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Clinical and quality of life outcomes in the first United Kingdom randomized trial of endobronchial brachytherapy (intraluminal radiotherapy) vs. external beam radiotherapy in the palliative treatment of inoperable non-small cell lung cancer

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Abstract

Background and purpose: A randomized controlled trial was designed to evaluate the clinical and quality of life (QL) outcomes of patients receiving endobronchial brachytherapy (EBT) or external beam radiotherapy (XRT) as a primary palliative treatment in advanced lung cancer.

Materials and methods: Ninety-nine patients presenting de novo with lung cancer were randomized to receive EBT or XRT. Eleven key symptoms or clinical signs were assessed by clinicians and patient ratings using self-assessment questionnaires were obtained at the same time. The primary endpoints were a comparison of EBT and XRT for symptom relief and acute and late side-effects (palliation) and their effect on patients' functional status and patient-rated QL outcomes. A secondary objective was a comparison of clinician assessments with patient self-reported symptoms.

Results: Both treatments produced good levels of symptom relief. They were better for XRT at the expense of more acute morbidity. Late side-effects were similar. The functional status of patients was well maintained and changed similarly with time in both groups. XRT gave a better duration of palliation. Twenty-eight percent of XRT patients required EBT (at a median time of 304 days) whereas 51% of EBT patients subsequently had XRT (at a median of 125 days). There was a significant modest gain in median survival with initial XRT (287 vs. 250 days). When clinician and patient assessments were compared, doctors were found to underestimate the severity of breathlessness, anorexia, tiredness and nausea.

Conclusions: Fractionated XRT is preferred to EBT as an initial treatment in better performance patients because it provides better overall and more sustained palliation with fewer retreatments and a modest gain in survival time. QL assessment is required in the evaluation of palliative treatments because clinicians frequently underestimate the incidence and severity of key symptoms.

Keywords: Non-small cell lung cancer; Clinical and quality of life outcomes; Endobronchial brachytherapy; External beam radiotherapy

1. Introduction

Approximately 75% of patients with non-small cell carcinoma of the lung (NSCLC) present with locally advanced or metastatic disease which renders them inoperable and virtually incurable. Where the aim of treatment is palliation, radiotherapy is often recommended and can give considerable relief of troublesome thoracic symptoms thereby improving the quality of remaining life. A number of patients at present have thoracic symptoms which may only be caused by the endobronchial component of their disease such as cough, haemoptysis, breathlessness and obstructive pneumonitis.

Endobronchial radiotherapy (EBT) would be attractive in such patients if it could produce similar palliation to external beam radiotherapy (XRT). It is a much more localized form of radiotherapy and any adverse effects on normal tissues should be confined to the immediate vicinity of the

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bronchus, sparing the lung parenchyma and nearby oesophagus. Adequate symptom relief may be achievable with less treatment-related morbidity and EBT would not preclude the use of subsequent XRT if that proved necessary.

Technological advances in the late 1980s led to the development of a miniature, high-activity radioactive iridium source for use in a remote after-loading system. This overcame many of the problems previously associated with EBT, making it a practical and tolerable alternative to XRT. After a pilot study from 1988–89, we embarked on a randomized trial to compare the efficacy of EBT with XRT [1].

2. Patients and methods

2.1. Study design and eligibility criteria

The trial opened in July 1989 and closed in July 1993 after recruiting 108 patients. The most observable difference with EBT in our pre-trial study appeared to be a major reduction in acute morbidity (radiation oesophagitis). The trial was powered to detect a fall in the incidence of acute oesophagitis in the 4 weeks following treatment of at least 35% using a two-tailed chi-square test with 80% power. All patients were followed up until death and the final analysis of the trial data was performed in July 1999.

