Chemoradiotherapy of lung cancer

High-dose radiotherapy or concurrent chemo-radiation in lung cancer patients only induces a temporary, reversible decline in QoL

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ABSTRACT

Background and purpose: Aggressive radiotherapy or concurrent chemo-radiation therapy for lung cancer leads to a high incidence of severe, mostly esophageal, toxicity. The purpose of this study was to investigate the evolution of quality of life (QoL) in patients with lung cancer, selected for curative radiotherapy (RT) or chemo-RT.
Methods: Seventy-five lung cancer patients completed a longitudinal the EORTC QLQ-C30 and LC13. Linear mixed regression models were fitted to investigate the impact of different factors on overall QoL.
Results: Overall QoL decreased shortly after the end of RT (4 points, $p = 0.19$), but increased back to baseline within 3 months. Mean scores of role functioning ($p = 0.018$), cognitive functioning ($p = 0.002$), dyspnoea (EORTC QLQ-LC13; $p = 0.043$), dysphagia ($p = 0.005$) and hoarseness ($p = 0.029$), showed a significant worsening over time. Emotional functioning ($p = 0.033$) improved significantly over time.
Severe esophagitis ($\geqslant$ grade 2) was reported in only 12% of the patients. Next to maximal esophageal toxicity $\geqslant$ grade 2 ($p = .0010$), also tumor stage IIIA ($p < 0.001$), tumor stage IIIB ($p = 0.003$), gender ($p = 0.042$) and fatigue ($p < 0.001$) appeared to be significant predictors of QoL.
Conclusion: High-dose radiotherapy or concurrent chemo-radiation in the treatment of lung cancer seems to be a well-tolerated treatment option with preservation of QoL.

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Lung cancer remains a major public health problem worldwide because of its high incidence, rapid progression, and poor outcome [1]. The majority of patients who develop lung cancer die of this disease within a year [2]. Aggressive radiotherapy or concurrent chemo-radiation therapy for lung cancer is standard care for patients with locally advanced disease, i.e. stage III non-small cell lung cancer (NSCLC) or limited stage small cell lung carcinoma (LD-SCLC) [3,4].

Combined concurrent modality treatment increases long-term survival, but at the expense of a higher incidence of severe esophagitis [5–8]. In order to allow proper balancing between expected benefits and drawbacks of aggressive therapy, knowledge of the effects of a given treatment on the quality of life (QoL) is needed.

An optimal therapy could be defined as one that increases survival or provides benefit through reduction in cancer-related symptoms and improved QoL.

To the best of our knowledge, in only one study, QoL assessment was performed in patients receiving high-dose radiotherapy for NSCLC [9]. No data are at present known on the influence of concurrent chemo-radiation on the QoL.

Moreover, a broad Medline search using the terms "QoL and SCLC" (December 2008) revealed only 15 studies of which none examined QoL after radiotherapy treatment.

The purpose of this study was to investigate the evolution of QoL on NSCLC stages I–III and LD-SCLC patients, referred for hyperfractionated accelerated high-dose radiotherapy (RT) with or without concurrent chemotherapy, with curative intent. Since we hypothesized that QoL would be considerably influenced by esophageal toxicity, we specifically studied the relationship between QoL and esophageal toxicity.

Patients and methods

Study population and design

We used a longitudinal design to assess different aspects of symptoms and functioning regarding QoL in lung cancer patients

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treated with high-dose radiotherapy. Patients with small cell lung carcinoma (SCLC) and patients with non-small cell lung carcinoma (NSCLC) selected for curative treatment with high-dose radiotherapy, were asked to participate in this study.

