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External irradiation versus external irradiation plus endobronchial brachytherapy in inoperable non-small cell lung cancer: a prospective randomized study

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Abstract

Purpose: No randomized studies are available on the additional value of endobronchial brachytherapy (EBB) to external irradiation (XRT) regarding palliation of respiratory symptoms (RS). A prospective randomized study was initiated to test the hypothesis that the addition of EBB to XRT provides higher levels of palliation of dyspnea and other RS and improvement of quality of life (QoL) in patients with non-small cell lung cancer (NSCLC) with endobronchial tumour.

Materials and methods: Patients with previously untreated NSCLC, stages I-IIIb, WHO-performance status of 0–3 and with biopsy proven endobronchial tumour in the proximal airways were eligible. EBB consisted of two fractions of 7.5 Gy at 1 cm on day 1 and 8. XRT started at day 2. The XRT dose was 30 Gy (2 weeks) or 60 Gy (6 weeks). The EORTC QLQ-C30 and QLQ-LC13 were assessed before treatment and 2 weeks, 6 weeks, 3, 6 and 12 months after treatment. Re-expansion of collapsed lung was tested by the inspiratory vital capacity (IVC) and CT scan of the chest.

Results: Ninety-five patients were randomized between arm 1 (XRT alone) ($n = 48$) or arm 2 (XRT + EBB) ($n = 47$). The arms were well balanced regarding pre-treatment characteristics and QoL scores. The compliance for QoL-assessment was >90% at all times. No significant difference between the trial arms was observed with respect to response of dyspnea. However, a beneficial effect of EBB was noted concerning the mean scores of dyspnea over time ($P = 0.02$), which lasted for 3 months. This benefit was only observed among patients with an obstructing tumour of the main bronchus. A higher rate of re-expansion of collapsed lung was observed in arm 2 (57%) compared to arm 1 (35%) ($P = 0.01$). The inspiratory vital capacity (IVC) assessed 2 weeks after radiotherapy improved with 493 cm^3 in arm 2 and decreased 50 cm^3 in arm 1 ($P = 0.03$). No difference was noted regarding the incidence of massive haemoptysis (13 vs. 15%).

Conclusion: The addition of EBB to XRT in NSCLC is safe and provides higher rates of re-expansion of collapsed lung resulting in a transient lower levels of dyspnea. This beneficial effect was only observed among patients with obstructing tumours in the main bronchus.

Keywords: External irradiation; Endobronchial brachytherapy; Non-small cell lung cancer

1. Introduction

Radiotherapy is an effective treatment modality in the palliation of most respiratory symptoms among patients with inoperable non-small cell lung cancer (NSCLC) [18,20,21,26]. In two randomized studies conducted by the Medical Research Council (MRC) investigating different palliative schedules in inoperable NSCLC, the rates of symptom relief varied from 48 to 65% for cough, from 72 to 86% for haemoptysis and from 59 to 80% for chest pain [20,21].

In a large number of studies, the results of endobronchial brachytherapy (EBB) with or without external irradiation (XRT) as palliative treatment for centrally localized lung cancer have been reported [5,6,11,13,22,24,30]. In earlier

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studies, EBB was particularly used as palliative treatment in case of endobronchial recurrences after XRT. In this category of patients, EBB offered adequate symptomatic relief in a substantial proportion of patients [3,9,12,23–25,27,32]. Later, EBB was also combined with XRT as primary treatment [2,6,8,30]. Speiser and co-workers [27] reported on a prospective study among 342 patients with endobronchial tumours treated by the combination of XRT (30 to 60 Gy) and concomitant EBB during week 1, 3 and 5. The results achieved with this approach were quite remarkable, with response rates of 99% for haemoptysis, 85% for cough and 86% for dyspnea. In a retrospective study, Chang and co-workers [6] reported comparable results with the combination of XRT (20 to 70 Gy) and concomitant EBB (3×7 Gy HDR) during week 2, 4 and 6. They observed response rates of 79% for cough, 95% for haemoptysis and 87% for dyspnea.

Many patients with centrally localized lung cancer present with post-obstructive pneumonia or atelectasis. With XRT alone, the proportion of patients in whom a partial or complete re-expansion of collapsed lung has been achieved varies from 21 to 61% [7,19,29]. With the combination of EBB and XRT, much higher rates of re-expansion have been observed, varying from 67 to 99% [2,6,30].

These results suggest that with the combination of XRT and EBB, post-obstructive features such as pneumonitis and atelectasis are likely to be treated more adequately compared to XRT alone. This could also account for the higher response rates for those respiratory symptoms associated with post-obstructive features, in particular, for dyspnea.

However, the definitions used for response of symptoms, re-expansion of collapsed lung, and the methods used to assess these responses, differed widely between the aforementioned studies. Moreover, the inclusion criteria of these studies differed widely and no randomized studies have been published investigating the additional value on palliation of respiratory symptoms of EBB plus XRT versus XRT alone. Therefore, the additional value of EBB concomitantly with XRT is not yet well defined.

