

# Pretreatment Quality of Life of Inoperable Non-Small Cell Lung Cancer Patients Referred for Primary Radiotherapy

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This study examined the association between the most important prognostic factors in non-small cell lung carcinoma (NSCLC) and self-reported pretreatment quality of life (QoL) and the impact of the presence, severity and changes in respiratory symptoms on general symptoms and QoL. The study included 262 patients. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-LC13 were used to assess symptoms and QoL before radiotherapy. Patients with inoperable NSCLC showed major differences in self-reported QoL as a function of clinical prognostic factors. A significant association was found between World Health Organization (WHO) performance status and QoL but not other prognostic factors. Dyspnoea was the only respiratory symptom associated significantly with general symptoms, physical and psychosocial functioning and QoL. Furthermore, changes in dyspnoea were associated significantly with changes in physical and role functioning, global QoL and fatigue as assessed 6 weeks after radiotherapy. These results indicate that palliation of dyspnoea may have a significant beneficial effect on QoL and that palliation of other respiratory symptoms is not necessarily associated with improvement of general symptoms, physical and psychological functioning or global QoL.

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Lung cancer is the leading cause of cancer-related death. Approximately 75% of lung cancer patients are diagnosed with non-small cell lung carcinoma (NSCLC). For these patients, surgery is presently the best treatment for stage I and II disease (UICC 1997) and may play a role in selected cases with stage IIIa disease. Patients with NSCLC may be inoperable for several reasons, including advanced locoregional tumour extension, the presence of distant metastases and/or comorbidity. Many of these inoperable patients are treated by radiotherapy with or without chemotherapy.

Patients' self-reported quality of life (QoL) has become an important endpoint for treatment comparisons in many clinical trials. For this purpose, several methods have been developed to allow reliable and valid measurement of various aspects of QoL (1–4). It is generally believed that patients with good prognosis experience a higher level of health-related QoL than those with poor prognosis. In general, prognosis in cancer depends on factors such as

disease extension, performance status and weight loss. Aaronson et al. found that lung cancer patients with poor values on these indicators experienced significantly lower QoL than those with higher values (5). Cella et al. examined the relationship between extent of disease, performance status and psychological distress in a cohort of patients with small cell lung cancer (6). They found that performance status correlated significantly with psychological distress but that the extent of disease correlated significantly with psychological distress only for the patients with poor performance status. Ringdal et al. investigated the differences in QoL between patients with good, intermediate and poor prognosis (7). They found that prognosis was moderately related to physical aspects of QoL but not to social and psychological wellbeing. In this study, patients with a range of cancer diagnosis were involved. These results indicate that the presumed association between QoL, prognosis and individual prognostic factors is far from consistent. In particular, this association has

never been documented among patients with inoperable NSCLC referred for radiotherapy.

Most patients with inoperable NSCLC are irradiated to improve locoregional tumour control and to palliate respiratory symptoms. It is also generally believed that a relationship exists between respiratory symptoms and general aspects of QoL, and that palliation of these symptoms leads to improvement of QoL. To the authors' knowledge, this putative association has never been studied.

The first aim of this study was to examine the pretreatment QoL characteristics, as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, of patients with NSCLC referred for radiotherapy, classified into three different prognostic groups. The second aim was to examine the impact of the most important prognostic factors in NSCLC and the impact of the presence and severity of respiratory symptoms on general symptoms and QoL before radiotherapy. The third objective was to evaluate the association between changes in local symptoms and changes in general symptoms, functioning and global QoL.

Four hypotheses were tested in this analysis. (i) QoL in the poor prognostic groups was expected to be worse than in the groups with better prognosis. (ii) Self-reported QoL was expected to be significantly better among patients with high versus low performance status, limited versus extended disease, and limited versus substantial weight loss. (iii) The severity of respiratory symptoms, as assessed by the supplementary QLQ-LC13 questionnaire, was expected to be associated negatively with patients' levels of self-reported physical and psychological functioning, and with their experience of more general symptoms such as fatigue. (iv) Improvement of respiratory symptoms, as assessed by the QLQ-LC13 questionnaire after radiotherapy, was expected to be associated positively with improvement of the more general symptoms, physical and psychological functioning, and with global QoL.

## MATERIAL AND METHODS

### *Patients*

The study sample included patients with inoperable NSCLC who were to receive primary external irradiation only of the primary tumour site and/or regional lymph nodes. Other eligibility criteria included World Health Organization (WHO) performance status score  $\leq 3$ , good command of the Dutch language, no prior chemotherapy, no prior surgery, no prior radiotherapy and no signs of brain metastases.

