Palliation of symptoms in non-small cell lung cancer: a study by the Yorkshire Regional Cancer Organisation thoracic group

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Abstract

Background—Although most treatment for non-small cell lung cancer is palliative, data on the adequacy of symptom control are scanty and there has been little discussion about the appropriate indices.

Methods—Two hundred and eighty nine unselected patients presenting sequentially to six specialists were studied; 242 cases were confirmed histologically and all were managed as non-small cell lung cancer. At presentation and two monthly for one year or until death each of 12 symptoms was graded by a physician at a clinic interview on a four point scale as absent, mild, moderate, or severe. For each symptom a palliative index (median duration of control/median duration of survival) was calculated, where control was defined as an improvement in symptoms of any severity by one grade or more.

Results—Sixty four (22%) patients had surgery, 15 (5%) radical and 107 (37%) palliative radiotherapy, and 103 (36%) best supportive care. Analysis showed that most symptoms inexorably worsened with time. The palliation index for haemoptysis was 86%, chest pain 73%, cough 34%, and breathlessness 30%; for systemic symptoms it was 54% for anorexia and 47% for malaise. Palliation was poor in many patients after surgery. Breathlessness was a particular problem in the group having best supportive care.

Conclusions—The frequency of most symptoms in non-small cell lung cancer increases inexorably with time until malaise and anorexia are almost universal. Haemoptysis and chest pain are better palliated than cough and breathlessness. Present treatments fail to give adequate palliation for many patients, and the emphasis in future therapeutic studies should be on the relief of the more severe symptoms.

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there is no evidence that most patients have their prognosis appreciably altered by medical treatment or that their prognosis has improved over the last 10 years.^{2,3} Consequently the role of non-surgical management in non-small cell lung cancer is to palliate symptoms. Apart from studies on radiotherapy regimens^{4,5} and a little work on terminal care,^{6,7} however, there have been no detailed assessments of the efficacy of symptom relief or of the pattern and development of symptoms after presentation. It is important to acquire such data because any consequent changes in the management of non-small cell lung cancer will have major practical and economic consequences.⁸

As part of a multicentre prospective study in the management of non-small cell lung cancer in our region, we have examined the pattern of symptoms and palliation in nearly 300 unselected patients presenting to four physicians and two radiotherapists.

Methods

PATIENTS AND CLINICAL DATA

Patients were recruited sequentially from the clinics of four chest physicians (CKC, MFM, MDP, SBP) and two radiotherapists (DA and HJC). Any patient being managed on the basis of a diagnosis of non-small cell lung cancer was entered and no selection criteria within this category were applied. Patients were asked at the consultation at which management was decided to grade each of 12 symptoms relevant to lung cancer on a four point scale (severe, moderate, mild, or absent). Activity was assessed on a World Health Organisation (WHO) scale.⁹ Assessments were repeated in the same way at two month intervals for one year or until death. Interviewers were hospital doctors of registrar grade or above. The study was approved by the clinical research ethics committees of the participating physicians' health districts. All data were entered on structured forms and analysed on a Bull PC with the statistical package SAS.

At the end of the study the presenting features and the clinical course of all patients without histological confirmation were reviewed. Patients were finally accepted as having non-small cell lung cancer without histological confirmation only if (1) they had no evidence of any other disease to explain their clinical presentation and course; (2)

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About 35 000 new cases of lung cancer occur each year in the United Kingdom. Most of these are non-small cell lung cancer. Apart from the 20% who are offered surgery and the very few who have radical radiotherapy¹

they had an abnormality on their chest radiograph at presentation that worsened during the period of observation; (3) they had a clinical course during observation that was compatible with progressive carcinoma or they died during the period of observation with evidence of an enlarging tumour or metastatic disease; (4) they did not have a serum neurone specific enolase value greater than 12 U/ml; (5) they had no evidence of a primary tumour elsewhere. The clinical course of these patients was indistinguishable from that of patients with histological confirmation.

STATISTICAL METHODS

Trends in symptoms with time

As symptoms at presentation represent a cross section of times during the natural history of the disease, trends in the proportion of patients having a particular symptom, regardless of its severity, were related to death rather than presentation. Thus cohorts were identified according to how many months before death a patient presented. The trends were described for each of these cohorts to confirm that the changes were similar throughout; the data were then combined and the resulting trend was assumed to be representative of the experience of all patients irrespective of the time of presentation and therefore to be a true reflection of the actual changes.

Palliation of symptoms

The degree of palliation of symptoms was expressed in terms of a percentage palliation index:

$$\frac{\text{median duration of control of a symptom}}{\text{median duration of follow up period}} \times 100.$$

The duration of symptom control was defined as the period of time after onset during which a symptom's severity was reduced. The symptom follow up period was taken to extend from the point of the symptom's first occurrence either to death or to the end of the study. This method of measuring the palliation of symptoms was chosen as it took into account the variable duration of survival.