This prospective randomized phase III study was conducted to test two specific hypotheses. Firstly, we expected that among patients with centrally localized NSCLC, the addition of concomitant EBB during XRT would result in higher rates of re-expansion of post-obstructive infiltration/atelectasis and/or higher rates of prevention of these post-obstructive features. Secondly, we expected that these higher rates of re-expansion would result in higher levels of palliation of respiratory symptoms, in particular for dyspnea and cough, as well as in greater levels of improvement in quality of life (QoL). Furthermore, the higher dose that can be administered with EBB to the endobronchial-obstructing tumour may lead to higher a degree of desobstruction and an additional beneficial effect on respiratory symptoms, even in the absence of an atelectasis.

2. Materials and methods

2.1. Eligibility criteria

To be eligible for the study, patients had to have biopsy proven NSCLC, stage I, II, IIIa or IIIb disease according to the UICC 1992 [1], endobronchial tumour in the proximal main bronchus or lobar bronchus, a World Health Organization performance status 0–3 and no prior or planned chemotherapy, prior surgery, prior radiotherapy, other malignancies, pleuritis carcinomatosa, distant metastases or superior vena cava syndrome. Prior treatment with Neodymium-YAG laser was not allowed and, therefore, patients with a complete obstruction were not eligible. Patients requiring two or more catheters were also excluded. The local ethical committees of the participating centres approved the study and all patients provided written informed consent.

2.2. Study design

Eligible patients were randomized to receive external irradiation alone (treatment arm 1) or external irradiation in combination with endobronchial brachytherapy (treatment arm 2). For external irradiation, two fractionation schedules were allowed, i.e. a radical fractionation schedule (60 Gy) or a palliative fractionation schedule (30 Gy).

Patients with a WHO performance status 3, supraclavicular lymph node metastases and/or distant metastases with symptoms related to intrathoracic tumour, were considered to have the worst prognosis and were selected for the palliative fractionation schedule.

Patients with stage I or II disease (UICC 1992) with a tumour diameter > 4 cm or stage IIIa and stage IIIb disease (UICC 1992) without supraclavicular lymph node metastases and a WHO performance ≤ 2 were considered to have an intermediate prognosis and were selected for the radical fractionation schedule.

For both fractionation schedules, the target volume included the primary tumour and enlarged mediastinal and supraclavicular lymph nodes with a margin of 2 cm, as well as the mediastinal lymph node areas on both sides. For patients treated according to the palliative schedule, the target volume was irradiated with 3 Gy per fraction (four times a week) up to a total dose of 30 Gy (100%) without correction for lung tissue density. For patients treated according to the radical schedule, the aforementioned target volume was treated with fraction doses of 2.25 Gy (four times a week) to a total dose of 45 Gy, followed by a boost up to 60 Gy, using fraction doses of 2.5 Gy (four times a week) on the gross tumour volume with a 1 cm margin. When the radical schedule was used, correction was made for lung tissue density (0.3). In case of the presence of atelectasis, resulting in difficulties in distinguishing tumour from collapsed lung, all abnormalities were included in the target volume. Patients allocated to

treatment arm 2 received an additional two fractions of 7.5 Gy with high dose rate (HDR) EBB in weeks 1 and 2. The choice of the external fractionation schedule was left to the decision of the treating physician. Stratification was applied for the external fractionation schedule (palliative; radical), stage (stage I, II; stage IIIa, IIIb) and the participating centre (Radiotherapeutisch Instituut Limburg, Heerlen and Maastricht; Verbeeten Instituut, Tilburg; The Antoni van Leeuwenhoek Hospital, Amsterdam).

2.3. Endobronchial brachytherapy

Under local anaesthesia, the localization and the extension of the endobronchial tumour were assessed by bronchoscopy. After bronchoscopic localization, a plastic afterloading catheter was inserted beyond the endobronchial tumour and its position was verified by fluoroscopy and documented with orthogonal radiographs. The diameter of the catheter used was 3 mm. The target volume consisted of the extent of the endobronchial tumour with a margin of 1 cm on both ends. When the distal border of the tumour was not visible by bronchoscopy, the distal extension was estimated using CT scan of the thorax. Then, the catheter was connected to the HDR-microselectron (Nucletron, Leersum, The Netherlands) and treatment was performed using an $Iridium^{192}$ stepping source, using a stepping size of 2.5 or 5 mm. All doses used were prescribed on a distance of 1 cm perpendicularly to the central axis of the source. In all patients, a single catheter was used and dose optimization was not performed. EBB and XRT were not administered on the same day. Following treatment, the patients were observed and discharged after a few hours.

2.4. Quality assurance

The quality assurance programme particularly paid attention to the sequence of XRT and EBB, the dose per fraction and total dose of XRT and EBB, the dose distribution of the XRT and the dose prescription and distribution of the EBB.

2.5. Staging procedures and follow up assessments

The staging procedure consisted of a physical examination, postero-anterior and lateral chest radiography, CT scan of the chest including the liver and adrenal glands, and bronchoscopy in all patients. Lung function tests were performed by spirometry. Bone scintigraphy was performed only when indicated. A lymph node was considered pathological if the smallest diameter was 1 cm or more.

