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Recovery of quality of life in 574 patients with inoperable lung cancer undergoing (chemo)radiotherapy

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ABSTRACT

Introduction: Quality of life (QoL) of patients with inoperable lung cancer can be negatively affected by both the disease and its treatment, generally consisting of (chemo)radiotherapy. The aim of this study was to prospectively assess QoL in patients with inoperable lung cancer, treated with (chemo)radiotherapy and to assess whether patient- and/or treatment-related characteristics were associated with poorer QoL.
Methods: This prospective cohort study evaluated QoL and patient-, tumor-, and treatment characteristics from inoperable lung cancer patients, treated with fractionated (≥40 Gy) (chemo)radiotherapy. Patients were evaluated at baseline, upon finishing radiotherapy, and 3 months, 6 months, 1 year, and yearly thereafter up to 5 years after radiotherapy. The QoL assessment consisted of questionnaires evaluating lung cancer-specific and treatment-related complaints using scale scores.
Results: Compliance rates of the 574 analyzed patients ranged from 87 to 97 % during follow-up. Complaints increased after radiotherapy, as the QoL scale scores increased from median 8 (interquartile range, IQR 4–14) to 17 (IQR 4–25) after completing radiotherapy ($P < 0.0004$), indicating more complaints. From 3 months to 24 months of follow-up, scale scores returned to a median of 13, but were significantly higher compared to baseline ($P < 0.0004$). However, no clinically relevant differences compared to baseline were observed. Patients with pulmonary comorbidity and WHO scores ≥ 2 generally reported more complaints.
Conclusion: Patients experienced a temporary increase in complaints after finishing (chemo)radiotherapy, QoL returned to baseline level and remained stable up to five years of follow-up.

Introduction

Lung cancer is a burdensome disease that heavily affects patients. It is the leading cause of cancer death [1], primarily because most patients present with synchronous lymphogenic or distant metastasis [2]. Most patients with locally advanced disease are deemed inoperable and therefore qualify for an intensive treatment regimen currently consisting of radiotherapy with curative intent, generally combined with chemotherapy and adjuvant immunotherapy.

Patients with lung cancer may experience disease specific [1,3–6] and treatment-related [7–10] complaints, which may negatively affect their quality of life (QoL). Complaints comprise physical, mental, social, and financial domains [11,12]. Moreover, poor QoL, especially physical and emotional functioning [13], is associated with worse survival [13,14].

QoL is dynamic and may change over time during diagnosis, treatment, and follow-up. The evolving landscape of lung cancer treatment emphasizes the need for repeated evaluation of QoL in these patients, especially since changes in radiation treatment strategies may result in less toxicity and prolonged survival [9,15,16]. Moreover, a good

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performance score is one of the key eligibility criteria for patients with non-small cell lung carcinoma (NSCLC) to receive adjuvant immunotherapy [17]. Previous studies on QoL in patients with lung cancer have several limitations due to their retrospective study design, limited follow-up time, small sample size, heterogenous populations, and in particular significant loss to follow-up entailing informative censoring [7,9,11,12,18].

Information on well-being of lung cancer patients with inoperable disease throughout their follow-up is valuable, however, little is known about long-term effects on QoL in these patients. Hence, the primary aim of this prospective study with very high compliance rates was to describe long-term QoL by assessing treatment-related complaints of patients treated with (chemo)radiotherapy for inoperable lung cancer up to five years of follow-up. The second aim was to evaluate which patient- and treatment-related characteristics were associated with complaints.

Material and methods

Standard follow-up program

Since February 2013, the department of Radiation Oncology of the University Medical Center Groningen (UMCG), the Netherlands, initiated a prospective data registration program for lung cancer patients referred to as the prospective platform for evaluation and development of lung radiotherapy (proPED) [19]. Patient-, tumor-, and treatment characteristics, doctor and patient rated outcome measures (DROMs and PROMs, respectively), and imaging data are collected. PROMs, including QoL questionnaires, are assessed via telephone or mail, coordinated by dedicated research assistants.

