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Patient-reported health-related quality of life from a randomized phase II trial comparing standard-dose with high-dose twice daily thoracic radiotherapy in limited stage small-cell lung cancer

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ABSTRACT

Objectives: In a randomized phase II trial, twice daily (BID) thoracic radiotherapy (TRT) of 60 Gy/40 fractions improved survival compared with 45 Gy/30 fractions in limited stage small-cell lung cancer (LS SCLC). Notably, the higher dose did not cause more toxicity. Here we present health related quality of life (HRQoL) reported by the trial participants during the first 2 years.

Materials and methods: 170 patients were randomized 1:1 to TRT of 45 Gy or 60 Gy concurrently with cisplatin/etoposide chemotherapy. The 150 patients who commenced TRT and completed a minimum of one HRQoL-questionnaire were included in the present study. Patients reported HRQoL on the European Organization for Research and Treatment of Cancer Core 30 and Lung Cancer 13 Quality of Life Questionnaires. Questionnaires were completed weeks 0, 4 (before TRT), 8 (end of TRT), 12 (response evaluation after chemoradiotherapy) and 16 (end of prophylactic cranial irradiation), then every 10 weeks year one, and every 3 months year two. Primary HRQoL endpoints were dysphagia and dyspnea. A difference in mean score of $\geq$10 was defined as clinically significant.

Results: Maximum dysphagia was reported on week 8, with no significant difference between treatment arms (mean scores 45 Gy: 44.2, 60 Gy: 51.1). The 60 Gy arm had more dysphagia in the convalescence period, but dysphagia scores returned to baseline levels at week 16 in both arms. For dyspnea there were no significant changes, or differences between treatment arms, at any timepoint. There were no significant differences between treatment arms for any other HRQoL-scales.

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Conclusion: TRT of 60 Gy did not cause significantly higher maximum dysphagia, though patients on the 60 Gy arm reported more dysphagia the first 8 weeks of convalescence. The higher dose was well tolerated and is an attractive alternative to current TRT schedules in LS SCLC.
Trial reg Clinicaltrials.gov NCT0204184.

1. Introduction

Small cell lung cancer (SCLC), accounting for 13% of lung cancer cases, is a malignancy with an aggressive clinical course [1]. At the time of diagnosis, approximately one-third of the patients have limited-stage (LS SCLC). Standard treatment for these patients is concurrent chemotherapy and thoracic radiotherapy [2,3]. Up to 36% are alive after 5 years, but since the majority of the patients experience relapse and die from SCLC, there is a need for better treatment [4–6].

Approximately 1/3 of patients experience local failure, and it has been hypothesized that higher doses of thoracic radiotherapy (TRT) might improve local control and, thereby survival [5]. We conducted a phase II trial comparing high-dose, twice-daily (BID) TRT of 60 Gy in 40 fractions with the standard dose of 45 Gy BID in 30 fractions, and our primary analyses show that the high-dose arm achieved a significantly improved 2-year survival (primary endpoint, 74% vs. 48%; $p = .0005$) and median overall survival (37.2 vs. 22.6 months; $p = .012$) [7]. This is the first randomized trial of LS SCLC to show a significant survival improvement in more than 20 years. Objectively assessed toxicity did not reveal any significant differences between the treatment arms, and the proportion of patients who experienced severe radiotoxicity was lower than in older trials and similar to other, recent trials of TRT in LS SCLC [5,6,8–10].

Several studies conclude that physicians often underestimate treatment related side-effects, and that patient reported outcomes provide important additional information about the impact of cancer therapies [11,12]. It is well known that a large proportion of LS SCLC patients experience severe treatment toxicity, and radiotherapy induced esophagitis appears to be an important reason for the poor implementation of twice-daily TRT in LS SCLC [5,6,13,14]. However, to our knowledge, a previous study by our group is the only other randomized study of TRT in LS SCLC including patient reported HRQoL [8]. Our trial participants reported health related quality of life (HRQoL) on validated questionnaires. The aim was to assess patient reported HRQoL before, during, and after study treatment and compare HRQoL between patients receiving standard dose (45 Gy) and those receiving the high dose (60 Gy) BID TRT.