The improvement between different points on a symptom scale cannot be assumed to have the same impact and so the palliation index (PI) was calculated in two ways:

PI[1]: when all grades at presentation (severe, moderate, mild) improved by one grade or more;

PI[2]: when severe or moderate symptoms were improved at least to mild and initially mild symptoms improved by one grade or remained unchanged.

Patients for whom the symptom was recorded as absent throughout were excluded. The palliation index for performance status was expanded from PI[1] to include the maintenance of grade 0.

Results

PATIENTS

The original population consisted of 330 patients. Two hundred and forty two had tumours histologically confirmed as non-small cell lung cancer. Review of the 88 patients without histological confirmation showed that 11 had small cell lung cancer and 23 had non-cancerous lesions; data were insufficient in seven cases. The remaining 47 fulfilled the criteria given above in support of a diagnosis of primary non-small cell lung cancer and were included in the analysis. Thus the final population consisted of 289 patients (232 men), mean age 66 (SD 9.64) years. The distribution between centres was: physician 1—92 patients; physician 2—83; physician 3—47; physician 4—17; radiotherapist 1—35; radiotherapist 2—12.

Data on patients at presentation were complete. The numbers of patients potentially providing data at the subsequent follow up visits were: 2 months—260 (90%), 4 months—234 (81%), 6 months—214 (74%), and 12 months—165 (57%).

MANAGEMENT AND SURVIVAL

The initial management of these 289 patients was surgery in 64 patients (22%), radical radiotherapy in 15 (5%), immediate palliative radiotherapy in 107 (37%), and best supportive care in 103 (36%). The patients having best supportive care had no immediate anti-cancer treatment and only 12 had later palliative radiotherapy. Their mean age was 70 years and the distribution of their initial performance status ratings was not different from that of the group as a whole. The proportions of the group having best supportive care and of the whole group falling into the different WHO grades were: Grade 0—23% and 87/289 (30%); grade 1—37% and 36%; grade 2—29% and 28%; grade 3—8% and 5%; grade 4—3% and 2%.

The patients' survival at 12 months according to their initial management was: surgery 33/64 (52%), radical radiotherapy 7/15 (47%), palliative radiotherapy 22/107 (21%), best supportive care 20/103 (19%). The median survival was 6 (interquartile range 3–14) months overall, 6 (3–11) months after palliative radiotherapy, and 4 (1–8) months with best supportive care.

SYMPTOMS AT PRESENTATION (TABLE 1)

As expected, the most common and severe symptoms were cough and breathlessness.

Table 1 Numbers (and percentages) of the 289 patients with non-small cell lung cancer reporting particular symptoms at presentation

Symptoms	No (%) of patients			
	All grades	Severe	Moderate	Mild
Cough	228(79)	12(4)	101(35)	116(40)
Haemoptysis	101(35)	4(1)	30(10)	67(23)
Breathlessness	216(75)	23(8)	95(33)	98(34)
Chest pain	107(37)	9(3)	40(14)	58(20)
Other pain	37(13)	6(2)	14(5)	17(6)
Hoarseness	32(11)	6(2)	6(2)	20(7)
Anorexia	130(45)	10(3)	47(16)	73(25)
Malaise	136(47)	6(2)	43(15)	87(30)
Dysphagia	20(7)	0	6(2)	14(5)
Abdominal pain	15(5)	0	9(3)	6(2)
Headache	22(8)	0	4(1)	18(6)
Others	49(17)	4(1)	38(13)	7(2)

Percentages of patients experiencing the six major symptoms of lung cancer in the 12 months before death.

These were experienced by three quarters of patients, and were moderate or severe in about half of these. Haemoptysis and chest pain were present in just over one third but severe symptoms were rare. Other localised symptoms were much less common. One hundred and thirty (45%) of the 289 patients presented with systemic symptoms of anorexia or malaise, which were moderate or severe in 57 (19%) and 49 (17%).

CHANGE OF SYMPTOMS WITH TIME (FIGURE)
As the figure shows, most symptoms eventually became more common despite efforts at palliation. Although haemoptysis and cough showed less change, chest pain, breathlessness and in particular the systemic symptoms malaise and anorexia increased inexorably. This illustrates why the last two are such powerful negative prognostic factors in the disease.