DROMs and PROMs are collected at the start of radiotherapy (baseline, T0), at the end of radiotherapy, and at 3 months, 6 months, 1 year, and yearly thereafter up to 5 years. Patients are actively reminded by the research assistants to complete the PROMs if no response is received. All patients treated with curative intent are asked to enroll in the proPED. The proPED received approval from the medical ethics committee of the UMCG and is registered at clinicaltrials.gov (NCT02421718). Since the introduction of the European General Data Protection Regulation in May 2018, written informed consent was obtained in all patients.

Participants

For the current analysis, we selected patients diagnosed with primary NSCLC or small cell lung cancer (SCLC), treated with curatively intended fractionated (<3 Gy/fraction) (chemo)radiotherapy (≥40 Gy) from a cohort treated from 2013 to 2020. Patients receiving stereotactic radiotherapy, proton therapy, patients treated with surgery followed by postoperative (chemo)radiotherapy, patients included for treatment of recurrent disease and/or patients that received adjuvant immunotherapy were excluded. Patients receiving immunotherapy and proton therapy were excluded because both modalities were upcoming and only few patients in this cohort received these treatments. The most commonly administered chemotherapy regimen during the study period for NSCLC patients was gemcitabine and cisplatin; pemetrexed and cisplatin; or gemcitabine and carboplatin. For SCLC patients these were cisplatin and etoposide or carboplatin and etoposide.

Quality of life (QoL)

QoL evaluation was PROM-based and consisted of assessing treatment-related complaints using a questionnaire that was adapted from the Dutch version of the modular supplement of The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13: the EORTC QLQ-LC13 [20]. The EORTC QLQ-LC13 evaluates QoL by assessing lung cancer-specific and treatment-related complaints. Patients were asked to report on complaints that they experienced the last week. Possible answers on the 4-point Likert scale ranged from "1 – not at all" to "4 – very much". In the proPED cohort, a modification of EORTC-QLQ-C13 was used, tailored to aspects particularly relevant for (chemo)radiotherapy and consisted of eight administered questions: "How much did you cough?"; "Did you cough up blood?"; "Where you short of breath when you rested?"; "Where you short of breath when you walked?"; "Where you short of breath when you climbed stairs?"; "Did you have trouble swallowing?"; "Have you had pain in your chest?"; and "Have you had pain in your arm or shoulder?".

Study definitions

Time to last evaluation was defined as the time between start of radiotherapy and last QoL evaluation. Survival time was defined as date of start of radiotherapy to date of death or the last moment of last known alive status.

Statistical analysis

Normally distributed data are shown as mean ± standard deviation (SD), whereas non-normally distributed data are shown as median (interquartile range, IQR). A Kaplan-Meier survival analysis was performed to calculate the median survival time. For our first aim, QoL scores were transformed into scale scores per time point of evaluation similarly to the EORTC QLQ-C30 scoring manual [21]. *Raw scores* were calculated by estimating the average score of the eight questions. Thereafter, raw scores were linearly transformed to *scale scores* ranging from 0 to 100 (0: patient answered "not at all" and 100: patient answered "very much" on every question, respectively). Hence, higher scale scores indicate more complaints. Scale scores at follow-up were compared with the scale score at baseline using dependent t-tests, since the difference scores at baseline and follow-up were normally distributed. A difference of ≥ 10 points on the scale scores [22,23] was defined as a clinically relevant difference. Subsequently, to provide insight in which complaints were the most frequent, answers for each question were evaluated separately.

Patients were excluded from all analyses if no baseline data were present. In case of missing scale scores, patients were excluded from specific analyses when one or more answers per follow-up moment were missing.