In the 4th week during radiotherapy, a chest radiograph was made to evaluate whether it was necessary to change the original field set up for the boost, because of changes due to re-expansion of atelectasis or post-obstructive pneumonia. In case of major changes due to re-expansion of collapsed lung, a new planning-CT scan was made and the treatment plan was adjusted.

Definitive re-expansion of atelectasis or post-obstructive pneumonia was assessed by means of chest radiographs, CT scan of the chest and by changes in the inspiratory vital capacity (IVC), performed 2 to 6 weeks after the end of the entire course of treatment.

2.6. Quality of life assessment

To assess changes in quality of life (QoL) and respiratory symptoms, the Dutch version of the EORTC QLQ-C30 (version 1.0) and the lung cancer module QLQ-LC13 were used [1,4]. Quality of life and respiratory symptoms were assessed before the start of radiotherapy and subsequently 2 weeks, 6 weeks and 3, 6 and 12 months after the end of radiotherapy.

After informed consent was obtained, the questionnaire was distributed to the patients who were asked to return the questionnaire within 3 days by mail. During follow up, the questionnaires were send to the patients by mail. When the questionnaire was not returned within 4 days, the patient was telephoned and asked to complete and return the questionnaire.

2.7. Statistics

Randomization was carried out centrally by the Comprehensive Cancer Centre Limburg in Maastricht, the Netherlands. For randomisation, a permuted block design was used. Patients were stratified by institution, stage (I-II vs. III) and external fractionation schedule (radical vs. palliative).

The level of palliation of symptoms and QoL was evaluated in two different ways. First, short-term levels of palliation were examined by a subject-specific analysis, assessing response for each symptom and QoL domain in all patients individually. The response rate of symptoms is often calculated only over the subset of patients having a specific symptom at baseline and at least one follow-up assessment. When the follow-up score for a symptom is lower than that reported at baseline, the patient is considered palliated. Conversely, when the follow-up score is higher, the patient is considered to have deteriorated. In the current study we employed an alternative definition of palliation, derived from the proposal of Stephens and co-workers [31], which also takes into account patients with no or mild symptoms at baseline and those who died before the first follow-up assessment. To assess the response rate for symptoms, each symptom scale was first divided into four categories. For the single-item scales (cough, haemoptysis, pain arm/shoulder, pain chest wall and appetite loss), four ranges of scores were defined: 1 = nil, 2 = mild, 3 = moderate and 4 = severe. For the multi-item scales (dyspnea and fatigue), four ranges of scores were defined as well, based on the converted score ranging from 0 to 100: 0 = nil, 1 to 34 = mild, 35 to 67 = moderate and 68 to 100 = severe.

The criteria used to define palliation of symptoms, functioning scales and global QoL are described earlier [14] and are outlined in appendix 1 and 2.

Differences in response rates were tested for statistical significance with a chi-square test.

Secondly, long term results were evaluated by a group-based analysis, comparing changes in mean scores for the two treatment groups at each time point. Differences between the two arms were tested for statistical significance with a repeated measurement ANOVA using a mixed effect modelling procedure, SAS Proc Mixed. In contrast to a 'complete cases analysis', the mixed effect modelling retains in the analysis patients who dropout during follow-up. Trends over time for dropouts and complete cases are estimated under the assumption that all patients within the same group have the same change pattern over time. SAS Proc Mixed uses the method of restricted maximum likelihood to estimate the parameters of the model. F-tests are used for testing main effects of group and time, and an interaction effect of group × time.

Survival curves were estimated with the Kaplan–Meier method. The log rank test was used to test the statistical significance of differences between survival curves.

The primary endpoint of the study was the response rate of dyspnea, which was the symptom, considered to benefit most from the addition of EBB. The secondary endpoints were re-expansion of atelectasis, survival and complications. The other respiratory symptoms and QoL dimensions were evaluated on an exploratory basis. Assuming that the rate of palliation of dyspnea would increase from 50 to 75%, a total number of 160 patients was necessary with a two-sided type I error of 0.05 and a power of 80%. The analysis was performed on all eligible patients according to the intent-to-treat principle.

Before the study started, there was some concern regarding a possible increase of the incidence of massive haemoptysis in the experimental arm. Because of the relatively low incidence of massive haemoptysis, a stopping rule based on numbers was considered inappropriate. Therefore, an independent committee was installed. After each severe complication, including massive haemoptysis of fistulae, this committee was informed by the study coordinator regarding the total number of patients included in both arms at that time, the total number of severe complications in each arm and a detailed medical history of every patient with this complication. Based on this information, the committee was authorized to stop the study.

3. Results

3.1. Patient population

Between June 1994 and December 1998, 98 patients were randomized into the study. Unfortunately, the study was ended prematurely due to insufficient patient accrual. Of the 98 patients randomized, three were excluded because they did not fulfil the eligibility criteria of the study. The reasons for exclusion were the presence of distant metastases, cervical carcinoma in the history of one patient and no histologic confirmation of the diagnosis NSCLC. The analysis was based on the remaining 95 patients. Of the eligible patients, 47 were randomized to receive XRT alone and 48 to XRT and EBB. The two groups were well balanced concerning baseline clinical characteristics (Table 1). Furthermore, no significant group differences were observed in the baseline symptom and QoL scores (Table 2). In 75 patients (79%), the radical fractionation schedule and in 20 patients (21%), the palliative schedule was used. An atelectasis before treatment was present in 63 patients (66%).