PALLIATION OF SYMPTOMS (TABLE 2)
From the whole population of 289 the number of patients experiencing any grade of each symptom and the corresponding palliation indices are shown on the left hand side of table 2. Blanks indicate where the numbers are too small for analysis. For PI[1], among the respiratory symptoms haemoptysis and

chest pain are relatively well palliated (over 70%) whereas cough and breathlessness are much worse controlled (less than 35%). There is some palliation of anorexia and malaise (over 45%) and moderately good control of abdominal pain and hoarseness.
If we allow that the persistence of mild symptoms indicates *some* palliation, in the face of generally increasing frequency (figure), then PI[2] is a more appropriate index than PI[1]. Its use keeps the relative success of management in palliating different symptoms constant but changes some absolute values considerably. For example, the palliation of cough increases from 34% to 78% and breathlessness from 30% to 59%.
If we consider only moderate or severe symptoms (table 2 right hand columns) then PI[1] and PI[2] are the same. Comparisons across the whole table show that PI[2] for all grades generally corresponds better than PI[1] to the effect of management on moderate or severe *respiratory* symptoms. In particular, it is dominated less than PI[1] by the persistence of mild symptoms of cough and breathlessness. For systemic symptoms, on the other hand, PI[1] is better as fewer patients with anorexia or malaise improved.

ACTIVITY SCORE ANALYSIS
Palliation indices, which are medians, were zero for activity score. Nevertheless, 40 patients (20%) showed an improvement for part of the follow up period, ranging from 56 to 330 days, and the proportion of control in these patients ranged from 15% to 90%. Thirty eight (19%) reported an improvement throughout the entire period of follow up.

PALLIATION AND INITIAL TREATMENT MODALITY (TABLE 3)
Table 3 shows symptom palliation in each initial treatment group on the basis of PI[2] for all grades (left hand columns). PI[1] and PI[2] are the same where moderate or severe symptoms only are considered (right hand columns).

Table 2 Palliation indices* (PI, %) for symptoms among the 289 patients with non-small cell lung cancer

	All grades			Moderate and severe	
	n	PI[1]*	PI[2]*	n	PI[1]/[2]*
Cough	177	34	78	95	76
Haemoptysis	81	86	98	27	90
Breathlessness	175	30	59	113	55
Chest pain	99	73	84	48	76
Hoarseness	30	74	68	16	—
Other pain	47	75	85	26	77
Malaise	114	47	72	38	42
Anorexia	98	54	79	38	54
Dysphagia	17	—	—	5	—
Abdominal pain	21	62	90	7	—
Headache	19	—	—	2	—
Others	59	66	76	53	66

*For definition see under "Methods."

Table 3 Numbers (and percentages) of palliation indices* (PI) by initial treatment among the 289 patients with non-small cell lung cancer

Symptom	All grades (PI[2]*)			Moderate and severe (PI[1][2]*)		
	S	RT(P)	BSC	S	RT(P)	BSC
Cough	42 (69)	66 (72)	57 (95)	25 (62)	39 (46)	25 (93)
Haemoptysis	22 (100)	29 (98)	26 (100)	9†	11†	6†
Breathlessness	44 (75)	66 (61)	52 (37)	23 (74)	52 (53)	30 (28)
Chest pain	29 (63)	32 (82)	26 (83)	10†	22 (72)	15†

S—surgery; RT(P)—palliative radiotherapy; BSC—best supportive care.

*For definition see under "Methods."

†Numbers too small for analysis.

Haemoptysis of any severity was well palliated whatever treatment was given. Surgery is considered curative treatment but it did not eliminate all the symptoms found at presentation. For example, chest pain, including both tumour related pain and post-thoracotomy pain, had a palliative index of only 63% in the surgically treated patients. The pattern of palliation after radiotherapy was broadly similar to that in the whole group. For the patients having best supportive care, however, the pattern was unexpected. Cough was surprisingly well controlled (PI 95%) but breathlessness responded poorly to treatment (PI 37%).

MEDICAL TREATMENT

Two hundred and twenty nine (79%) of all the patients were recorded as having had drugs for symptom relief at some stage. Corticosteroids were given to 69 (24%), new bronchodilators to 29 (10%), antitussives to 46 (16%), and analgesics to 103 (36%). The group having best supportive care did not receive proportionately more treatment of this type than the other patients.

Discussion

In this paper we have shown that for unselected patients with non-small cell lung cancer systemic and some respiratory symptoms become more common as time passes even though they receive appropriate conventional treatment. Palliation therefore is variable, with haemoptysis and chest pain well controlled but cough and breathlessness much less so.

Much effort and study has been applied to the measurement of the "quality of life" of patients undergoing treatment for cancer.¹⁰⁻¹³ Complex questionnaires are available that have been validated by correlation with in depth psychometric interviews. We deliberately did not attempt to derive or use a global score for quality of life because we particularly wanted to concentrate on the success or otherwise of control of the physical symptoms for which patients with this disease are referred for treatment.

The clinical grading system we used has the merit of rapidity and simplicity. The only comparisons between clinic recall and the diary card system that we know of is a Medical Research Council (MRC) study.¹⁴ This showed a good concordance between the two methods and supports the contention that the symptom gradings reported by our

patients did represent what they were really experiencing.