For the second aim, we compared scale scores between various subgroups of patients at each time point. Mann Whitney U tests were used in case of two subgroups, and Kruskal Wallis tests in case of more than two subgroups. The 12 evaluated subgroups were: lung cancer subtype (SCLC vs. NSCLC), sex, pulmonary or cardiac morbidity, smoking status (current vs. not current), World Health Organization (WHO) performance score at baseline (0–1 vs. 2–4), weight loss in the three previous months before diagnosis (0–5 % vs. > 5 % of their original weight), radiotherapy technique (three-dimensional conformal radiation therapy [3DCRT], vs. partial volumetric modulated arc therapy [VMAT] or intensity modulated radiotherapy [IMRT], vs. full VMAT/IMRT), and lymph node involvement (N0-1 vs. N2-3). The cut-off points for the categories of mean lung dose (MLD), mean heart dose (MHD), and gross tumor volume GTV) were determined based on the median values of all selected patients. This resulted in the subgroups: MLD (<12 vs. ≥ 12 Gy), MHD (<7 vs. ≥ 7 Gy), and mean GTV (<55 vs. ≥ 55 cm^3).

IBM SPSS Statistics for Windows version 28 (IBM, Armonk, NY) was used for statistical analyses. Statistical tests were performed two-sided. A Bonferroni multiple testing correction was performed. Since 116 hypotheses were tested (8 follow-up moments compared to baseline + 12 subgroups * 9 moments of evaluation; P-value 0.05/116 tests = 0.0004), P-values < 0.0004 were considered significant.

Results

Patients

Of the 753 proPED cohort patients, 577 patients fit our in- and exclusion criteria and were eligible for the current study (Supplemental Fig. 1). Baseline QoL evaluation was available for 574 patients (99 %). The mean age at diagnosis was 67 (SD ± 9) years (Table 1). Most patients were male (n = 336, 58 %). SCLC was diagnosed in 110 patients (19 %). Most patients had WHO performance scores of 0 or 1 at baseline (n = 486, 85 %). The median time to last QoL evaluation was 13 months (IQR 7–47), and the median overall survival time was 24 months (IQR 13–38). After 2 years of follow-up, 50 % of NSCLC patients (n = 232) and 39 % of SCLC patients survived (n = 43).

Treatment characteristics

Stage III disease was diagnosed in 79 % of NSCLC and 88 % of SCLC patients (Table 2). NSCLC patients were mainly treated with 60 Gy in 25 fractions (92 %). Most SCLC patients (41 %) received 45 Gy in 30 fractions twice daily. Chemotherapy (induction, concurrent and/or sequential) was administered in most patients, and 9 % of the NSCLC and 0 % of the SCLC patients did not receive any chemotherapy.

Overall quality of life

At 6, 12, 24, 48, and 60 months after radiotherapy, the compliance rates for QoL assessment of the surviving patients were 97 %, 98 %, 97 %, 92 %, and 87 %, respectively (Fig. 1 and Supplemental Table 1).

The summed scale scores statistically significantly increased from a median of 8 (IQR 4–17) at baseline to 17 (IQR 4–25) at the end of radiotherapy ($P < 0.004$), reflecting an increase in complaints (Fig. 1). From 3 to 60 months of follow-up median scale scores decreased to 13 (3–48 months IQR 4–21, 60 months IQR 8–21). Scale scores remained statistically significantly increased compared to baseline up to 24 months of follow-up ($P < 0.004$). However, for none of the follow-up moments a clinically relevant difference in complaints in scale scores was seen. Compared to baseline, the largest increase in scale scores was seen at the end of radiotherapy, as 66 % of patients reported an increase in complaints. Scale scores were missing for one patient since he did not complete all questions at baseline.

At baseline, being short of breath when climbing stairs (25 %) and coughing (16 %) were the most frequently reported moderate-to-severe complaints (Fig. 2 and Supplemental Table 2). At the end of radiotherapy, 24 % of the patients reported moderate-to-severe swallowing problems, compared to 2 % at baseline. Moderate-to-severe chest pain was reported by 12 % of the patients at the end of radiotherapy, compared to 4 % at baseline.