3.2. Compliance to treatment

In the group of patients randomized to XRT alone, 40 out of 48 patients (83%) received the planned dose. Of the remaining eight patients who did not receive the planned dose, seven were treated according to the radical schedule and one according to the palliative schedule. The reason for not receiving the planned dose were distant metastases in three patients, local progression in two patients, deteriorating general condition in one patient, massive haemoptysis in one patient and death of intercurrent disease in one patient. In the group of patients randomized to XRT + EBB, 41 out of 47 patients (87%) received the planned dose of external irradiation. Of the six patients who did not receive the planned dose, four were treated according to the radical schedule and two according to the palliative schedule. In this group, 41 patients (87%) received the planned two fractions of brachytherapy. Three patients were not treated with brachytherapy at all: two patients refused and one patient experienced deteriorating general condition and bronchoscopy was considered too burdensome. Three patients received one fraction of brachytherapy: two patients refused to undergo a second session and one patient experienced deteriorating general condition due to massive malignant pleural effusion. In five patients (11%) randomized to receive XRT and EBB, the field arrangements during radiotherapy had to be adjusted because of re-expansion of atelectasis. In all of these five patients, the radiation portals could be reduced.

3.3. Compliance with QoL assessments

Of the 95 patients included in the study, 90 completed a baseline questionnaire (95%). The five patients without baseline QoL assessments were excluded from further QoL analysis. Compliance at subsequent assessments was high: 95% at 2 weeks (76 out of 81 patients at risk), 89% at 6 weeks (66 out of 74 patients at risk), 94% at 3 months (59 out of 63 patients at risk), 93% at 6 months (41 out of 43 patients at risk) and 83% at 12 months (20 out of 24 patients at risk).

3.4. Re-expansion and prevention of atelectasis

Re-expansion of atelectasis was evaluated in two differ-

Table 1
Pre-treatment characteristics of the eligible patients stratified by treatment arm

Variables	Treatment arm				*P*-value[a]
	XRT ($n = 48$)		XRT + EBB ($n = 47$)		
Sex					0.75
Male	40	83%	38	81%	
Female	8	17%	9	19%	
Age (mean)	68	SD 9	67	SD 9	0.61
T-classification					0.55
T2	17	35%	16	34%	
T3	12	25%	8	17%	
T4	19	40%	23	49%	
N-classification					0.63
N0	13	27%	17	36%	
N2	25	52%	21	45%	
N3	10	21%	9	19%	
Stage (UICC 1992)					0.64
Stage I	5	10%	4	9%	
Stage IIIa	15	31%	19	40%	
Stage IIIB	28	58%	24	51%	
WHO performance status					0.80
WHO 0	12	25%	11	11%	
WHO 1	28	58%	26	55%	
WHO2	5	10%	8	17%	
WHO3	3	6%	2	4%	
Total dose external irradiation					0.65
30 Gy	11	23%	9	19%	
60 Gy	37	77%	38	81%	
Localization					0.71
Right upper lobe	13	27%	14	29%	
Right middle lobe	4	8%	4	9%	
Right lower lobe	4	8%	2	4%	
Right main bronchus	10	21%	6	13%	
Left upper lobe	8	17%	14	30%	
Left lower lobe	6	13%	4	9%	
Left main bronchus	3	6%	3	6%	
Atelectasis					0.17
Yes	35	73%	28	60%	
No	13	27%	19	40%	
Inspiratory vital capacity					
Absolute (cm^3)	2845	SD 846	2731	SD 870	0.53
Relative (%)	73.5	SD 20.5	72.2	SD 20.3	0.71

[a] None of the differences were statistically significant.

ent ways. First, the (IVC), expressed as the percentage observed from predicted (IVCr), was measured before and 2 weeks after treatment. Pre- and post-treatment values were available for 32 patients treated with XRT alone and for 31 patients treated with XRT + EBB. After XRT alone, the IVCr decreased from 72% from predicted to 69% from predicted. In the group treated with XRT and EBB, the IVCr improved from 68% from predicted to 78% from predicted, which was significantly better compared to XRT alone ($P = 0.02$).

Significantly higher rates of radiological re-expansion assessed with chest radiograph and CT scan of the chest were observed with XRT and EBB compared to XRT alone. In the group of patients with an atelectasis before radiotherapy, nine out of 26 (35%) improved with XRT alone, while 17 out of 30 (57%) improved with XRT and EBB (Table 3). Among patients without atelectasis before radiotherapy, progression was observed in none of the patients randomized for XRT and EBB, while three patients became progressive after XRT alone (Table 3).