To assess the extent of disease, physical examination, chest radiography, computed tomography (CT) of the chest, including the liver and adrenal glands, and bronchoscopy were performed on all patients. CT of the brain and bone scintigraphy were not performed routinely, but only in case of suspicion of brain or bony metastases.

WHO performance status and weight loss were assessed prospectively.

From June 1994 to December 1996, 262 patients were entered in the study and completed a baseline QoL questionnaire. There were 36 females (14%) and 226 males (86%), with a median age of 69 years (37–88 years).

### *Prognostic groups*

Patients with a WHO performance status of 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. These patients were treated with a total dose of 30 Gy using fraction doses of 3 Gy (four times a week).

Patients with stage I or II disease (UICC 1992) with a tumour diameter  $> 4$  cm or stage IIIa and IIIb disease (UICC 1992) without supraclavicular lymph-node metastases and a WHO performance  $\leq 2$  were considered to have an intermediate prognosis and were selected for the radical fractionation schedule. These patients received a total dose of 60 Gy in 6 weeks.

In cases of stage I or II disease (UICC 1992) with a maximum diameter of 4 cm and a WHO performance  $\leq 2$ , the curative fractionation schedule was selected. These patients received a total dose of 70 Gy in 7 weeks.

In the present study, 35 patients (13%) were selected for the curative schedule, 142 patients (54%) for the radical schedule and 65 patients (25%) for the palliative schedule.

### *Quality of life assessment*

QoL was assessed by means of the EORTC core questionnaire, the QLQ-C30, and the supplemental lung cancer specific module, the QLQ-LC13. The QLQ-C30 (version 1.0) contains 30 questions. The questionnaire is organized into five functional scales (physical, role, emotional, cognitive and social), three symptoms scales (fatigue, pain, and nausea and vomiting), a global health/QoL scale, and a number of single items assessing additional symptoms (dyspnoea, sleep disturbance, constipation and diarrhoea) and perceived financial impact. This questionnaire has proven to be a valid and reliable tool when used among a wide range of cancer patient populations, including lung cancer patients (1). It has been translated and validated for use among Dutch patients. The QLQ-LC13 contains 13 questions concerning symptoms frequently present in lung cancer patients and treatment-related symptoms. This supplemental questionnaire has proven to be a valid and reliable tool among lung cancer patients (8).

The questionnaires were administered approximately 1 week before the start of radiotherapy, and at regular intervals during and after the course of treatment. This paper focuses primarily on the pretreatment assessment. To investigate the association between changes over time in respiratory symptoms and in other more general symp-

toms and QoL, limited use is made of the follow-up data, i.e. the assessment at 6 weeks post-radiotherapy. Prior to participation in the study, patients were informed by the radiation oncologist about the seriousness of their illness, the prognosis and the aims of treatment. Informed consent was obtained from all patients according to local ethical standards.

### Statistics

All scales of the QLQ-C30 and QLQ-LC13 were linearly converted to a 0–100 scale. For the functional and global health status/QoL scales, higher scores represent a better level of functioning. For symptom scales, higher scores represent a greater degree of symptoms. For the purpose of this study only the general symptom scales assessing the most relevant symptoms for lung cancer patients were included in the analysis, i.e. fatigue and appetite loss. With regard to respiratory symptoms, baseline scores for cough, haemoptysis, dyspnoea, dysphagia, pain in the arm/shoulder and pain in the chest wall were analysed. For the single-item scales (cough, haemoptysis, dysphagia, arm/shoulder pain, chest wall pain), four ranges of scores were defined: 1 = nil, 2 = mild, 3 = moderate and 4 = severe. For the multi-item scale (dyspnoea), four ranges of scores were also defined, based on the converted score ranging from 0 to 100: 0 = nil, 1–34 = mild, 35–67 = moderate and 68–100 = severe.

To analyse the association between the clinical prognostic factors and QoL, the general linear model (GLM) multivariate analysis of variance (MANOVA) was used. The GLM-MANOVA approach can be used to test the hypothesis of a significant association between a set of interrelated dependent variables, e.g. the QoL scales, and one or more grouping variables. This method was preferred over analysis of each QoL scale separately, because it also takes into account the correlation among the individual QoL scales. This multivariate approach also protects against type I errors. In the present study, MANOVA was performed in two steps. First, to investigate the association of a given prognostic factor with QoL, an overall analysis was performed to establish whether the prognostic factor was associated significantly with any of the QoL measures. Wilks' lambda (often referred to as the U-statistic) was used to test the impact of each prognostic variable included in the multivariate model on QoL. Wilks' lambda can take on values ranging between 0, indicating large differences in group means, and 1, indicating no differences in group means. In the case of a significant association between a prognostic factor and all QoL scales taken together, a second analysis was performed to investigate the association between that factor and each QoL scale separately.