Table 1
Patient characteristics of inoperable lung cancer patients treated with (chemo) radiotherapy.

Characteristic	All patients n = 574	NSCLC n = 464	SCLC n = 110
Age at diagnosis [years]	67 ± 9	67 ± 10	65 ± 8
Sex, n (%)			
Male	336 (58)	290 (63)	46 (42)
Female	238 (42)	174 (37)	64 (58)
Cardiac morbidity[1], n (%)	263 (46)[2]	205 (44)[3]	58 (53)
Pulmonary morbidity[4], n (%)	195 (34)[5]	159 (34)[6]	36 (33)
WHO performance score, n (%)			
0 or 1	486 (85)	392 (84)	94 (85)
2, 3, or 4	88 (15)	72 (16)	16 (15)
Smoking status, n (%)			
Current	192 (33)	155 (33)	37 (34)
Former < 3 months	106 (19)	74 (16)	32 (29)
Former ≥ 3 months	261 (46)	222 (48)	39 (35)
Never	8 (1)	8 (2)	0 (0)
Unknown	7 (1)	5 (1)	2 (2)
Weight loss > 5 %[7], n (%)	193 (34)[8]	163 (35)[9]	30 (27)[10]
Time to last evaluation [months]	13 (7–47)	13 (7–48)	13 (7–43)
Survival time [months]	24 (13–38)	24 (13–39)	23 (14–36)

Age is shown as mean ± standard deviation. Time to follow-up and survival time are shown as median (interquartile range). Abbreviations: WHO = world health organization; NSCLC = non-small cell lung carcinoma; and SCLC = small cell lung carcinoma. [1] Including hypertension, arrhythmia, valvular disease, or ischemia. [2] 1 missing case. [3] 1 missing case. [4] Including chronic obstructive pulmonary disease, interstitial lung disease, fibrosis, or asthma. [5] 1 missing case. [6] 1 missing case. [7] wt loss in the three months before diagnosis, compared to initial weight. [8] 46 missing cases. [9] 38 missing cases. [10] 8 missing cases. [11] 16 missing cases with no date of diagnosis.

Table 2
Disease and treatment characteristics of inoperable lung cancer patients treated with (chemo)radiotherapy.

Characteristic	NSCLC n = 464	SCLC n = 110
Disease stage, n (%)		
I	18 (4)	2 (2)
II	66 (14)	5 (5)
III	330 (71)	97 (88)
IV	50 (11)	6 (5)
Mean GTV volume [cm^3]	51 (25–109)	69 (31–109)
Radiotherapy treatment, n (%)		
60 Gy, 25 fractions	428 (92)	2 (2)
60 Gy, 30 fractions	12 (3)	0 (0)
50 Gy, 25 fractions	3 (1)	24 (22)
45 Gy, 30 fractions	0 (0)	45 (41)
45 Gy, 25 fractions	0 (0)	34 (31)
Other	21 (4)	5 (4)
Radiotherapy technique, n (%)		
Partial IMRT or VMAT	306 (66)	63 (57)
Full IMRT or VMAT	132 (28)	24 (22)
3DCRT	26 (6)	23 (21)
Chemotherapy, n (%)		
Induction and concurrent	291 (63)	93 (85)
Concurrent	93 (20)	0 (0)
Sequential	37 (7)	17 (16)
None	43 (9)	0 (0)
Mean heart dose [Gy]	6 (2–13)	8 (4–13)
Mean lung dose [Gy]	12 (9–15)	11 (10–14)