The entry criteria were as follows: cytological or histological proven NSCLC or LD-SCLC with the exclusion of mixed pathology between NSCLC and small-cell cancer and bronchioloalveolar carcinoma; UICC stages I–III, with the exclusion of T4 lesions in case of malignant pleural effusion; WHO performance status 0–3; measurable disease; age at least 18 years; adequate pulmonary function (FEV1 > 1 l); no severe recent cardiac disease (arrhythmia, congestive heart failure, infarction); able to comply with the protocol; able to give written informed consent. Distant metastases had to be absent both on CT and on whole-body ^{18}F-deoxyglucose (FDG)-PET scan. In stage III NSCLC or LD-SCLC, a CT or an MRI scan of the brain was performed to rule out asymptomatic brain metastases.

To assess the QoL, patients were asked to complete the European Organization for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30) with a lung cancer module (EORTC QLQ-LC13). The questionnaire was completed at baseline (before radiotherapy) and 2, 6 weeks and 3, 6, 9, 12, and 18 months after radiotherapy. Additionally, at each time point, standard toxicity scores were registered by the radiation-oncologist. Pulmonary and esophageal toxicities were scored according to the EORTC/RTOG criteria for acute or late side-effects [10,11].

The local Medical Ethical Committee approved the protocol in accordance with Dutch law and regulations. All patients gave written informed consent before the start of the treatment.

Measurement instruments

Background variables included age, gender, tumor staging, and the WHO performance level. The EORTC Quality of Life Questionnaire (QLQ-C30, version 3.0) is a 30-item cancer-specific core questionnaire that addresses various domains of QoL [12]. It contains five function scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting), two items assessing global health and quality of life, and a number of single items addressing various symptoms and perceived financial impact. The additional Lung cancer module (EORTC QLQ-LC 13) contains 13 items concerning specific symptoms with regard to lung cancer [13].

Treatment

Radiotherapy planning was performed with a Focal (Computerized Medical Systems, Inc.™) treatment planning system, using inhomogeneity corrections based on a convolution algorithm. For the delivery of the radiotherapy treatment, multiple photon fields from a 6-10-MV linear accelerator were used. Dose specification was done according to ICRU 50 guidelines ICRU [14].

For NSCLC, three dose-escalation groups were defined, according to the risk of severe radiation pneumonitis based on the V_{20Gy} [15]. As in RTOG 93-11, three risk groups were identified: V_{20Gy} < 25%, V_{20Gy} 25–37%, and V_{20Gy} > 37% [15]. For each risk group a 3D conformal treatment plan was calculated. The dose was administered in three steps: 61.2 Gy/34 fractions/23 days, 64.8 Gy/36 fractions/24 days, and 68.40 Gy/38 fractions/25 days (all schedules used 1.8 Gy BID with 8 h interval), according to ICRU 50 guidelines [14]. More detailed information can be found in an earlier publication [16].

For LD-SCLC, a 3D conformal treatment plan was calculated, with a prescribed dose to the PTV of 45 Gy in 30 fractions in 3 weeks (1.5 Gy BID, 6–8 h interval), according to ICRU 50 guidelines [14]. More detailed information can be found in an earlier publication [17].

Chemotherapy cycles were repeated every 21 days for a total of three (NSCLC) or five cycles (LD-SCLC). The carboplatin dose (in milligrams) was based on the target area under the curve (AUC) (5 mg/ml/min) × (glomerular filtration rate + 25), with the glomerular filtration rate calculated according to the Cockroft–Gault formula.

For NSCLC, in cases where induction chemotherapy was administered, patients received carboplatin (AUC 5 mg/ml/min) on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8, according to the standard protocol of the Comprehensive Cancer Center Limburg, the Netherlands. Standard dose-reduction rules were applied if indicated. No patient received concurrent chemotherapy and radiotherapy. Radiotherapy was initiated not earlier than 14 days after the last gemcitabin administration, and no later than 21 days after the last chemotherapy delivery.

All LD-SCLC patients received carboplatin (AUC 5 mg/ml/min) on day 1 and etoposide 120 mg/m^2 on days 1, 2, and 3 per cycle. Standard dose-reduction rules were applied if indicated. Chest radiation started after a mean time of 17.7 ± 9.7 days standard deviation (SD) after the beginning of chemotherapy.