The variance in QoL scores sustained by a given prognostic factor is expressed by the effect size (explained variance). For example, an effect size for a prognostic

factor of 0.18 indicates that 18% of the variance in QoL scores is accounted for by the prognostic factor being evaluated.

To investigate the association between changes in respiratory symptoms and general symptoms, physical and psychological functioning and global QoL, the same multivariate procedure was carried out. For this purpose, the change scores between baseline and 6 weeks follow-up were calculated. The change scores for the respiratory symptoms were organized into three categories: worse (change score  $> 5$ ), no change ( $-5 \leq$  change score  $\leq 5$ ) or improved (change score  $< -5$ ).

## RESULTS

### *Prognostic groups and survival*

The patients' pretreatment characteristics, stratified by prognostic groups, are presented in Table 1. Although weight loss was not taken into account in the selection of one of the three prognostic groups, significant differences concerning this prognostic factor were observed between the three groups. This difference was observed not only between the palliative group and the other two groups ( $p < 0.001$ ), but also between the radical and the curative group ( $p = 0.008$ ). As expected, performance status was significantly lower in the palliative group than in the other two groups ( $p < 0.001$ ). The difference in performance status noted between the radical and curative group was not significantly different.

The median survival was 19.1 months [95% confidence interval (CI) 15.4–22.9] for the curative group, 8.5 months (95% CI 6.7–10.4) for the radical group and 4.1 months (95% CI 2.4–5.8) for the palliative group (Fig. 1).

### *Prognostic groups and baseline quality of life*

The mean baseline QoL scores stratified by prognostic groups are shown in Fig. 2. In general, the baseline scores for the functioning scales and global QoL scale of those selected for curative treatment were slightly higher than the scores observed in those selected for radical radiotherapy. However, these differences were not statistically significant. For the symptom scales, a significant difference in baseline scores between the aforementioned two treatment groups was observed for appetite loss ( $p = 0.003$ ). The mean score for appetite loss was 8.6 (SE 3.4) in the curative group and 27.1 (SE 2.7) in the radical group. No significant differences between these two groups were observed for the other general symptoms or for any of the respiratory symptoms.

In the palliative group, the mean baseline scores for all functioning scales and the global QoL scale were significantly lower than those observed in the curative and radical groups. Furthermore, the mean baseline scores for the general and respiratory symptoms in the palliative group were significantly higher than those observed in the

**Table 1**  
Pretreatment characteristics stratified by the selected treatment schedule

| Variables                 | Curative<br>n (%) | Radical<br>n (%) | Palliative<br>n (%) | All patients<br>n |
|---------------------------|-------------------|------------------|---------------------|-------------------|
| <b>T classification</b>   |                   |                  |                     |                   |
| T1                        | 17 (49%)          | 12 (7%)          | 2 (3%)              | 31 (12%)          |
| T2                        | 18 (51%)          | 59 (36%)         | 20 (31%)            | 96 (37%)          |
| T3                        | 0                 | 28 (17%)         | 11 (17%)            | 39 (15%)          |
| T4                        | 0                 | 65 (40%)         | 32 (49%)            | 96 (37%)          |
| <b>N classification</b>   |                   |                  |                     |                   |
| N0                        | 35 (100%)         | 53 (32%)         | 14 (22%)            | 102 (39%)         |
| N1                        | 0                 | 3 (2%)           | 0                   | 3 (1%)            |
| N2                        | 0                 | 86 (52%)         | 29 (45%)            | 113 (43%)         |
| N3                        | 0                 | 22 (13%)         | 22 (34%)            | 44 (17%)          |
| <b>Stage (UICC 1992)</b>  |                   |                  |                     |                   |
| I                         | 35 (100%)         | 18 (11%)         | 2 (3%)              | 55 (21%)          |
| II                        | 0                 | 2 (1%)           | 0                   | 2 (1%)            |
| IIIa                      | 0                 | 65 (40%)         | 9 (14%)             | 73 (28%)          |
| IIIb                      | 0                 | 79 (48%)         | 37 (57%)            | 115 (44%)         |
| IV                        | 0                 | 0                | 17 (26%)            | 17 (7%)           |
| <b>Tumour type</b>        |                   |                  |                     |                   |
| Squamous cell             | 23 (66%)          | 95 (58%)         | 32 (49%)            | 149 (57%)         |
| Adeno                     | 2 (6%)            | 28 (17%)         | 12 (19%)            | 42 (16%)          |
| Undifferentiated          | 10 (29%)          | 41 (25%)         | 21 (32%)            | 71 (27%)          |
| <b>Weight loss</b>        |                   |                  |                     |                   |
| None                      | 30 (86%)          | 76 (47%)         | 21 (33%)            | 127 (49%)         |
| 1–10%                     | 2 (6%)            | 54 (33%)         | 19 (30%)            | 74 (29%)          |
| > 10%                     | 3 (9%)            | 3 (20%)          | 23 (38%)            | 58 (22%)          |
| Unknown                   | 0                 | 3                | 1                   | 3                 |
| <b>Performance status</b> |                   |                  |                     |                   |
| WHO 0                     | 20 (57%)          | 63 (38%)         | 6 (9%)              | 87 (33%)          |
| WHO 1                     | 13 (37%)          | 78 (48%)         | 21 (32%)            | 112 (43%)         |
| WHO 2                     | 2 (6%)            | 23 (14%)         | 16 (25%)            | 41 (16%)          |
| WHO 3                     | 0                 | 0                | 22 (34%)            | 22 (8%)           |