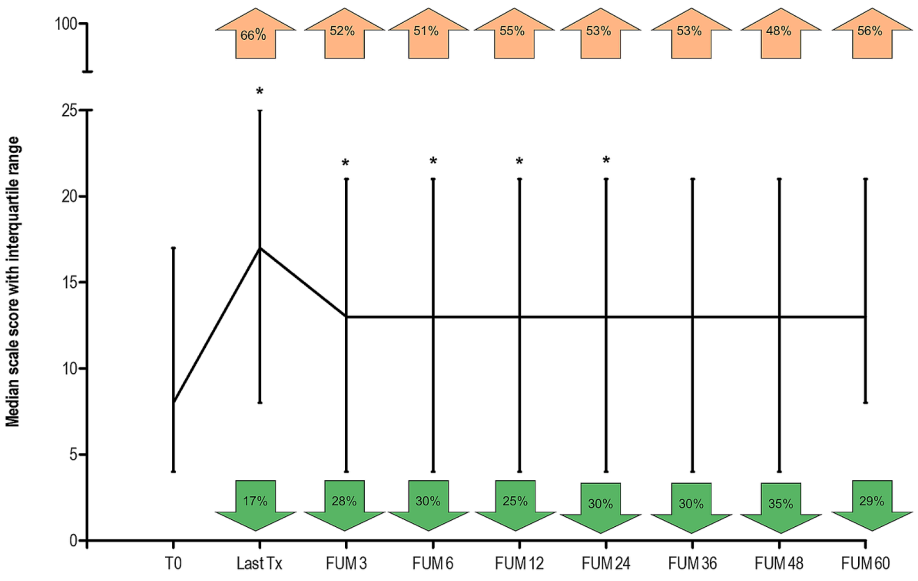
Abbreviations: NSCLC = non-small cell lung carcinoma; SCLC = small cell lung carcinoma; 3DCRT = three-dimensional conformal radiation therapy; IMRT = intensity modulated radiotherapy; and VMAT = volumetric modulated arc therapy or intensity modulated radiotherapy. Continuous variables are shown as median (interquartile range).

Quality of life in subgroups

Patients with pulmonary comorbidity and patients with baseline WHO-performance scores ≥ 2 reported statistically significant higher scale scores (i.e., more complaints) at baseline and during follow-up (Supplemental Fig. 2). At baseline, patients with NSCLC, more than 5 % weight loss before diagnosis, and/or a 0–1 nodal stage reported statistically significantly more complaints. Only at 48 months of follow-up, clinically relevant higher scale scores were seen for patients with worse WHO performance scores at baseline (although not statistically significant). The comparison between the subgroups based on sex, smoking, cardiac comorbidity, radiotherapy technique, MLD, MHD, and GTV did not show statistically significant or clinically relevant differences.

Discussion

This large prospective cohort study primarily evaluated QoL by assessing treatment-related complaints in patients treated with fractionated (chemo)radiotherapy for inoperable lung cancer. Results show a temporary decrease in QoL upon completing radiotherapy, particularly caused by an increase of problems with swallowing and chest pain.



n	n=574	n=559	n=525	n=484	n=396	n=266	n=172	n=103	n=66
Compliance		97%	98%	97%	98%	97%	93%	92%	87%
Compared to T0, n(%)									
Less complaints		93 (17)	149 (28)	146 (30)	100 (25)	80 (30)	52 (30)	36 (35)	19 (29)
No change		95 (17)	102 (19)	91 (19)	79 (20)	44 (17)	29 (17)	18 (17)	10 (15)
More complaints		370 (66)	273 (52)	246 (51)	216 (55)	142 (53)	91 (53)	49 (48)	37 (56)