Statistical analysis

Descriptive statistics were calculated for demographics and treatment characteristics. Changes in symptom and QoL scores

Table 1
Demographics of 75 patients undergoing high-dose curative radiotherapy for lung cancer.

	NSCLC % (n = 45)	SCLC % (n = 30)	Total group % (n = 75)
Gender			
Male	64	36	75
Female	47	53	25
Age (years)			
Mean	69	64	67
SD	8.1	9.0	8.8
Range	(54–89)	(47–85)	47–89
Compliance (population alive)*			
Baseline	84 (60)	87 (40)	85 (100)
2 weeks	93 (60)	10 (40)	60 (100)
6 weeks	89 (60)	100 (40)	93 (100)
3 months	91 (59)	97 (41)	93 (97)
6 months	97 (56)	79 (44)	89 (85)
9 months	85 (59)	79 (41)	83 (77)
12 months	90 (57)	74 (43)	83 (72)
18 months	88 (56)	55 (44)	73 (60)
Tumor stage			
I–II	23	1	24
IIIA	19	9	28
IIIB	19	24	43
LD	0	5	5
WHO			
0	36	17	53
1	23	13	36
2	1	4	5
3	0	1	1
Unknown	0	5	5
Radiotherapy			
TTD:			
61.2 Gy/1,8GyBID	33	0	33
64.8 Gy/1,8GyBID	19	0	19
68.4 Gy/1,8GyBID	8	0	8
45 Gy/1,5GyBID	0	40	40
Chemotherapy			
Yes	29	40	69
No	31	0	31

Values are percentages unless stated otherwise.
Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation; LD, limited disease; WHO, World Health Organization; TTD, total tumor dose; Gy, gray; BID, twice daily.
* Completed questionnaires per time point.

over time (days after start of treatment) were evaluated with a mixed models linear regression analysis with time as the only independent variable and an unstructured repeated measures covariance type, using SPSS software (version 15.0).

Mixed linear regression models were fitted to investigate the impact of different factors (and especially esophagus toxicity) on overall QoL (item 30 on the EORTC QLQ-C30). As independent variables, chemotherapy (yes/no), WHO performance status (2 dummies: WHO 0 = reference, WHO 1 = dummy 1, WHO 2 = dummy 2), tumor stage (2 dummies: ⩽stage II = reference, stage IIIA = dummy 1, stage IIIB = dummy 2) and maximal esophagus toxicity (2 dummies: no tox. = reference, grade 1 = dummy 1, grade ⩾ 2 = dummy 2) were included. The dependent variable in these regression analyses was overall QoL (EORTC QLQ-30, item 30); age, gender and histology (SCLC/NSCLC), were included as potential confounders. Since fatigue is the most frequently reported cancer-related side-effect, being of significant influence on QoL, we also adjusted for this variable [18–20].

The following steps were taken to attain a model that fitted the data best. First, exploratory analyses were carried out by visual inspection of individual and mean patient profiles to provide information on the structural form (i.e. random intercept, random slope, variability in variance, linear relationships and possible interaction) and through scatter plot and correlation matrices of residuals obtained from ordinary least squares (OLS) regression which provide information on the correlation or covariance structure. Second, a full linear model was formed based on the exploratory analyses and several covariance structures were compared using the log likelihood ratio test. Restricted Maximum Likelihood (REML) estimation methods were used during this step. The model with the least parameters to be estimated was preferred, unless the log likelihood ratio test showed that addition of more parameters improved the model significantly. This procedure was repeated until addition of extra parameters did not improve the model any-

more. The different models that were compared included a random intercept on the patient level with covariance types Unstructured, Toeplitz heterogeneous, Toeplitz, Compound Symmetry, and Scaled Identity, or no random components with covariance structures Unstructured, Toeplitz heterogeneous, and Unstructured. Finally, after the best covariance structure was chosen, the model was then reduced using a top-down procedure and the Maximum Likelihood (ML) estimation method. The primary predictor (esophagus toxicity) and possible confounders (gender, age, and histology) always remained in the model.