3.5. Response of dyspnea

Among patients allocated to receive XRT alone, the response rate for dyspnea was 37% (16 out of 43) compared to 46% (18/39) among those allocated to receive XRT + EBB, which was not statistically significant ($P = 0.29$). In the XRT-alone arm, 42% were classified as 'no response' and 21% as 'progressive', compared to 41 and 13% respectively in the XRT + EBB arm (Table 4).

Table 2
Pre-treatment quality of life characteristics of the eligible patients stratified by treatment arm[a,b]

Variables	Treatment arm				*P*-value[a]
	XRT ($n = 47$)		XRT + EBB ($n = 48$)		
	Mean	(SD)	Mean	(SD)	
Functioning scales					
Physical functioning	59.0	(27.2)	59.1	(30.3)	0.99
Role functioning	55.7	(36.1)	58.5	(36.6)	0.71
Emotional functioning	68.8	(24.3)	71.4	(24.9)	0.60
Cognitive functioning	82.6	(26.4)	88.3	(18.4)	0.23
Social functioning	73.8	(25.8)	76.2	(28.2)	0.68
Global quality of life	54.0	(23.7)	56.6	(23.0)	0.60
Symptom scales					
Cough	54.5	(23.9)	48.6	(21.9)	0.22
Haemoptysis	13.6	(24.2)	15.2	(23.0)	0.75
Dyspnea	33.8	(22.5)	36.5	(28.7)	0.62
Chest pain	21.2	(29.7)	15.2	(26.0)	0.44
Pain arm/shoulder	17.4	(28.3)	13.0	(24.8)	0.31
Fatigue	44.9	(28.9)	43.0	(28.7)	0.75

[a] For the functioning scales, higher scores represent better functioning.
[b] For the symptom scales, higher scores represent more symptoms.
[c] None of the differences were statistically significant.

3.6. Changes in mean scores for dyspnea

Analyzing differences of the mean scores, a significant difference between the two treatment arms was observed with regard to dyspnea (Fig. 1). After XRT alone, dyspnea became worse at the first follow up time point (2 weeks) and continued to worsen with time. After XRT and EBB, a temporary improvement in dyspnea was observed which disappeared after 3 months ($P = 0.02$). The results regarding dyspnea were further analyzed separately in the subset of patients with obstructive tumour in the main bronchus and in the subset of patients with obstructive tumour in the lobar bronchus (Fig. 2). A striking difference was observed in the former group but not in the latter group. The level of improvement of dyspnea was highest among those with a complete re-expansion of collapsed lung and worsened in those with progression of atelectasis (Fig. 3).

3.7. Response of other respiratory symptoms and QoL

The response rates for the other respiratory symptoms did not differ significantly between the XRT-alone group and the XRT + EBB group. For cough, the response rates were 38 vs. 24%, respectively, 82 vs. 86% for haemoptysis, 67 vs. 80% for chest pain and 69 vs. 74% for pain in the arm/shoulder. The results regarding the other QoL dimensions will be reported in a separate report.

Table 3
Response and prevention of atelectasis stratified by treatment arm

Response	Treatment arm				*P*-value
	XRT ($n = 47$)		XRT + EBB ($n = 48$)		
	Number	%	Number	%	
Atelectasis before radiotherapy					0.009
Complete disappearance	0	0	8	27	
Partial disappearance	9	35	9	30	
No change	11	42	9	30	
Progression	6	23	4	13	
Not evaluable	2		5		
No atelectasis before radiotherapy					0.11
Prevention	8	67	8	100	
Progression	4	33	0	0	
Not evaluable	7		5		

Table 4
Response classification for dyspnea stratified by treatment arm

Response classification	Treatment arm			
	XRT ($n = 44$)[a]		XRT + EBB ($n = 39$)[a]	
	Number	%	Number	%
Response	16	36	18	46
Improvement	7	16	9	23
Control	7	16	6	15
Prevention	2	5	3	8
No response	19	43	16	41
No response	9	21	10	26
Dead without palliation	10	23	6	15
Worse	9	21	5	13

[a] The number between brackets refer to the number of evaluable patients.

3.8. Changes in mean scores of symptoms and quality of life

There was a tendency towards worse palliation of cough and chest pain after XRT and EBB compared to XRT alone, however, these differences did not reach conventional levels of statistical significance. The results regarding the other QoL dimensions will be reported in a separate report.

3.9. Survival, causes of death and complications

The median survival after XRT alone was 8.5 months (95%-ci: 5.4–11.6 months) and for XRT and EBB 7.0 months (95%-ci: 5.3–8.9) (Fig. 4) ($P = 0.21$). The causes of death are shown in Table 5. No significant differences were observed between the two treatment groups. In particular, six patients treated with XRT died of massive haemoptysis (13%) compared to seven patients treated with XRT and EBB (15%). One of these patients who died from massive haemoptysis and who was treated with XRT and EBB, also developed a broncho-esofageal fistula 2 weeks before massive lung bleeding. Furthermore, in this treatment group, one patient developed a broncho-pleural fistula approximately 9 months after radiotherapy.