2. Methods

2.1. Design and approval

This open labeled randomized phase II trial was approved by the Regional Ethics Board in Gothenburg, Sweden, the Regional Committee for Medical Research Ethics, Central Norway, and the National Committee on Health Research Ethics in Denmark.

2.2. Patients and treatment

Details on the trial design are published earlier [7]. Briefly, patients ≥ 18 years, performance status (PS) 0–2, and confirmed LS SCLC were to receive 4 courses of platinum/etoposide and were randomized in blocks stratifying for PS, stage, and presence of pleural effusion to TRT of 45 Gy in 30 fractions or 60 Gy in 40 fractions. Whole body FDG PET CT scan was mandatory for staging and TRT target volumes were limited to PET positive lesions. TRT started 20–28 days after the first day of the first course of chemotherapy. Responders were offered prophylactic cranial irradiation of 25–30 Gy in 10–15 fractions. Patients were then followed every 10 weeks year 1, every 3 months years 2–3, and every 6 months years 4–5. Relapses were treated according to each hospital's routine. The first publication reported treatment outcomes when the primary endpoint, 2-year survival, was assessed in July 2020, which was also when data collection for the present study was completed. Final survival data will be published when all patients have been followed for five years (June 2023).

2.3. Patient reported outcomes

Patients reported HRQoL on the European organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality-of-Life Questionnaire-Lung Cancer 13 (QLQ-LC13). The questionnaires are translated and validated into more than 100 languages, including Norwegian, Danish, and Swedish, and are among the most commonly used for assessing HRQoL in lung cancer research [15–17].

The QLQ-C30 consist of five multiple-items functional scales (social, emotional, cognitive, role, and physical), three multiple-item symptom scales (fatigue, pain, and nausea/vomiting), six single-item symptom scales (insomnia, constipation, diarrhea, loss of appetite, dyspnea, and financial impact), and global quality of life (one multiple-item scale). The HRQoL questionnaire LC-13 measures dyspnea on a multiple-item scale. The single items measure hair loss, hemoptysis, cough, soremouth, neuropathy, dysphagia, pain medicine use, pain in chest, arms, shoulder, or other parts. A higher score on global QoL and functional scales reflects a better HRQoL, a higher score on the symptom scales represents a worse HRQoL.

Patients completed the questionnaires on paper at weeks 0 (inclusion), 4 (before TRT), 8 (end of TRT), 12 (response evaluation), 16 (end of PCI), every 10 weeks year one and every 3 months year two, as well as after progression. Questionnaires were handed to the patients by study personnel at all timepoints in Sweden and Denmark. In Norway, the questionnaires were handed to patients by study personnel at baseline, before and after TRT. At all other timepoints, questionnaires were mailed to the patients from the study office. The patients returned the completed questionnaires in an enclosed, prepaid envelope. A reminder was mailed to patients if completed questionnaires were not received at the study office within two weeks.

2.4. Endpoints

The primary HRQoL-endpoints were defined as dysphagia and dyspnea reported on the LC- 13. All other HRQoL items were defined as secondary endpoints. The period of interest was defined as the time from randomization until the primary endpoint of 2-year survival.

2.5. Analyses

The study was powered for the primary endpoint of 2-year survival [7], and no estimation of power for the HRQoL analyses was performed. Raw scores were transformed to a scale from 0 to 100 according to the EORTC scoring manual [18], and compared between each timepoint and between treatment arms. We did not perform imputations of missing data.