radical and curative group, with the exception of insomnia, cough and pain in the arm/shoulder.

#### Multivariate analysis of the association between prognostic factors and quality of life

In the first step of the MANOVA, the association between WHO performance status (WHO 0–1 vs. WHO 2–3), weight loss (none vs. 1–10% vs. > 10%) and different aspects of disease extension such as tumour classification (T1–T2 vs. T3–T4), nodal status (N0 vs. N+) and distant metastases (M0 vs. M1) and QoL was investigated. Age (0–70 vs. > 70) and gender were used as covariates. In this analysis, a linear combination of the five functioning scales, the global QoL scale and the general symptoms fatigue and appetite loss assessed with the QLQ-C30 were used as the dependent variables. The results of this analysis are shown in Table 2. WHO performance status, weight loss and age were associated significantly with the overall QoL outcome. Statistically significant differences between patients with WHO performance scores 0–1 versus 2–3 were observed for all of the individual QLQ-C30 scales, with the exception of emotional functioning. However, the

effect sizes were relatively small, varying from 0.02 for social functioning to 0.12 for physical functioning (Table 3).

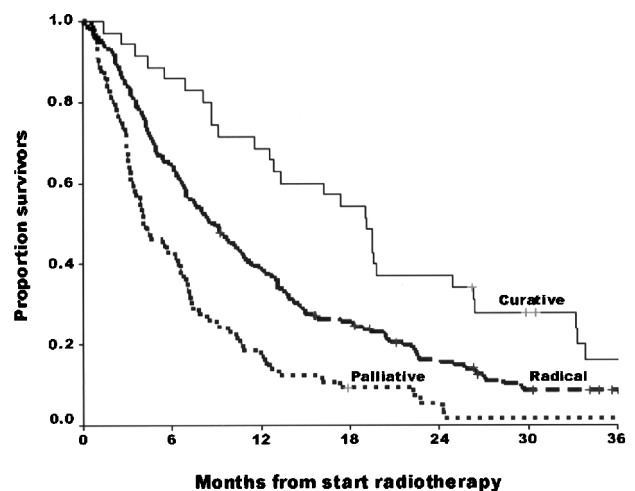
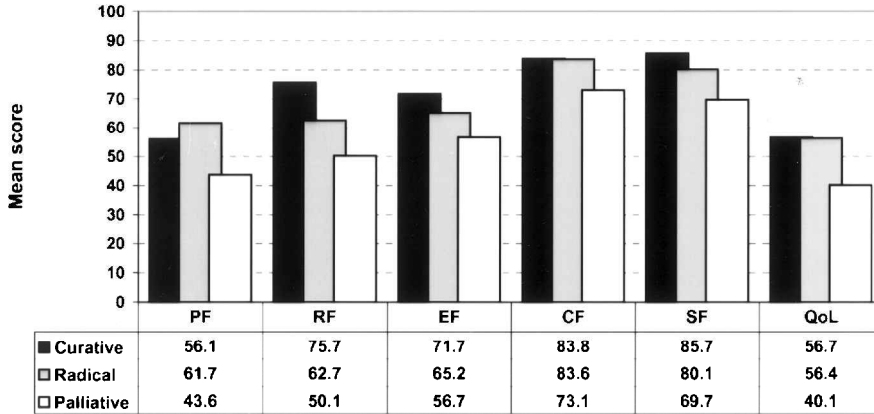
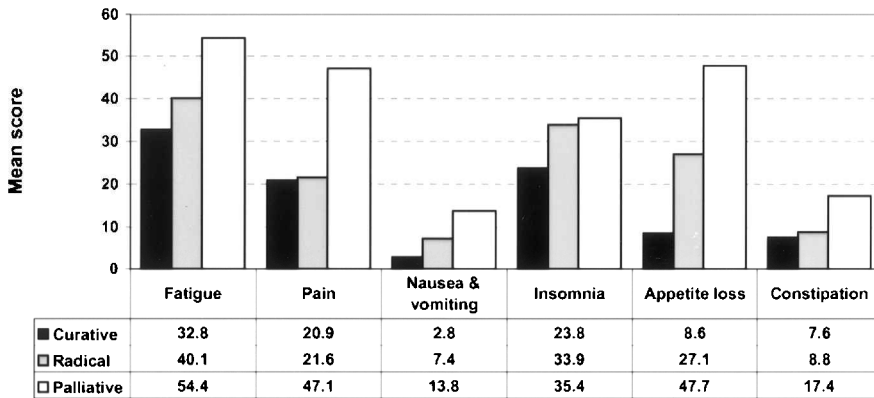