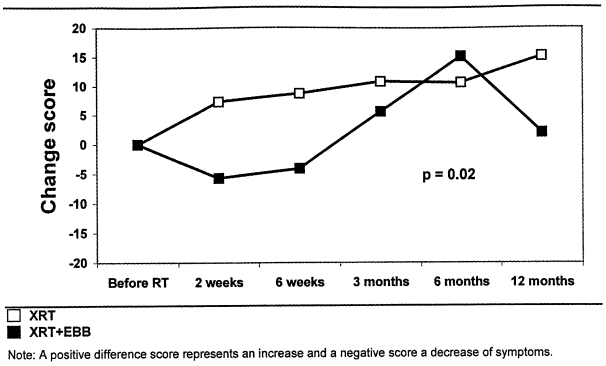

Fig. 1. Change scores for dyspnea over time, stratified by treatment arm.

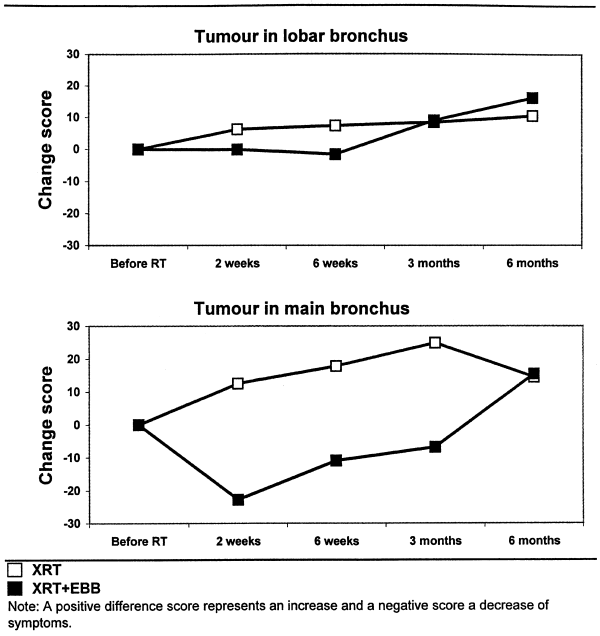

Fig. 2. Change scores for dyspnea for obstructing tumors in the lobar bronchus and main bronchus.

4. Discussion

In the present study, the additional value of early concomitant EBB during XRT was investigated with a prospective randomized design. The two treatment groups were well balanced concerning pre-treatment characteristics. The first hypothesis to be tested was whether the addition of EBB to XRT offered better rates of re-expansion of collapsed lung. Both methods used to evaluate this, i.e. radiological re-expansion and improvement of the inspiratory vital capacity showed that the level of improvement was significantly higher when XRT was combined with EBB

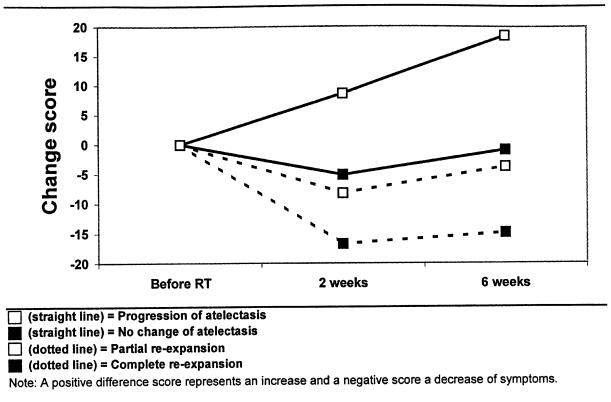

Fig. 3. Change scores for dyspnea over time, stratified by re-expansion of collapsed lung.

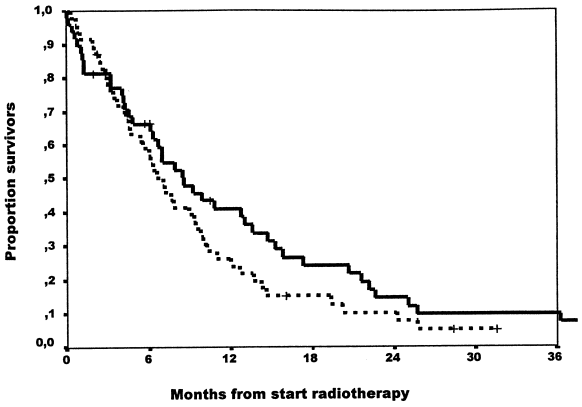

Fig. 4. Overall survival stratified by treatment arm. The straight line = XRT alone and dotted line = XRT+EBB (P=0.21).