One hundred and eight patients with histologically confirmed inoperable NSCLC were prospectively randomised after written informed consent to receive EBT or XRT. Nine, stratified separately, had relapsed after surgery and are excluded from this analysis. The remaining 99 previously untreated patients are presented. There was no significant difference in the distribution of patient characteristics between the two treatment groups. The mean age was 68 years (range 40–84), 79 were male and squamous carcinoma occurred in 81. Slightly more in the EBT group had a performance status score of 2 (13/49 vs. 8/50). Seven patients with a score of 3 were randomized, four in the EBT and three in the XRT arm. Tumour bulk (primary plus nodes) and the incidence of pulmonary collapse as assessed by CXR was almost identical in each arm.

Patients with endobronchial tumours were eligible for the trial if (a) their thoracic symptoms were limited to cough, haemoptysis or breathlessness (persistent chest pain or dysphagia due to mediastinal or chest wall involvement were exclusion criteria since EBT alone would not relieve those symptoms), (b) they were fit to undergo therapeutic bronchoscopy or fractionated XRT (WHO performance status 0–2, namely ambulatory and capable of all self-care and up and about more than 50% of waking hours, whether or not able to work) and (c) there was no clinical evidence of malignant disease beyond the thorax (stage 3 without supraclavicular node involvement).

2.2. Treatment

Forty-nine received a single exposure of EBT using the HDR-microSelectron giving 15 Gy at a distance of 1 cm from the iridium source in the bronchus, treating the estimated length of the endobronchial tumour plus a margin of 2 cm of normal bronchus proximal and distal to the tumour. Flexible bronchoscopy and placement of the treatment applicator were performed by Barber. Details of this day-case procedure are reported elsewhere [9].

Fifty received eight exposures of megavoltage XRT over 10–12 days, giving 30 Gy (maximum subcutaneous dose) using a parallel-opposed pair of fields to cover the tumour visible on chest X-ray (CXR) plus a margin of 2 cm of normal tissue. Treatment was given on an out-patient basis where transport arrangements allowed.

2.3. Assessments

Patients were seen by one of two clinicians (Burt or Stout) and a research sister (Hodgetts or Lomax) before treatment and at 4, 8, 16, 26, 38 and 52 weeks and every 3 months thereafter. The 4 week assessment was considered to be an appropriate time to identify any acute treatment-related side-effects. The 8 week assessment allowed enough time to elapse for acute morbidity to subside and the majority of responses to be evident. A four or five-point scoring system was used by the doctor to monitor performance status, cough, haemoptysis, breathlessness, hoarseness, chest pain, dysphagia, anorexia, tiredness, nausea and the presence of symptomatic or clinically apparent metastases. The follow-up assessments were compared with baseline to derive a measure of palliation. Following suggestions recently published by the MRC Cancer Trials Office, palliation was defined in terms of (1) improvement (a reduction of moderate or severe symptoms to nil or mild), (2) control (no deterioration in mild symptoms) and (3) prevention (no deterioration in those with no symptoms) [7]. Patients with baseline data who died before a subsequent assessment were included in the analysis as treatment failures, i.e. not palliated. It became apparent during the trial that the severity of some symptoms was difficult to quantify using the five-point scale chosen. After the trial was completed, symptoms with a five-point variable were reduced to 4, e.g. cough: score 0, none; 1, occasional with no sputum; 2, daily with no sputum; 3, daily with some sputum; 4, severe with copious sputum, was reduced to a four-point scale by combining categories 1 and 2. All symptom scores were reclassified as 0, none; 1, mild; 2, moderate; 3, severe. ‘Positive’ and ‘negative’ endpoints were agreed by consensus among the clinicians for each symptom so that palliation could be expressed in a way which included symptom ‘improvement’, ‘control’ and ‘prevention’, Table 1. The data was analyzed using a chi-squared test for contingency tables (2/2). Changes from baseline to subsequent assessments were analyzed using a Mann–Whitney (non-para-