Fig. 1. Survival according to prognostic group.

**Prognostic groups and functioning scales**



**Prognostic groups and general symptom scales**



**Prognostic groups and respiratory symptoms**

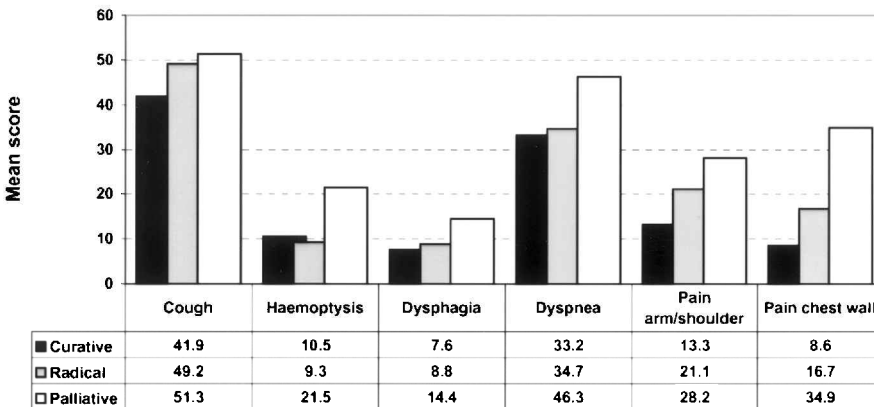


Fig. 2. Pretreatment mean scores according to prognostic group.

A significant overall effect on QoL was also found for weight loss (Table 2). More detailed analysis showed that weight loss was associated significantly with patients' self-reported physical and social functioning, fatigue and appetite loss (Table 4). However, the effect sizes were very

small, varying from 0.02 for social functioning to 0.11 for appetite loss.

Age was also found to be related significantly to QoL, although this appeared to be restricted to self-reported physical functioning. Neither patients' gender nor TNM

**Table 2***Effect of the classical prognostic factors on all EORTC QLQ-C30 scales<sup>1</sup>*

| Independent variable | Wilks' lambda | F    | Significance | Effect size<br>(explained variance) |
|----------------------|---------------|------|--------------|-------------------------------------|
| T classification     | 0.954         | 1.46 | ns           | –                                   |
| N classification     | 0.969         | 0.97 | ns           | –                                   |
| M classification     | 0.968         | 0.99 | ns           | –                                   |
| Weight loss          | 0.830         | 2.97 | <0.001       | 0.09                                |
| Performance status   | 0.821         | 6.65 | <0.001       | 0.18                                |
| Age                  | 0.901         | 3.36 | 0.001        | 0.10                                |
| Gender               | 0.972         | 0.87 | ns           | –                                   |

<sup>1</sup> Results of GLM multivariate analysis of variance.

Abbreviation: ns = not significant.

**Table 3***Effect of WHO performance status on the individual EORTC QLQ-C30 scales<sup>1</sup>*

| Domain                 | Estimated mean scores |         | Pairwise comparisons <sup>2</sup><br>(p-values) | Effect size<br>(explained variance) |
|------------------------|-----------------------|---------|---|-------------------------------------|
|                        | WHO 0–1               | WHO 2–3 |   |                                     |
| Functioning scales     |                       |         |   |                                     |
| Physical functioning   | 62.1                  | 38.2    | <0.001  | 0.12                                |
| Role functioning       | 71.8                  | 42.6    | <0.001  | 0.10                                |
| Emotional functioning  | 64.8                  | 57.2    | ns  | –                                   |
| Cognitive functioning  | 82.7                  | 73.3    | 0.01  | 0.03                                |
| Social functioning     | 83.5                  | 74.8    | 0.04  | 0.02                                |
| Global quality of life | 53.6                  | 41.1    | 0.001   | 0.04                                |
| General symptoms       |                       |         |   |                                     |
| Fatigue                | 39.2                  | 50.3    | 0.01  | 0.03                                |
| Appetite loss          | 23.1                  | 39.3    | 0.001   | 0.04                                |

<sup>1</sup> Results of GLM multivariate analysis of variance.<sup>2</sup> Based on the estimated mean scores in the multivariate analysis.