as compared to XRT alone. It has to be stressed that no significant difference between the two arms was observed with respect to response of dyspnea, which was one of the primary endpoints of the study. However, a significantly greater degree of improvement regarding the mean values of dyspnea was achieved by the addition of concomitant EBB during XRT. This beneficial effect lasted for only 6 weeks and disappeared after 3 months. Furthermore, the beneficial effect on dyspnea did not translate into an improvement in functioning or global QoL. There has been some concern that improving ventilation areas that are not perfused because of malignant infiltration of the pulmonary vessels could increase the physiological dead space and lead to worsening of dyspnea. However, in the present study, patients with a complete re-expansion showed the best improvement in the level of palliation of dyspnea, and no difference was noted between those with a partial re-expansion and no change of collapsed lung. Goldman and co-workers [10] investigated physiological changes among patients treated with HDR EBB for major airway occlusion by malignant diseases. They observed a significant increase in fractional ventilation and perfusion for the affected lung and no worsening of shortness of breath in case of re-expansion. These findings suggest that re-expansion of collapsed lung does not necessarily lead to worsening of dyspnea, and may actually improve dyspnea in case of a complete re-expansion. A striking finding was that the difference in palliation of dyspnea in favour of the patients randomized for XRT and EBB was only observed in the subset of patients with a tumour obstructing the main bronchus, and not in the patients with obstructing tumours in the lobar bronchus. This finding is supported by the report of Goldman and co-workers [10]. They found that patients with tumours occluding a main bronchus had greater improvement in physiological indices, including spirometric indices, fractional ventilation and perfusion, and 5 min walking distance, than those who had a tumour in a lobar bronchus. In the latter group, no improvement was observed for any of the physiological indices mentioned. One explanation for this finding could be that re-expansion of an entire lung results in a relatively higher increase of the total lung volume compared to re-expansion of a lobe. Second, the failure to observe symptomatic improvement among patients with lesions located in the more distal airway segments may also be due to radiation damage arising from the use of an uniform dose prescription along the entire length of the target. The results of some studies support dosing in accordance with the bronchial diameter [14]. It has to be emphasized that no definitive conclusions can be drawn from this subset analysis. However, these findings stress the need for further prospective evaluation in the group of patients with obstructing endobronchial tumour in the main bronchus.

In the present study, a single catheter with a diameter of 3 mm was used in all patients. No centering devices and/or dose optimization were used. Recent literature shows [28] that applicators are commonly eccentrically located at the carina level which could lead to a less adequate dose distribution in the tumour volume [15]. One could argue that the brachytherapy technique as applied in the present study accounts for the short duration of palliation observed. It has to be stressed that we did not intend to include the entire gross tumour volume into the brachytherapy volume, but to

Table 5
Causes of death stratified by treatment arm

Cause of death	Treatment arm			
	XRT ($n=47$)		XRT + EBB ($n=48$)	
	Number	%	Number	%
Alive	7	15	4	9
Local progression	17	35	12	26
Massive haemoptysis	6	13	7	15
Metastases	11	23	16	34
Local progression + metastases	2	4	1	2
Intercurrent disease	4	8	1	2
Unknown	1	2	6	13

deliver a supplemental radiation dose to the endobronchial tumour in order to achieve higher response rate of endobronchial tumour obstruction and post-obstructive features including pneumonitis and atelectasis with an additional beneficial effect on pulmonary symptoms. Taken into account the extension of most tumours at the time of brachytherapy (day 1 and 8), the consequences of using a centering device regarding the dose distribution in the tumour volume would have been relatively small. Furthermore, even in case of a more adequate dose distribution in the tumour volume, it remains uncertain if that would have resulted in better palliation of pulmonary symptoms. In one of our recent publications no clear association was found between objective tumour response and palliation of most pulmonary symptoms [16].

Although, in the analysis comparing mean scores a significant difference between the two treatment arms was observed regarding dyspnea, no such difference was noted in the analysis comparing response rates for dyspnea. This apparent inconsistency could be explained by the fact that 'improvement' of a symptom was defined as a decrease on two consecutive assessments in the first 3 months after therapy. The same holds for the definition of 'control' and 'prevention'. As the beneficial effect in favor of EBB and XRT tended to disappear at 3 months, few patients experienced a response on at least two consecutive assessments.

One of the shortcomings of the current study is that it ended prematurely due to a decreasing accrual of patients. The main reason for this decreasing accrual was the increasing use of chemotherapy, which is now currently used in the majority of patients with locally advanced NSCLC. Patients with prior or planned chemotherapy were ineligible for the current study. The limited number of patients entered in the present study raises the question whether there was sufficient power to detect differences if they were actually there (i.e. protecting against type II errors).

Massive haemoptysis has frequently been described as a major complication after EBB. The results of a previous analysis indicated that the relatively high incidence of massive haemoptysis observed among patients treated with EBB was probably due to selection of patients and not to EBB itself [17]. In that study, a dramatic increase in the incidence of massive haemoptysis was only observed among those patients treated with XRT in combination with a single fraction of 15 Gy. The incidence of massive haemoptysis of those treated with XRT and EBB with two fraction of 7.5 Gy was similar to that observed in the group of patients treated with XRT alone but who would have been eligible for EBB. In the current prospective randomized study, the findings of the retrospective study were confirmed; no difference was noted in the incidence of massive haemoptysis between the two treatment arms. Huber and co-workers reported on the results of another prospective study in which patients were randomized between XRT (60 Gy) and XRT (60 Gy) and two session of EBB with 4.8 Gy applied 1 week before and 3 weeks after completion of XRT. It has to be emphasized that in only 50% of the patients in their study actually received the 2nd planned brachytherapy. The incidence of massive haemoptysis was 15.4% after XRT alone and 20.8% after XRT plus EBB; a difference which was not statistically significant [15]. These findings indicate that the addition of EBB to XRT does not lead to an increase of massive haemoptysis.