All results were regarded as statistically significant if the probability of change was 5% or less (p-value < 0.05).

Results

Patient characteristics

Patient characteristics are depicted in Table 1. The studied dataset contained 75 patients, of which 19 (25%) were women; 45 patients (60%) had NSCLC and 30 (40%) had SCLC. The mean age of the total group was 67 years (SD 8.8). At 18 months after radiotherapy 45 patients (60%) were alive and without recurrence of disease.

Compliance with QoL assessment

At baseline (before start of radiotherapy) 85% of the patients (n = 64) completed the questionnaire (Table 1). After radiotherapy the compliance rates were 60% at 2 weeks (45 of 75 patients alive), 93% at 6 weeks (70 of 75 patients alive), 93% at 3 months (68 of 73 patients alive), 89% at 6 months (57 of 64 patients alive), 83% at 9 months (48 of 58 patients alive), 83% at 12 months (45 of 54 patients alive), and 73% at 18 months (33 of 45 patients alive).

Table 2
Mean baseline disease-related symptom QoL scores and mean changes from baseline as measured by the EORTC QLQ-C30 and lung cancer-specific questionnaire LC13.

Mean (±SD) score baseline			Mean (±SD)		Score change from baseline (ΔT_0)												
	T_0		2 weeks		6 weeks		3 months		6 months		9 months		12 months		18 months		p-value
QoL subscales (QLQ-C30)																	
Physical functioning	60.3	(24.0)	−3.4	(4.9)	−3.5	(4.8)	0.6	(4.4)	−2.5	(4.8)	0.1	(4.9)	3.4	(5.0)	−12.0	(8.1)	ns
Role functioning[*]	59.5	(35.8)	−9.5	(7.5)	−12.4	(6.7)	−8.0	(6.8)	−7.7	(6.8)	−2.9	(8.2)	−3.8	(7.8)	−22.4	(10.1)	0.018
Emotional functioning[*]	64.3	(27.1)	4.9	(5.3)	2.4	(5.0)	5.0	(4.9)	4.7	(5.4)	9.9	(5.4)	7.6	(5.4)	9.1	(5.6)	0.033
Cognitive functioning[*]	82.0	(24.6)	−3.5	(4.8)	−2.7	(4.2)	−4.3	(4.6)	−5.7	(4.9)	−3.6	(5.1)	−6.0	(5.0)	−8.3	(5.5)	0.002
Social functioning	74.1	(26.7)	5.4	(5.1)	−7.4	(5.1)	−4.0	(5.1)	−3.6	(5.5)	−1.4	(5.7)	3.1	(5.3)	−6.9	(5.9)	ns
Fatigue	43.0	(28.5)	7.5	(5.6)	5.1	(5.5)	0.2	(4.8)	−1.3	(5.1)	−3.0	(5.6)	−3.2	(5.4)	0.4	(6.3)	ns
Nausea/vomiting	8.7	(18.4)	4.5	(4.2)	3.2	(7.5)	1.1	(3.3)	3.6	(3.9)	−1.6	(3.4)	−1.6	(3.2)	0.1	(3.9)	ns
Pain	21.0	(29.5)	8.6	(5.9)	8.4	(7.6)	4.7	(5.2)	4.7	(5.9)	2.2	(5.7)	0.8	(5.7)	5.3	(6.8)	ns
