall tumor regrowth.

The improvement in obstruction scores was excellent and consistent across groups. The extent of improvement was not significantly different when the arms were compared. Likewise, the radiological response was also similar between groups. This was expected since the endobronchial component of radiotherapy is responsible for improvement in obstruction scores and obstructive radiological signs.

The overall rate of complications was very low. The procedure itself was extremely well tolerated in all patients. All acute complications were mild and self-limiting. All cases of odynophagia and mild cough subsided within 2 weeks of treatment. None of the cases required admission or parenteral medications. Fibrosis was the only definite chronic complication seen. Only five cases showed radiological evidence of mild fibrosis and even these patients were asymptomatic. Patients in Arm C had low rates of odynophagia and fibrosis because external radiation was not delivered; however, in view of the mild nature of complications, a difference in the three groups would have no clinical relevance.

Bronchial stenosis and radiation bronchitis have been reported as long-term complications.[15] This was not encountered in our study probably because only a moderate dose of XRT was administered and EBBT was administered for a maximum of two sessions, resulting in a lower total dose to the bronchial mucosa.

Fatal hemoptysis is the most significant long-term complication of endobronchial brachytherapy. Reported rates of fatal hemoptysis have varied between 0 and 32%. Most of the large series of data however report a low rate of hemoptysis (4 to 7%). Studies by Gollins *et al*[6] and Langendijk *et al*[16] have identified 'dose per fraction' of EBBT as a predictive factor for hemoptysis, with a greater incidence when doses above 15-20 Gy were used. However, other authors like Hennequin *et al*[17] have not found any consistent correlation with dose. These authors have questioned the role of EBBT in causing hemoptysis in those patients who have persistent or recurrent endobronchial disease after treatment. It is highly probable that the fatal hemoptysis in these patients is from the tumor and not from the late effects of radiotherapy. In our study, one patient belonging to Arm C died of fatal hemoptysis 7 months after treatment. He had documented persistence of disease after treatment and at the time of hemoptysis showed extensive signs of disease progression radiologically (massive pleural effusion and increase in lung mass). Thus the cause of the bleed in this patient was likely to be the disease itself.

Improvement in the quality of life is one of the primary goals of cancer treatment. Though improvements in quality of life have been mentioned in a few previous studies, no published study has reported the results of quality-of-life outcomes after endobronchial brachytherapy using a validated questionnaire. In this study, the EORTC QLQ-C30 (general) and LC-13 (for lung cancer) were used and the outcomes were assessed for all patients. It was seen that there was a statistically significant improvement in nearly all the parameters that were initially impaired. The improvement spanned the global health status, functional scores and all the major endobronchial symptom scores. Patients in Arm A showed the most consistent benefit, with an improvement in 10 parameters; while those in Arm B and C improved in 7 and 8 parameters respectively.

Given the limited number of patients in this study, the comparison between schedules is underpowered. However, the results of this phase II trial indicate that a combination of XRT and fractionated EBBT results in a more prolonged symptom palliation and a better overall improvement in the quality of life. Yet in patients with poor performance status, a single fraction of EBBT of 15 Gy could provide an equivalent benefit in response rates and objective signs, thus qualifying to be an effective and cost-effective method of palliation.

CONCLUSION

Endobronchial brachytherapy is a safe and effective modality for palliation of endobronchial symptoms in inoperable

advanced lung cancer. All endobronchial symptoms are palliated and the duration of response is satisfactorily prolonged. Significant improvement was achieved in the quality of life of patients. The optimal dose, fractionation and the combination with XRT remain a matter a debate. Patients treated with a single fraction EBBT alone had a shorter duration of symptom palliation, though comparable rates of palliation of all symptoms and objective signs were achieved.

ACKNOWLEDGMENT

REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. IARC cancer. Base No. 5. Version 2.0. IARC Press: Lyon, France; 2004.
2. Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710-7.
3. Bedwinek J, Petty A, Bruton C, Sofield J, Lee L. The use of high dose rate endobronchial brachytherapy to palliate endobronchial recurrence of previously irradiated bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1992;22:23-30.
4. Speiser BL, Spratling L. Remote after loading brachytherapy for the local control of endobronchial carcinoma. Int J Radiat Oncol Biol Phys 1993;25:579-87.
5. Chang LF, Horvath J, Peyton W, Ling S. High dose rate after loading Intraluminal brachytherapy in malignant airway obstruction in lung cancer. Int J Radiat Oncol Biol Phys 1994;28:589-96.
6. Gollins SW, Burt PA, Barber PV, Stout R. High dose rate intaluminal radiotherapy for carcinoma bronchus: Outcome of treatment of 406 patients. Radiother Oncol 1994;33:31-40.
7. Muto P, Ravo V, Panelli G, Liguori G, Fraioli G. High dose brachytherapy of bronchial cancer: Treatment optimization using three schemes of therapy. Oncologist 2000;5:209-14.
8. Speiser B, Spratling L. Intermediate dose rate remote afterloading brachytherapy for intraluminal control of bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1990;18:1443-8.
9. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
10. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: A modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994;30A:635-42.
11. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group and the European organization for research and treatment in cancer. Int J Radiat Oncol Biol Phys 1995;31:1341-6.
12. Nag S, Kelly JF, Horton JL, Komaki R, Nori D. Brachytherapy for carcinoma of the lung. Oncology 2001;15:371-81.
13. Behera D, Balamugesh T. Lung cancer in India. Indian J Chest Dis Allied Sci 2004;46:269-81.
14. Sharma SC, Behera D, Beriwal S, Singh DP, Gupta D, Ghosal S, *et al*. Evaluation of addition of endobronchial brachytherapy for symptom relief in locally advanced bronchogenic carcinoma - A prospective, randomized study. J Clin Radiother Oncol 2002;2:14-9.
15. Speiser BL, Spratling L. Radiation bronchitis and stenosis secondary to high dose rate endobronchial irradiation. Int J Radiat Oncol Biol Physics 1993;25:589-97.
16. Langendijk JA, Tjwa MK, de Jong JM, ten Velde GP, Wouters EF. Massive haemoptysis after radiotherapy in inoperable non-small cell lung carcinoma: Is Endobronchial Brachytherapy really a risk factor? Radiother Oncol 1998;49:175-83.
17. Hennequin C, Tredaniel J, Chevret S, Durdux C, Dray M, Manoux D, *et al*. Predictive factors for late toxicity after Endobronchial Brachytherapy: A multivariate analysis. Int J Radiat Oncol Biol Phys 1998;42:21-7.