The survival rate in the group of patients randomized to receive XRT and EBB was not significantly different from those randomized to XRT alone, although, the curves diverged after 6 months. We could not find an explanation for this finding. The incidence of major complications was similar and the same holds for the other causes of death.

In conclusion, concomitant EBB during XRT provides higher response rates for re-expansion of collapsed lung compared to XRT alone. A temporary but significant higher level of palliation of dyspnea was observed with additional EBB. However, the findings suggest that this beneficial effect of additional EBB is confined to the group of patients with obstructing tumours of the main bronchus. We believe that the results of this study do not support the addition of endobronchial brachytherapy to external radiotherapy as standard approach. In individual cases, brachytherapy added to external irradiation could be considered in those patients suffering from severe dyspnea due to endobronchial tumour obstruction in the main bronchus.

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Appendix 1

A.1. Response criteria for general and respiratory symptoms

A.1.1. 'Response' is defined as

- Baseline score 'moderate or severe', with improvement to 'mild' or 'nil' on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'improvement'.
- Baseline score 'mild', with improvement to 'nil' on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'improvement'.
- Baseline score 'mild', with 'mild' on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'control'.
- Baseline score 'nil', with 'nil' on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'prevention'.

A.1.2. 'No response' is defined as

- Baseline score 'moderate or severe', without improvement to 'mild or nil' on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'no change'.
- Baseline score 'moderate or severe' and dead before first assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score 'moderate or severe' without improvement to 'mild or nil' on the first assessment and dead before the second assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score 'mild', without improvement to 'nil' and without deterioration to 'moderate or severe' on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'no change'.
- Baseline score 'mild' and dead before first assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score 'mild', without improvement to 'nil' on the first assessment and dead before first assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score 'nil', without 'nil' and without deterioration to 'mild, moderate or severe' on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'no change'.
- Baseline score 'nil', with deterioration to 'mild, moderate or severe' on the first assessment and dead before the second assessment after the end of radiotherapy = 'dead without palliation'.

A.1.3. 'Progression' is defined as

- Baseline score 'mild', with deterioration to 'moderate or severe' on at least two consecutive assessments in the first 3 months after the end of radiotherapy.
- Baseline score 'nil', with 'mild, moderate or severe' on at least two consecutive assessments in the first 3 months after the end of radiotherapy.

A.1.4. 'Not evaluable' is defined as

- Baseline score 'moderate or severe', with improvement to 'nil or mild' on the first assessments and dead before the second assessment after the end of radiotherapy.
- Baseline score 'mild', with improvement to 'nil' on the first assessment and dead before the second assessment after the end of radiotherapy.
- Baseline score 'nil' and dead before the first assessment after the end of radiotherapy.
- Baseline score 'nil', with 'nil' at the first assessment and dead before the second assessment after the end of radiotherapy.

Appendix 2

B.1. Response criteria for functioning scales and global quality of life

B.1.1. 'Response' is defined as

- Baseline score '0–59', with improvement of at least 5 points on at least two consecutive assessments in the first 3 months after the end of radiotherapy to a minimal value of 40 = 'improvement'.
- Baseline score '60–79', with improvement of at least 5 points on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'improvement'
- Baseline score '60–79', with no change (i.e. <5 points) on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'control'
- Baseline score '80–100', with improvement of at least 5 points on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'improvement'
- Baseline score '80–100', with no change (i.e. <5 points) on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'prevention'

B.1.2. 'No response' is defined as

- Baseline score '0–59', with no change (i.e. <5 points) on at least two consecutive assessments in the first 3 months after the end of radiotherapy = 'no change'
- Baseline score '0–59' and dead before first assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score '0–59' without improvement of at least 5 points to a minimal value of 40 on the first assessment and dead before the second assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score '60-79' and dead before first assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score '60-79' without improvement of at least 5 points on the first assessment and dead before the second assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score '80-100', and dead before first assessment after the end of radiotherapy = 'dead without palliation'.
- Baseline score '80-100' without improvement of at least 5 points on the first assessment and dead before the second assessment after the end of radiotherapy = 'dead without palliation'.

B.1.3. 'Progression' is defined as

- Baseline score '0-59', with a decrease of at least 5 points on at least two consecutive assessments in the first 3 months after the end of radiotherapy.
- Baseline score '60-79', with a decrease of at least 5 points on at least two consecutive assessments in the first 3 months after the end of radiotherapy.
- Baseline score '80-100', with a decrease of at least 5 points on at least two consecutive assessments in the first 3 months after the end of radiotherapy.

B.1.4. 'Not evaluable' is defined as

- Baseline score '0–59, with improvement of at least 5 points to a minimal value of 40 on the first assessments and dead before the second assessment after the end of radiotherapy.
- Baseline score '60–79', with improvement of at least 5 points on the first assessment and dead before the second assessment after the end of radiotherapy.
- Baseline score '80–100', with improvement of at least 5 points on the first assessment and dead before the second assessment after the end of radiotherapy.

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