Table 1
The definition of 'positive' and 'negative' endpoints for palliation

Baseline symptom	8-week assessment	Category	Comment
None	None	Positive	Prevention
None	Mild, moderate, severe	Negative	
Mild	None or mild	Positive	Control
Mild	Moderate or severe	Negative	
Moderate or severe	None or mild	Positive	Improvement
Moderate or severe	Moderate or severe	Negative	
Any	Death	Negative	

metric) *U*-test. Quality of life questionnaires (the Hospital Anxiety and Depression Scale and the Rotterdam Symptom Check-list modified for lung cancer) were completed by patients at each visit. Ordered numerical values for each symptom and anxiety and depression were derived within each treatment group. Patients were asked to record the severity of each symptom as 0, not at all; 1, a little; 2, somewhat; 3, very much. 'Positive' and 'negative' endpoints were defined as for the clinician assessments.

Clinician and patient assessments for nine key symptoms (cough, haemoptysis, breathlessness, chest pain, dysphagia, anorexia, tiredness, nausea and hoarseness) were also combined to obtain an estimate of global palliation in the two treatment arms. Each negative symptom endpoint was assigned a score of 0 and a positive endpoint 1, giving a range of scores 0–9. A total score of 0–4 was considered to be poor palliation and 5–9 good palliation.

The clinician and patient assessments were compared by taking the positive and negative endpoints and observing how many times they disagreed in their assessments and whether or not there was a 50:50 split in the disagreement, as one would expect if it were a random phenomenon. Statistical significance was determined using McNemar's test. CXR and spirometry were obtained on each occasion except at the 4 week assessment.

3. Results

3.1. Clinician assessments

The most common presenting symptoms, similar in both groups, were cough 92%, breathlessness 87%, haemoptysis 50%, tiredness 42%, anorexia 33%, hoarseness 15% and nausea 10%.

Relevant results for the nine key symptoms and for each treatment as recorded by clinicians and patients at 4 and 8 weeks are shown in Table 2 as 'the percentage of patients achieving a positive symptom end-point'. The 4-week assessment, timed to capture acute morbidity, is based on 41 assessments in the EBT group and 29 in the XRT arm. Due to an administrative error several patients were inadvertently recalled to clinic 1 month late and missed their first post-treatment assessment. This problem was more frequent in the XRT group because our normal practice outside of the trial is to see patients for first follow-up 8 weeks after day 1 of treatment. Although there was more breathlessness, chest pain, dysphagia, anorexia, tiredness and nausea in the XRT group (i.e. lower % scores for positive end-points) the only difference which reached statistical significance in favour of EBT, was for dysphagia (85 vs. 45% $P = 0.00085$).

Forty-six patients in each trial arm had baseline and 8-week assessments available for analysis. Cough was relieved in 50% of patients receiving EBT (23 positive and 23 negative symptom end-points out of 46) and in 67% of those treated with XRT (31 positive and 15 negative end-points out of 46), Table 2. None of the differences between the treatments reached statistical significance, although the trend throughout was in favour of XRT.

Fifty-one percent of 49 patients treated initially with EBT required subsequent XRT, six within 84 days mostly for persisting and deteriorating presenting symptoms and a further 19 after this for recurrent or new symptoms. The median time to retreatment was 125 days (range 15–511). Twenty-eight percent (14 of 50) of the XRT group had subsequent EBT at a median time of 304 days (range 98–1037) for recurrent cough, haemoptysis and or breathlessness.

No serious late morbidity was encountered. Massive fatal haemoptysis occurred in seven patients (four EBT, three XRT) and all had evidence of local tumour recurrence.