Fig. 1. Scale scores per evaluation, shown as median with interquartile range. A lower score indicates less complaints. Scale scores range from 0 (patient reported "no complaints" on all 8 questions) to 100 (patient reported "very much complaints" on all 8 questions). Median sum scores apply since the distribution of sum scores was skewed towards the lower scores and scales are ordinal level. Wilcoxon Signed Rank tests were used to compare median T0-scores to medians at follow-up. Statistically significant differences are indicated as * $P < 0.0004$. No clinically relevant differences (a difference of ≥ 10) were found. The red and green arrows show the percentage of patients with increased and decreased scale scores compared to baseline, respectively. At baseline (T0), data of 573 patients are shown, 1 patient did not fill in the questionnaire completely. Abbreviations: T0 = baseline; Last Tx = last treatment; FUM = follow-up month. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Three months after finishing radiotherapy, QoL improved to a level that was comparable to baseline level and remained stable for at least up to five years of follow-up. We did not find clinically relevant differences in complaints beyond the point of 3 months of follow-up compared to baseline. Our analyses showed that patients with worse WHO performance scores at the start of (chemo)radiotherapy reported more complaints at baseline, after radiotherapy, and at 6 months. Patients with pulmonary comorbidity reported more complaints at baseline, at the end of radiotherapy, and at 3, 6, 24, and 36 months of follow-up compared with patients not having pulmonary co-morbidity at study inclusion.

We demonstrated the course of QoL in a large and well defined patient group, primarily consisting of patients with stage III lung cancer treated with (chemo)radiotherapy (Table 2), while previous large studies reported on more heterogenous groups of lung cancer patients with various disease stages and/or treatments [9,12,24]. Nevertheless, current results are comparable to previous assessments in smaller studies on patients with locally advanced/inoperable lung cancer [7,11,16]. The temporary rise in complaints after (chemo)radiotherapy has been reported in previous studies [7,8,19,25]. The highest peak in complaints in our cohort resulted in a scale score of 17 out of 100 (e.g., a patient reporting having "a little" complaints on 4 out of 8 questions) upon finishing radiotherapy, while returning to baseline and stable QoL thereafter. Most patients report a small increase in complaints during follow-up, but none of these changes were clinically relevant according to current definitions [22,23]. This indicates that these changes in complaints somewhat affect patients' QoL, but QoL overall is favorable. Ran et al. also reported a relatively high QoL in five-year survivors of lung cancer treated with radiotherapy [11]. It is important to note survivors of lung cancer in general demonstrate resilience [18,26], which might also add to the favorable long-term QoL we observed.

However, this certainly does not indicate that patients do not experience any complaints or that QoL does not require attention. Based on the current and previous results, persistent complaints that should receive most attention are dyspnea, fatigue, and coughing [11,12,16,24]. Moreover, our results show that patients with pulmonary comorbidity and/or worse WHO performance scores at the start of radiotherapy report more complaints at multiple moments of evaluation. This means that patients who start radiotherapy with a disadvantage are at risk of experiencing persistently poorer QoL after treatment. The isolated observation of more complaints at baseline in patients with lower nodal stages was not seen during follow-up and is not an intuitive finding. Patients with N0-1 stage will only receive (chemo)radiotherapy when they are considered inoperable or irresectable. Although subgroups are small, additional analysis of our data showed that patients with T3-4 and N0-1 tumors reported slightly more complaints than other groups (data not shown). In previous studies, poor QoL was associated with worse survival [11,13,14]. Although assessing the relationship between QoL and survival was not one of our aims, we found that if patients survived less than half a year after start of radiotherapy, they reported more complaints at baseline (data not shown).

In the last decade, the treatment landscape of lung cancer evolved by the introduction of adjuvant immunotherapy after treatment with (chemo)radiotherapy, improving overall survival in stage III NSCLC patients [17,27]. Current data reports on QoL of patients that were treated before immunotherapy was clinically introduced. At present, only patients with good performance scores are eligible for treatment with immunotherapy [17]. Additionally, a poor performance score before commencing immunotherapy is a predictor of shorter survival [28,29]. Hence, it is important that patients experience minimal health deterioration due to locoregional treatment. Of note, our data show a