Abbreviations: WHO = World Health Organization; ns = not significant.

**Table 4***Effect of weight loss on the individual EORTC QLQ-C30 scales<sup>1</sup>*

| Domain                 | Estimated mean scores |                   |                   | Pairwise comparison <sup>2</sup><br>(p-values) | Effect size<br>(explained variance) |
|------------------------|-----------------------|-------------------|-------------------|--|-------------------------------------|
|                        | No weight loss        | Weight loss 1–10% | Weight loss > 10% |  |                                     |
| Functioning scales     |                       |                   |                   |  |                                     |
| Physical functioning   | 55.4                  | 52.5              | 42.6              | 0.02   | 0.03                                |
| Role functioning       | 56.2                  | 59.9              | 55.6              | ns   | –                                   |
| Emotional functioning  | 66.6                  | 60.0              | 56.4              | ns   | –                                   |
| Cognitive functioning  | 80.2                  | 76.2              | 77.6              | ns   | –                                   |
| Social functioning     | 83.6                  | 81.3              | 72.5              | 0.05   | 0.02                                |
| Global quality of life | 51.0                  | 48.9              | 42.1              | ns   | –                                   |
| General symptoms       |                       |                   |                   |  |                                     |
| Fatigue                | 33.9                  | 44.7              | 55.7              | <0.001   | 0.08                                |
| Appetite loss          | 14.7                  | 35.4              | 43.9              | <0.001   | 0.11                                |

<sup>1</sup> Results of GLM multivariate analysis of variance.<sup>2</sup> Based on the estimated mean scores in the multivariate analysis.

Abbreviation: ns = not significant.

**Table 5***Effect of respiratory symptoms on all EORTC QLQ-C30 scales<sup>1</sup>*

| Independent variable | Wilks' lambda | F    | Significance | Effect size (explained variance) |
|----------------------|---------------|------|--------------|----------------------------------|
| Cough                | 0.911         | 0.89 | ns           | –                                |
| Haemoptysis          | 0.879         | 1.24 | ns           | –                                |
| Dyspnoea             | 0.645         | 4.44 | <0.001       | 0.14                             |
| Dysphagia            | 0.963         | 1.01 | ns           | –                                |
| Arm/shoulder pain    | 0.860         | 1.46 | ns           | –                                |
| Chest wall pain      | 0.871         | 1.33 | ns           | –                                |

<sup>1</sup> Results of GLM multivariate analysis of variance.

T classification, N classification, M classification, WHO performance, weight loss, age and gender were entered in the model as covariates.

Abbreviation: ns = not significant.

status was found to be related significantly to self-reported QoL (Table 2).

*Effect of respiratory symptoms on quality of life*

An additional multivariate analysis was performed to determine whether the presence and the severity of respiratory symptoms affected QoL. Of the six respiratory symptoms, only dyspnoea was associated significantly with overall QoL (Table 5), with an effect being evident on physical, role, cognitive and social functioning, global QoL and fatigue (Table 6). The effect sizes ranged from 0.04 for role and social functioning to 0.20 for physical functioning.

**Table 7***Effect of changes in respiratory symptoms on all EORTC QLQ-C30 scales<sup>1</sup>*

| Independent variable | Wilks' lambda | F    | Significance | Effect size (explained variance) |
|----------------------|---------------|------|--------------|----------------------------------|
| Cough                | 0.851         | 1.59 | ns           | –                                |
| Haemoptysis          | 0.889         | 1.14 | ns           | –                                |
| Dyspnoea             | 0.827         | 1.88 | 0.02         | 0.09                             |
| Dysphagia            | 0.912         | 0.88 | ns           | –                                |
| Arm/shoulder pain    | 0.921         | 0.80 | ns           | –                                |
| Chest wall pain      | 0.867         | 1.39 | ns           | –                                |

<sup>1</sup> Results of GLM multivariate analysis of variance.

Abbreviation: ns = not significant.