3.2. Patient assessments

The incidence of presenting symptoms was similar to the clinician assessments except for tiredness and anorexia which were under-estimated by doctors (tiredness 83 vs. 42%, $P = 0.001$, anorexia 45 vs. 33%, $P = 0.06$). When

Table 2
Palliation expressed as the % of positive symptom end-points (refer to Table 1) for each treatment as recorded by clinicians at 4 weeks to capture morbidity and 8 weeks to assess response and by patients at 8 weeks for comparison[a]

	Clinician assessments				Patient assessments	
	4 Weeks		8 Weeks		8 Weeks	
	EBT	XRT	EBT	XRT	EBT	XRT
The number of completed assessments	41	29	46	46	40	43
Cough (%)	59	59	50	67	45	65
Haemoptysis	85	90	78	89	71	90
Breathlessness	78	66	59	78	38	49
Chest pain	85	83	61	80	43*	77*
Dysphagia	85*	45*	80	87	71	86
Anorexia	71	59	63	78	43*	77*
Tiredness	59	41	57	74	30*	65*
Nausea	88	83	83	87	58*	81*
Hoarseness	80	93	70	91	70	79

compared with the clinician assessments, slightly fewer patient questionnaires were available for analysis at 4, 8 and 16 weeks. Patients occasionally declined the assessment or failed to accurately complete the QL forms. Forty assessments were evaluable in the EBT group at 8 and 16 weeks and 43 and 44 in the XRT arm. There was a trend favouring XRT for palliation of all symptoms at 8 weeks reaching statistical significance in chest pain ($P = 0.003$), anorexia ($P = 0.003$), tiredness ($P = 0.0029$) and nausea ($P = 0.033$), Table 2. This significance was lost by 16 weeks with the exception of tiredness ($P = 0.01$).

No significant differences were recorded in acute morbidity at 4 weeks, based on 38 EBT and 28 XRT patient questionnaires.

No significant differences in the incidences of anxiety or borderline/case episodes of depression were found in the two treatment groups when baseline and 8-week assessments were compared.

A higher percentage of patients in the XRT group achieved good global palliation, 76 vs. 91% $P = 0.09$ in the clinician assessments and this difference reached statistical significance in the patient assessments, 59 vs. 83% $P = 0.029$.

3.3. Clinician and patient assessment comparison

This revealed significant disagreement in the estimation of the severity of breathlessness $P = 0.0002$, anorexia $P = 0.02$, tiredness $P = 0.003$ and nausea $P = 0.013$. Table 3, for breathlessness, is given as an example. There was agreement in 54 scores (32 positive and 22 negative) and disagreement in 29 with a 4:25 split. Twenty-five endpoints were rated positive by clinicians but negative by the patients. Doctors consistently underestimated the frequency of negative end-points.

3.4. Respiratory function

XRT resulted in more re-inflation than EBT (60 vs. 18%), but no consistent association was found between the resolution of pulmonary collapse and or consolidation on serial CXRs and patient-reported breathlessness. Changes in patient-rated breathlessness and objective measures of respiratory function will be the subject of a more detailed presentation and analysis in a subsequent paper.

Table 3
A comparison of clinician and patient positive and negative endpoint assessments for breathlessness at 8 weeks[a]

		Patient assessments		Total
		Positive	Negative	
Clinician assessments	Positive	32	25	57
	Negative	4	22	26
		36	47	83
		$P = 0.0002$		

[a] $n = 83$.

3.5. Survival

Survival was not an original end-point of the trial. Nevertheless a modest, but statistically significant better survival was recorded in the XRT group, median survival 287 vs. 250 days, survival at 1 year 38 vs. 22% and at 2 years 10 vs. 2%, $P = 0.04$, Fig. 1. The longest survivor died after 38 months having first received XRT.

4. Discussion

Response to treatment (improvement, control and prevention) was good for all symptoms in the clinicians' assessment and there was no statistical difference in benefit between the two treatment arms although the trend was consistently in favour of XRT. The patients' assessment, however, revealed a statistically significant benefit in favour of XRT for palliating chest pain and the more systemic symptoms of anorexia, tiredness and nausea. This is probably because XRT treats the gross tumour bulk in the thorax in addition to the endobronchial component of the disease. The shorter median time to retreatment in the EBT group (125 vs. 304 days) and the greater number requiring retreatment (51 vs. 28%) is also due, in no small part, to the progression of untreated tumour outside the bronchus in the lung and mediastinum.