Dyspnoea	40.1	(31.5)	5.8	(6.0)	4.2	(6.6)	3.5	(5.7)	3.8	(5.8)	0.2	(5.9)	6.9	(6.2)	4.3	(7.1)	ns
Insomnia	33.9	(35.4)	−2.7	(6.8)	−3.4	(7.3)	−4.0	(6.1)	−2.3	(6.4)	−6.9	(6.9)	−2.8	(6.8)	−8.6	(7.5)	ns
Appetite loss	22.4	(32.6)	12.4	(6.9)	7.1	(8.5)	1.1	(5.4)	4.5	(6.1)	2.6	(6.4)	4.3	(6.5)	6.8	(7.2)	ns
Constipation	15.3	(27.9)	4.4	(5.9)	5.6	(8.3)	−1.8	(4.9)	1.4	(5.5)	4.2	(6.2)	−2.4	(5.2)	1.9	(6.5)	ns
Diarrhoea	8.5	(19.8)	−5.5	(3.3)	−2.3	(6.4)	−3.5	(3.0)	−2.6	(3.6)	−3.5	(3.4)	−1.7	(3.9)	3.0	(4.7)	ns
Financial difficulties	9.1	(20.2)	−0.3	(3.7)	8.5	(9.4)	6.6	(4.2)	7.2	(4.5)	1.5	(3.9)	3.5	(4.1)	9.6	(4.7)	ns
Global health status/QoL	59.5	(23.9)	−4.7	(5.0)	−3.2	(4.0)	2.9	(4.1)	−2.1	(4.2)	3.1	(4.7)	−1.6	(4.3)	0.9	(5.1)	ns
Global health	59.0	(24.7)	−6.4	(5.1)	−2.3	(4.1)	2.3	(4.1)	−4.0	(4.5)	3.3	(4.7)	−1.2	(4.4)	1.2	(5.3)	ns
Overall quality of life	60.0	(25.3)	−2.9	(5.2)	−4.0	(4.2)	3.2	(4.3)	0.2	(4.4)	3.1	(4.9)	−1.8	(4.5)	−0.1	(5.3)	ns
Symptom scales (LC13)																	
Dyspnoea	35.1	(26.6)	5.3	(5.6)	3.6	(5.8)	0.1	(4.8)	−2.0	(5.0)	−1.8	(5.1)	0.9	(5.5)	4.5	(6.2)	0.043
Coughing	41.3	(29.8)	14.3	(6.4)	1.1	(6.0)	−0.5	(5.4)	2.2	(5.7)	−6.4	(5.8)	0.4	(6.1)	8.2	(6.8)	ns
Haemoptysis	5.8	(17.5)	2.9	(3.8)	−3.9	(6.0)	−2.3	(2.8)	−4.6	(2.5)	−4.3	(2.8)	−4.2	(2.9)	−4.7	(3.2)	ns
Dysphagia[*]	10.6	(23.8)	30.7	(6.3)	14.1	(10.0)	10.3	(4.9)	3.4	(4.2)	7.2	(5.2)	−2.3	(4.6)	4.5	(5.7)	0.005
Pain in chest	17.5	(26.7)	6.4	(5.7)	1.1	(7.6)	2.4	(5.0)	2.3	(5.4)	3.3	(5.4)	3.7	(5.6)	6.2	(6.1)	ns
Pain in arms or shoulder	21.2	(28.3)	7.3	(6.1)	4.0	(7.7)	−1.0	(4.8)	2.5	(5.5)	−1.9	(5.5)	−4.1	(5.5)	−3.4	(6.3)	ns
Hoarseness[*]	16.7	(26.8)	−7.1	(4.8)	1.9	(7.8)	−3.7	(4.5)	2.5	(5.0)	3.3	(5.4)	3.3	(5.5)	−0.5	(5.6)	0.029

[*] Based on mixed models linear regression analysis and repeated measures covariance analyses, indicating significance of time on the development of the specific aspect of QoL. No significance (ns) indicates no significant influence of time. Positive numbers indicate a higher degree of the item subject at follow-up, while negative numbers indicate a lower degree of the item subject. For example, a positive number for the global health indicates a better global health, while a positive value for fatigue indicates more fatigueness.