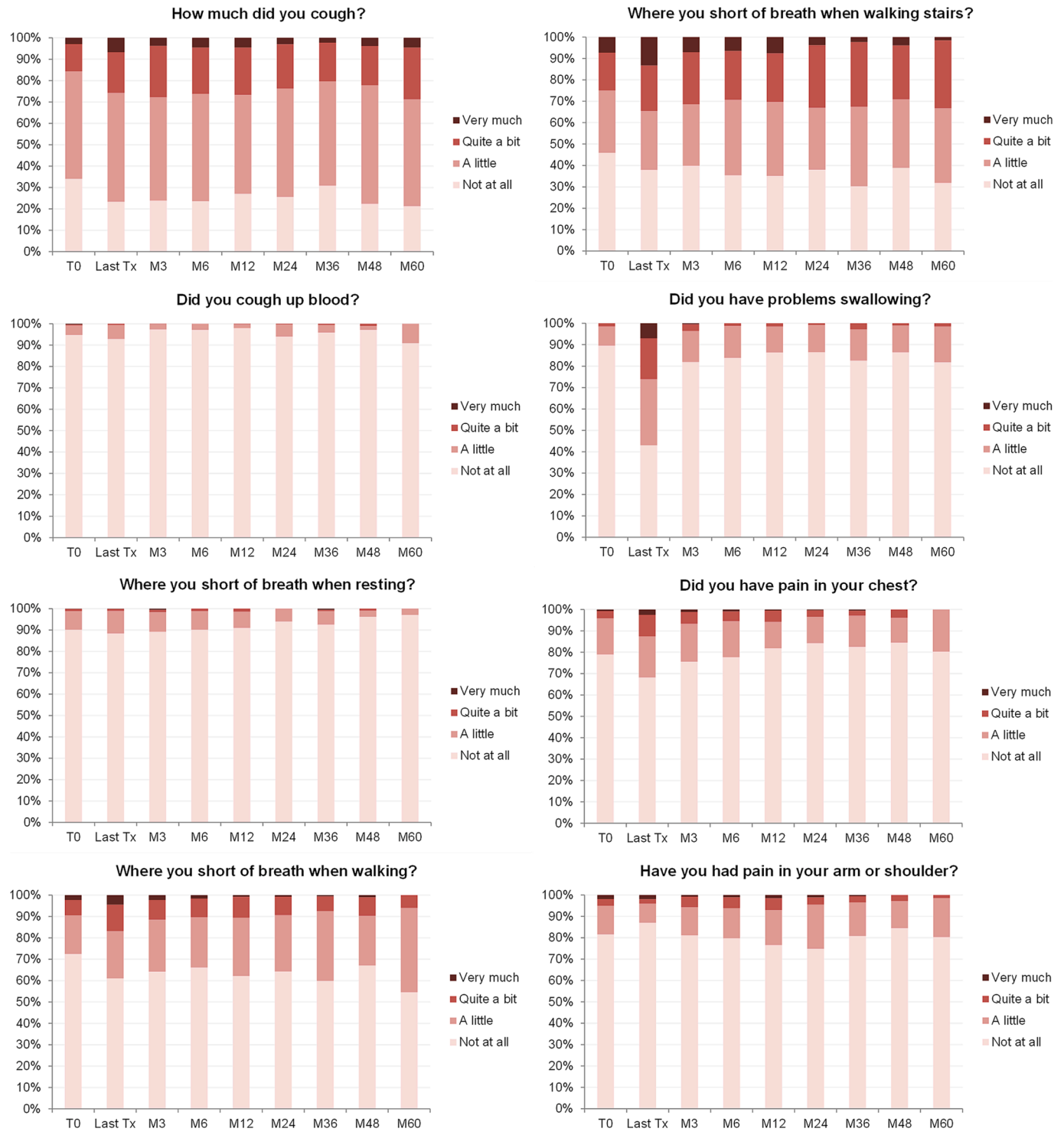


Fig. 2. Scores of patients shown per question and per evaluation. Abbreviations: T0 = baseline; Last Tx = last treatment; FUM = follow-up month.