COMPARISON WITH PREVIOUS STUDIES

Previous studies measuring palliation in non-small cell lung cancer have considered only patients referred particularly for radiotherapy^{4,5,15} or surgery.^{16,17} Primary chemotherapy is rarely used in the United Kingdom for non-small cell lung cancer, and no studies have focused particularly on palliation after it. Our study population included patients treated by radiotherapy and surgery and also the third of patients who were treated by physicians and not referred. This group has not previously been studied.

Nou *et al*¹⁶ showed that patients undergoing surgery and subsequently relapsing have substantial symptoms and our study reinforces this. Over 40% of our surgically treated patients died within the first year and the palliation indices in this group were not better than in the other groups (table 3).

The format of our study allows a comparison of symptom palliation in our patients and in those of the recent radiotherapy dosage study by the MRC working party, which used a similar index.⁵ If mild, moderate and severe breathlessness on our scale are equated with 3-5 on the MRC scale the comparisons are as follows:

For the PI[1] in our study: cough 18%, haemoptysis 98%, breathlessness 41%, chest pain 72%; for the MRC study: cough 50%, haemoptysis 80%, breathlessness 50% and chest pain 57%.

Comparison with the few other studies is more difficult. Slawson and Scott¹⁵ reported a study of radiotherapy, usually 60 Gy over six weeks (currently regarded in Britain as radical treatment), or less in iller patients. In their patients with non-small cell lung cancer undefined "responses" were: haemoptysis 77/90 (86%), breathlessness 34/59 (58%), and chest pain 40/69 (58%). More recently Collins *et al*⁸ studied 96 patients treated with palliative radiotherapy and assessed three and six months later as improved, the same, or worse by comparison with their presenting symptoms. The percentages of patients alive and reporting improvement in symptoms after these two intervals were: cough 68% and 27%, haemoptysis 88% and 63%, breathlessness 53% and 32%, and chest pain 72% and 33%. Eleven out of 94 patients (12%) died before their first follow up. The results of both of these studies confirm that, unlike haemoptysis, the other major symptoms of lung cancer, especially breathlessness, are not well palliated by radiotherapy.

SEVERITY OF SYMPTOMS AND THEIR IMPACT

The MRC study⁵ gave equal weight to the relief of a mild symptom (which becomes absent) and the improvement from severe to absent. There are reasons for believing that a more appropriate index in the setting of non-small cell lung cancer may be to regard palliation as adequate if severe or moderate symptoms are reduced to mild or absent and

mild symptoms remain and do not worsen (PI[2]). This is because nearly all patients with non-small cell lung cancer are current smokers or ex-smokers with a high background incidence of cough, sputum, breathlessness, and variable chest tightness due to diffuse airway disease, which pre-exists and persists alongside the local effects of their tumour. The focus of palliation then becomes the patient who presents with moderate or severe symptoms and in whom the target of palliation should be to make symptoms mild or absent. This suggestion seems clinically appropriate but needs validation for non-small cell lung cancer by correlating the reported severity of each symptom with an assessment of its impact and the concern a patient feels about it.

SYMPTOMS

Haemoptysis is palliated whatever treatment policy for non-small cell lung cancer is adopted (table 3). Chest pain deriving from lung cancer has not been analysed in detail in any prospective study. We have shown that it persists after surgery, when it presumably relates to the thoracotomy. We believe that this symptom merits a further, more detailed analysis to establish which types of pain respond to direct antitumour treatment. Cough and breathlessness are the major respiratory symptoms of lung cancer and are less well palliated. Coexistent diffuse airway disease, however, is likely to be a component of the symptom pattern in many patients and its severity and response to therapy has not, so far as we are aware, been studied prospectively in any series.

Corticosteroids are the only widely used treatment to ameliorate the systemic symptoms of malaise and anorexia in non-small cell lung cancer. Anecdotally they seem to have a transient effect in milder cases. As the analysis of symptom pattern shows (figure), systemic symptoms are likely to dominate activity scores and quality of life assessments later in the disease in all patients.

Palliation of the less common subsidiary symptoms in non-small cell lung cancer is fairly good, to judge by palliation indices of 60% or more (table 2). The number of patients presenting with moderate or severe subsidiary symptoms (less than 7%) is too small for comparisons between treatment modalities to be made.

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Appendix World Health Organisation classification of performance status

Grade	Summary	Description of performance status
0	Normal	Able to carry out all normal activity without restriction
1	With effort	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Restricted	Ambulatory and capable of all self care but unable to carry out any work; up and about more than 50% of waking hours
3	Dependent	Capable of only limited self care; confined to bed or chair more than 50% of waking hours
4	Immobile	Completely disabled; cannot carry on any self care; totally confined to bed or chair.

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