Evolution of QoL, functioning, and symptom scores over time

Mean baseline disease-related symptom QoL scores and mean changes from baseline are depicted in Table 2.

QoL decreased short after the end of RT ($\Delta T_0 - T_2$: mean = -4.0) but increased back to baseline within 3 months ($\Delta T_0 - T_3$: mean = 3.5), and remained relatively stable thereafter. None of

these changes over time are significant ($p = 0.943$). Mean scores of role functioning ($p = 0.018$), cognitive functioning ($p = 0.002$), dyspnoea (EORTC QLQ-LC13; $p = 0.043$), dysphagia ($p = 0.005$), and hoarseness ($p = 0.029$), showed a significant worsening over time. Emotional functioning ($p = 0.033$) improved significantly over time. The course over time of QoL and these variables are depicted in Fig. 1b–g. Although the changes in all functioning and
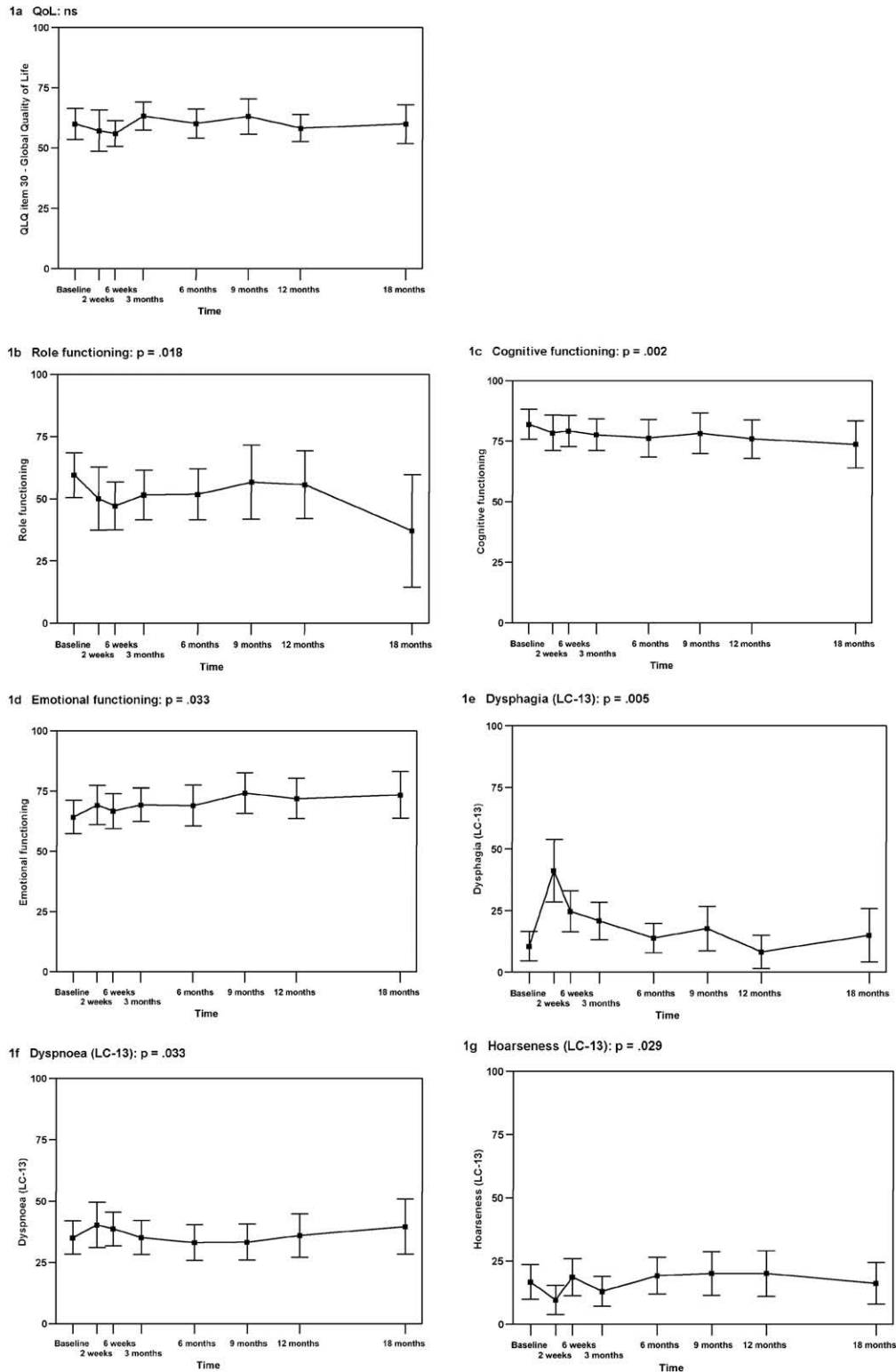