*Effect of changes in respiratory symptoms on general symptoms, functioning and global quality of life*

A multivariate analysis was performed to investigate the effect of changes of the respiratory symptoms assessed 6 weeks after the end of radiotherapy on general symptoms (i.e. fatigue and appetite loss), physical and psychosocial functioning, and global QoL. A significant association between the change scores of the EORTC QoL scales and changes in dyspnoea scores was found (Table 7). No such association was observed between changes in the other respiratory symptoms and self-reported functioning and QoL. A more detailed analysis showed that changes in dyspnoea were associated significantly with changes in physical and role functioning, global QoL and fatigue (Table 8). However, the effect sizes were relatively small, varying from 0.04 for role functioning to 0.09 for fatigue.

**Table 6***Effect of dyspnoea on the individual EORTC QLQ-C30 scales<sup>1</sup>*

| Domain                    | Estimated mean scores |      |          |        | Comparisons <sup>2</sup> (p-values) | Effect size (explained variance) |
|---------------------------|-----------------------|------|----------|--------|-------------------------------------|----------------------------------|
|                           | Nil                   | Mild | Moderate | Severe |                                     |                                  |
| <b>Functioning scales</b> |                       |      |          |        |                                     |                                  |
| Physical functioning      | 65.1                  | 55.2 | 38.1     | 27.8   | <0.001                              | 0.20                             |
| Role functioning          | 76.5                  | 69.6 | 57.0     | 54.6   | 0.02                                | 0.04                             |
| Emotional functioning     | 60.5                  | 66.7 | 59.0     | 54.9   | ns                                  | –                                |
| Cognitive functioning     | 81.2                  | 88.0 | 77.9     | 69.9   | 0.001                               | 0.07                             |
| Social functioning        | 79.3                  | 79.1 | 66.4     | 70.8   | 0.02                                | 0.04                             |
| Global quality of life    | 54.3                  | 53.4 | 34.0     | 32.7   | <0.001                              | 0.17                             |
| <b>General symptoms</b>   |                       |      |          |        |                                     |                                  |
| Fatigue                   | 26.8                  | 33.9 | 52.0     | 60.1   | <0.001                              | 0.18                             |
| Appetite loss             | 30.4                  | 28.6 | 32.2     | 35.8   | ns                                  | –                                |

<sup>1</sup> Results of GLM multivariate analysis of variance.<sup>2</sup> Based on the estimated mean scores in the multivariate analysis.

Abbreviation: ns = not significant.

**Table 8**  
Effect of changes in dyspnoea on the changes in individual EORTC QLQ-C30 scales<sup>1</sup>

| Domain                 | Estimated mean change scores at 6 weeks after radiotherapy <sup>2</sup> |                    |                | Comparisons <sup>3</sup><br>(p-values) | Effect size<br>(explained variance) |
|------------------------|---|--------------------|----------------|--|-------------------------------------|
|                        | Dyspnoea improved   | Dyspnoea unchanged | Dyspnoea worse |  |                                     |
| Functioning scales     |   |                    |                |  |                                     |
| Physical functioning   | 4.0   | -3.6               | -15.1          | 0.001                                  | 0.08                                |
| Role functioning       | -5.6  | -3.8               | -24.2          | 0.04                                   | 0.04                                |
| Emotional functioning  | 8.6   | 7.3                | 7.0            | ns                                     | -                                   |
| Cognitive functioning  | -1.8  | -0.2               | -5.6           | ns                                     | -                                   |
| Social functioning     | 0.1   | 0.1                | -8.3           | ns                                     | -                                   |
| Global quality of life | 12.9  | 8.2                | 1.0            | 0.02                                   | 0.05                                |
| General symptoms       |   |                    |                |  |                                     |
| Fatigue                | 0.7   | 5.7                | 19.3           | 0.001                                  | 0.09                                |
| Appetite loss          | -2.4  | -9.2               | 1.5            | ns                                     | -                                   |

<sup>1</sup> Results of GLM multivariate analysis of variance.

<sup>2</sup> For the functioning and global quality of life scores a negative change indicates deterioration. For the symptom scores a negative change indicates improvement.

<sup>3</sup> Based on the estimated mean scores in the multivariate analysis.

Abbreviation: ns = not significant.

## DISCUSSION

The primary question posed in the present study was whether pretreatment QoL differed significantly between inoperable NSCLC with different prognostic profiles established on the basis of WHO performance status and a range of factors related to the extent of the disease. Major differences were observed between these prognostic groups in survival. Although it is most likely that these differences in survival primarily reflect the clinical characteristics of the patients prior to treatment, it cannot be ruled out that an increase in the total dose contributed to the survival benefit observed in the radical and curative groups as well (9).