The excess acute morbidity (dysphagia) with XRT was expected and reached statistical significance in the clinicians' assessment. The loss of statistical significance in the patient assessment was probably a consequence of the way the questionnaire was worded and our failure, due to an administrative error, to recall as many of the XRT patients for their 4 week assessment. The clinician assessment at 4 weeks was more likely to document any dysphagia that had

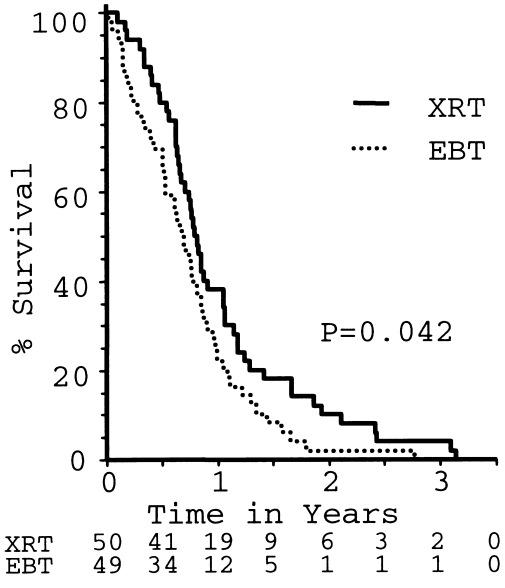

Fig. 1. Percentage crude survival by initial treatment. XRT $n = 50$. EBT $n = 49$.

occurred since treatment whereas the QL questionnaire directed patients to the preceding 7 days, i.e. 3–4 weeks after the commencement of treatment and in some cases after any acute morbidity had subsided.

A major concern following the more widespread use of EBT has been the occurrence of massive haemoptysis as a terminal event [3,6]. There is no evidence from this trial that a single dose of 15 Gy is responsible for any excess late serious morbidity. Massive fatal haemoptysis occured in 7% of patients (four in the EBT arm and three with XRT) and all cases had documented local recurrence.

The disparity between the clinician and patient assessments has been reported elsewhere and highlights the difficulty doctors have in defining and quantifying the severity of some symptoms [8]. In this trial, the best clinician-patient agreements were with haemoptysis, cough, dysphagia, hoarseness and chest pain. Nevertheless, significant doctor–patient disagreement, with doctors underestimating the severity of breathlessness, anorexia, tiredness and nausea, emphasizes the need for QL analysis in the evaluation of treatments where the primary aim is palliation.

In our opinion, XRT is preferred to EBT as the primary treatment in these patients with a good performance status even though half the patients who were given EBT on presentation did not require any additional radiotherapy and therefore obtained their palliation without the extra acute morbidity and inconvenience associated with XRT. XRT gave better overall and more sustained palliation with fewer retreatments, a modest gain in the median survival time of 287 vs. 250 days and a better 1 year survival of 38 vs. 22%.

The median time to retreatment in the EBT group of 125 days suggests that it might be the preferred form of palliative radiotherapy in poorer performance patients whose estimated median survival may be only 3–4 months. A controlled trial comparing EBT against a single or two fractions of XRT as recommended by the MRC fractionation trial would be required to confirm this [5]. The benefits of combining XRT and EBT as a primary treatment in patients with good or moderate performance status are uncertain and await confirmation in further clinical trials [4]. We are currently conducting such a trial and continue to use EBT for endobronchial relapse in patients previously treated with XRT (radical or palliative) and in patients with severe chronic obstructive airways disease where radical or fractionated palliative XRT might induce a further critical diminution in respiratory function. We have previously reported a small series which clearly demonstrates that small endobronchial tumours, albeit rare, can be controlled long term by EBT alone [2].

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