Fig. 1. Evolution of QoL (1a) and of functioning and symptoms with significant changes in time (1b–g).

Table 3
Estimates from linear regression analysis of fixed effects on QoL.

	Estimate	95% CI		Std. error	p-value
Parameter					
Gender	−6.14	−12.07	−0.22	2.95	0.042
Histology					ns
Age					ns
Fatigue	−0.42	−0.48	−0.35	0.03	<0.001
*Tumor stage**					
Stage III A	15.92	8.72	23.13	3.58	<0.001
Stage III B	10.95	4.03	17.88	3.42	0.003
*Maximal esophageal toxicity**					
Grade I					ns
Grade ⩾ II	−10.76	−18.91	−2.61	4.08	0.010

Dependent variable: item 30 EORTC QLQ-C30, adjusted for age, gender, and histology.
Chemotherapy and WHO performance status were not significant.
ns, not significant.
* Reference category for tumor stage = stage ⩽ II, and for maximal esophagus tox. = no tox. (grade 0).

symptoms depicted in Fig. 1b–g were statistical significant, the magnitude of these effects was small (regression coefficients in absolute terms ranging from 0.009 to 0.107). The remaining symptoms and functioning scores were stable over time.

The role of esophageal toxicity on QoL

Out of 75 patients, maximal esophageal toxicity could be calculated for 61 patients (31 grade 0, 21 grade 1, and 9 ⩾ grade 2). As hypothesized, esophageal toxicity significantly influenced QoL, however only if ⩾grade 2. Next to maximal esophageal toxicity ⩾ grade 2 ($p = .010$), also tumor stage IIIA ($p < 0.001$), tumor stage IIIB ($p = 0.003$), gender ($p = 0.042$), and fatigue ($p < 0.001$) appeared to be significant predictors of QoL (Table 3). WHO performance status, chemotherapy, age, and histology did not significantly influence the changes in QoL over time.

Discussion

To our knowledge, this is the first prospective QoL study on lung cancer treated with high-dose radiotherapy with or without chemotherapy, including patients with different stages and histology. The only previous study to report on QoL issues after treatment with an accelerated radiotherapy regimen was carried out by Auchter et al. [9], who investigated QoL in 30 NSCLC patients, all stage III. In their conclusion they reported that this aggressive approach did not cause a significant, long-term decrease in the QoL of the treated patients.

In the current study, these above results were confirmed.

Compliance rates were high, with a mean of 83% (range 60–93%) completed. However, unexpectedly, the compliance rate in the LD-SCLC group dropped to 10% in week 2. We hypothesize that this may be due to the too high burden to fill-out the QoL forms at a time when most patients experience side-effects.