relatively fast recovery of complaints after fractionated radiotherapy. However, ideally, even a temporary increase in complaints due to (chemo)radiotherapy should be prevented to maintain or obtain optimal performance scores and QoL. To achieve this, next to changes in systemic treatments, radiotherapy techniques also have evolved considerably in the past years. In a large trial primarily designed to evaluate the effect of different radiotherapy doses on QoL, a secondary analysis showed that patients treated with IMRT reported better QoL compared to patients treated with 3DCRT [30]. This superior QoL may be attributed to the improvement in precision of radiotherapy, as more precise dose delivery leads to less toxicity [31,32]. Although we did not find differences in QoL between photon radiotherapy techniques or MLD and MHD, future analyses may manifest differences if we compare outcomes of photon therapy with proton therapy. In agreement with this, proton therapy is known to be associated with less toxicity and better QoL [16,33,34].

The strength of the current study is that we were able to include many patients in this prospective study with exceptionally high compliance rates. More than 90 % of the surviving patients were evaluated at 4 years of follow-up, as well as 87 % at 5 years of follow-up. This

indicates that the data reported here represent a high-quality benchmark for real-life QoL assessment in patients with inoperable lung cancer undergoing (chemo)radiotherapy.

A limitation of the study is the fact that in this cohort, the proPED did not include the complete EORTC QLQ-LC13 module. To assess QoL more comprehensively, the proPED has been amended in a later stage, currently including the complete EORTC 30-item core instrument (QLQ-C30) and LC13-supplement, ultimately improving our future evaluations. Unfortunately, we were not able to report on the effect of chemotherapy on QoL, as standard regimen treatments changed over the study period, the chemotherapy regimen was often individualized to the patient, and we did not inquire data on dose reductions. This resulted in numerous treatment groups with small numbers of patients, making it invalid to derive statements. Due to the absence of quality data on esophageal dose, we were could not evaluate the possible effect of esophageal dose on QoL.

In conclusion, our prospective longitudinal evaluation of QoL based on assessment of treatment-related complaints in patients with inoperable lung cancer showed that, up to five years of follow-up, patients generally report little complaints and favorable QoL after a temporary increase in complaints upon finishing (chemo)radiotherapy. Most frequently reported transient complaints were swallowing problems and chest pain. Complaints that were most persistent during follow-up were shortness of breath and coughing. In particular, we found that patients with a pulmonary comorbidity or poor WHO performance scores at baseline experienced more complaints.

While the QoL observed in current patients suggests that the selection criteria for (chemo)radiotherapy are generally adequate, the higher incidence of complaints among patients with pulmonary comorbidities or poor WHO performance status highlights the ongoing need for careful patient selection.

Credit authorship contribution statement

Marloes Nies: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. **Robin Wijsman:** Investigation, Resources, Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Olga Chouvalova:** Investigation, Resources, Writing – review & editing, Project administration. **Fred J.F. Ubbels:** Investigation, Resources, Writing – review & editing. **Harriët J. Elzinga:** Investigation, Resources, Writing – review & editing, Project administration. **Ellen Haan-Stijntjes:** Investigation, Resources, Writing – review & editing, Project administration. **Marleen Woltman-van Iersel:** Investigation, Resources, Writing – review & editing. **Pieter R.A.J. Deseyne:** Investigation, Resources, Writing – review & editing. **Stefanie A. de Boer:** Investigation, Resources, Writing – review & editing. **Johannes A. Langendijk:** Conceptualization, Investigation, Resources, Writing – review & editing, Funding acquisition, Methodology, Supervision, Writing – original draft. **Joachim Widder:** Conceptualization, Investigation, Resources, Writing – review & editing, Funding acquisition, Methodology, Supervision, Writing – original draft. **Anne G.H. Niezink:** Conceptualization, Investigation, Resources, Writing – review & editing, Data curation, Funding acquisition, Methodology, Supervision, Visualization, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2025.100935.

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