In the palliative treatment group, significantly lower levels of physical and psychosocial functioning and global QoL and more severe general and respiratory symptoms were observed compared with the radical and curative groups. Only minor differences in functioning and symptom burden were observed between the radical and curative groups.

Prognostic group differences in self-reported QoL could be attributed to differences in WHO performance status, age and weight loss, and not to the TNM classification. Although a marginal difference was found in WHO performance status between the radical and curative groups, the differences between these two groups were determined mainly by the stage of the tumour.

Given the statistically significant association observed in this and other studies between WHO performance status and a number of the QoL scales (1, 10-12), one might be inclined to use performance status as a proxy measure for QoL. However, this remains controversial because of the

lack of responsiveness of performance status scores to worsening toxicity (13), the inconsistent ratings of the same patient by different evaluators (14, 15) and the poor correlation with symptom prevalence (16). Furthermore, although in the present study WHO performance status was the most important determinant in distinguishing different levels of QoL, the total amount of variance in various QoL scores accounted for by performance status was rather low, in particular for emotional, cognitive and social functioning.

The relationship between prognostic factors and baseline QoL has been investigated in several other studies. Curran et al. reported on a study in which baseline QoL was investigated in patients with advanced prostate cancer (17). The prognostic factors investigated included disease stage, pain caused by the primary tumour or bony metastases, WHO performance status and hormone resistance. Significantly more pain, worse physical and role functioning and worse overall QoL were found in the patients with poor versus good prognostic features. Ringdal et al. also investigated the relationship between QoL in different prognostic groups, i.e. curative, palliative treatment to delay tumour progression, or palliative treatment of symptoms (7). This classification into prognostic groups is comparable to that used in the present study. Although they found significant differences between the prognostic groups on a number of scales of the EORTC QLQ-C30, in contrast to the results of the present study, no such differences were observed in psychological or social functioning. These apparently conflicting results might be explained by differences in diagnosis and subsequent prognosis. In the study by Ringdal et al. (7), various sites of malignant diseases were included and the observed

survival varied from 5% after 200 months for the poor prognostic group to 80% after 150 months for the good prognostic group. These survival rates were much better than those found in the present study. In both studies, patients were fully informed about their diagnosis, prognosis and aims of treatment at the time of assessment of baseline QoL. These results suggest that psychological functioning may be affected primarily when the patients' prognosis is relatively poor.

One of the aims of the current study was to investigate the effect of respiratory symptoms on QoL. Results of the multivariate analysis indicated that dyspnoea was the most important respiratory symptom affecting all EORTC scales, with the exception of emotional functioning. The aetiology of dyspnoea is multifactorial. In this category of patients, it may be the result of pleural effusion, atelectasis due to bronchial obstruction by the primary tumour or enlarged mediastinal lymph nodes, pain in the chest wall by direct tumour extension, as well as comorbidity. Subsequently, the question arose as to whether palliation of dyspnoea by radiotherapy also resulted in an improved QoL. The results showed that there was a significant association between improvement of dyspnoea and changes in physical and role functioning, global QoL and fatigue. For patients who experienced worsening of dyspnoea, the change scores for physical and role functioning were  $-15.1$  and  $-24.2$ , respectively. The mean change score for global QoL increased by 12.9 points among patients who experienced improvement of dyspnoea. The question arises as to how the magnitude of these changes should be interpreted. Osoba et al. investigated the significance of changes in health-related QoL scores assessed with the QLQ-C30 by means of a subjective significance questionnaire (SSQ), in which patients were posed direct questions about perceived changes in physical, emotional and social functioning and in global QoL (18). For patients who indicated 'no change' in the SSQ, the mean scores of the corresponding QLQ-C30 domains was not significantly different from 0. For patients who indicated 'moderate' change either for better or for worse, the mean change in scores was about 10–20 points on a 100-point scale, and for 'very much' change, greater than 20 points. These results indicate that changes in dyspnoea may have a significant effect on these functioning scales and global QoL. The results showed that palliation of other respiratory symptoms is not necessarily associated with improvement of general symptoms, physical and psychological functioning or global QoL.

In conclusion, in inoperable NSCLC, classical prognostic factors including performance status and weight loss are associated significantly with self-reported QoL. However, changes in performance status account only partly for the variance observed in different QoL scales, indicating that performance status cannot be used as a proxy

measure for QoL. Although generally assumed, no association could be found between TNM classification and QoL. Dyspnoea is associated significantly with patients' functioning, fatigue and global QoL at baseline, and palliation of this symptom may have a beneficial effect on these health outcomes.

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