QoL decreased shortly after RT but increased again within 3 months after the end of RT. This short decrease in global quality of life could be explained by the side-effects of RT. In addition, the majority of the symptoms and functioning scores did not change much over time, and if so, it was reversible, and occurred only shortly after finishing radiotherapy. However, in some symptoms and functioning scores, a persistent worsening was seen: Physical state, accomplishing daily tasks (role) and cognitive functioning, dyspnoea, dysphagia, and hoarseness, detoriated after RT, and were significantly worse at the end of the follow-up period. Conversely, as also reported in a previous study [9], emotional functioning

scores were significantly higher at the end of the follow-up period as compared to baseline.

Histology (SCLC/NSCLC), WHO performance status and additional treatment with chemotherapy did not influence the overall QoL.

Adjusted for potential confounders, esophagitis appeared to be a strong predictor for QoL. However, the number of patients who suffer from severe esophagitis appeared to be very low. A substantial decrease in QoL after high-dose RT in the current study population did only occur in a very small proportion of patients (12%). More apparent predictors for QoL found in this study appeared to be gender, tumor stage, and fatigue. The latter finding is not surprising, as fatigue is identified as the most predominant factor that influences overall QoL [18,19,21]. In addition, the more persistent worsening of some symptoms and functioning scores may be caused by the occurrence of relapse. However, since we did not take this into account in our analysis we are not able to draw any conclusion on this.

Our results show that performance status (PS) did not significantly contribute to the overall QoL. Earlier publications that reported on the correlation between PS and QoL are ambiguous [18,22,23]. It could be, since we adjusted for fatigue, a variable which is identified as a strong potential confounder that the PS pales into insignificance. Another reason why PS did not correlate with QoL in the present study could be explained by the relatively good condition of the study population. The main group (53%) had a very good of PS (WHO PS = 0).

We found that the course of QoL over time differed between men and women. From baseline until 18 months after RT, in females their mean QoL scores were improved from 48.8 (SD 26.5) to 64.3 (SD 22.3), whereas in males their QoL scores decreased from 63.2 (SD 24.3) to 58.7 (SD 22.6) in the same period. This finding is in agreement with two recent publications [22,24]. Using the Functional Assessment of Cancer Therapy [FACT], Movsas et al. [24] observed pretreatment a clinically meaningful difference in lung cancer patients between males (FACT 87.3) and females (FACT 78.6). Siddiqui et al.[22] focused on a prospective randomized lung cancer trial on gender-specific baseline health-related QoL and Karnofsky performance score (KPS). They reported significant KPS-by-gender interactions in the physical well-being and additional concerns-lung subscales. Elaborating on this result, it is probable that the persistent decrease in role functioning noted in the current study, is associated with gender.

In the present study tumor stage appeared also to be associated with QoL. Patients with stage III, regardless of histology, reported a less variation of QoL over time as compared to patients with stages I–II. A trend towards higher baseline QoL scores for patients with stage III as compared to those with stages I–II (48.95 ± 26.9 vs. 63.89 ± 24.9, $p = 0.051$) was found. The lower QoL scores in stages I–II patients as compared to stage III patients could be explained by the fact that the main part of the stages I–II patients was referred for RT because they were medical inoperable due to a worse physical condition and/or co-morbidities. Correspondingly, Manser et al. [25] found higher utility scores on stage III NSCLC than on stages I–II, taking into account the proportion of operability and co-morbidities.

A gradual worsening was observed for dysphagia, dyspnoea and hoarseness. Although we did not correct for the natural history of chronic obstructive pulmonary disease [26,27] that would also explain increasing dyspnoea with time, in which radiation-induced lung damage could obviously also play a role.

High-dose radiotherapy or concurrent chemo-radiation in the treatment of lung cancer seems to be a well-tolerated treatment option with preservation of QoL.

After fatigue, acute esophagitis had the largest impact on QoL. In extension to this result, it is recommended when implementing

new innovations in RT for lung cancer [28,29] such as intensity-modulated RT, tomotherapy, stereotactic RT or particle therapy, to carefully monitor the QoL of patients, in order to evaluate this prognostic factor and the impact of the new technology.

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