According to Osoba et al and Kings et al, a change in mean score of 5–10 indicate a little change, while a change in mean score of 10–20 indicate a moderate change [19,20]. Based on these studies, a difference in mean score of 10 is commonly defined as the minimum required to detect a clinically significant difference in randomized clinical trials on

HRQoL [21]. Consequently, we defined a difference in mean scores of ≥ 10 as the clinical significance level in the present study. As discussed in the paper by Maringwa et al, in this setting, p-values does not provide information about clinical important differences in mean scores between groups or changes over time [21], and thus, we omitted statistical testing.

Finally, we performed exploratory analyses of the difference in numbers of patients with any (score > 0) or maximal level (score of 100) of dysphagia between treatment arms and change in dysphagia from baseline in individual patients.

3. Results

3.1. Participants

From July 8th 2014 to June 6th 2018, 176 patients were included, of these 170 eligible patients were randomised and included in the efficacy analyses (60 Gy: 89, 45 Gy: 81), 166 received TRT and were included in the safety population (60 Gy: 89, 45 Gy: 77). Of these, 150 patients (60 Gy: 80, 45 Gy: 70) completed at least one HRQoL questionnaire and were included in the present HRQoL-analyses (Fig. 1).

3.2. Baseline characteristics

Median age was 65 years, 43 (28%) were ≥70 years, 86 (57%) women, 146 (97%) current/former smokers, 133 (88%) had PS 0–1, 134 (89%) stage III disease (TNM v.7), 13 (8%) pleural effusion, and 31 (20%) a weight loss of >5% three months before enrolment. Baseline characteristics were well balanced between treatment arms (Table 1).

Table 1
Baseline characteristics.

		45 Gy (n=70)		60 Gy (n=80)	
		n	%	n	%
Age	Median (range)	65 (36-80)		65 (46-79)	
	≥70 years	23	32.9%	20	25.0%
Gender	Female	43	61.4%	43	53.8%
Performance status	0	29	41.4%	38	47.5%
	1	33	47.1%	35	43.8%
	2	8	11.5%	7	8.7%
Stage	IA	2	2.9%	-	-
	IIA	5	7.1%	9	10.1%
	IIB	4	5.7%	5	5.6%
	IIIA	24	34.3%	38	42.7%
	IIIB	35	50.0%	37	41.6%
Pleural fluid	Yes	5	7.1%	8	10.0%
Smoking history	Current	53	75.7%	49	61.3%
	Former	15	21.4%	29	36.3%
	Never	2	2.9%	1	1.3%
	Missing	-	-	1	1.1%
Pack years	Median (range)	30 (4-80)		35 (5-114)	
Weight loss last 3 months before inclusion	>5%	16	22.9%	15	18.8%
	Missing	7	10.0%	12	15%

3.3. Completion of HRQoL questionnaires

The completion rate of the questionnaires were 64–77% of patients in the intention-to-treat population (n = 170) being alive at each timepoint and similar in both arms (Fig. 2). At baseline, 123/170 (72%) patients completed the questionnaires. The lowest completion rate was at end of radiotherapy (week 8: 98/165 alive [59%]), the highest at week 12 (127/164 alive [77%]) and was 64–73% for the remaining study period. Among patients with recurrent disease the completion rate varied between 25 and 71%. During the second year of the study period 32–38% of the questionnaires were completed by patients with recurrent disease (Fig. 2).

3.4. Dysphagia and dyspnea

Overall, the baseline mean score of dysphagia was 10, the maximum mean score was 47 reported at week 8. Compared to baseline mean scores (45 Gy: 5.9, 60 Gy: 13.6), patients in both treatment arms reported a clinically significant higher mean score at week 8 and 12. The maximum mean scores were reported at week 8 (end of TRT) in both arms (45 Gy: 44.2, 60 Gy: 51.1). Patients in the 60 Gy arm reported significantly more dysphagia at week 12 and 16 than patients in the 45 Gy arm, though at week 16, the differences in mean scores from baseline values were less than 10 points in both arms (45 Gy: 7.1, 60 Gy: 17.5) (Fig. 3).

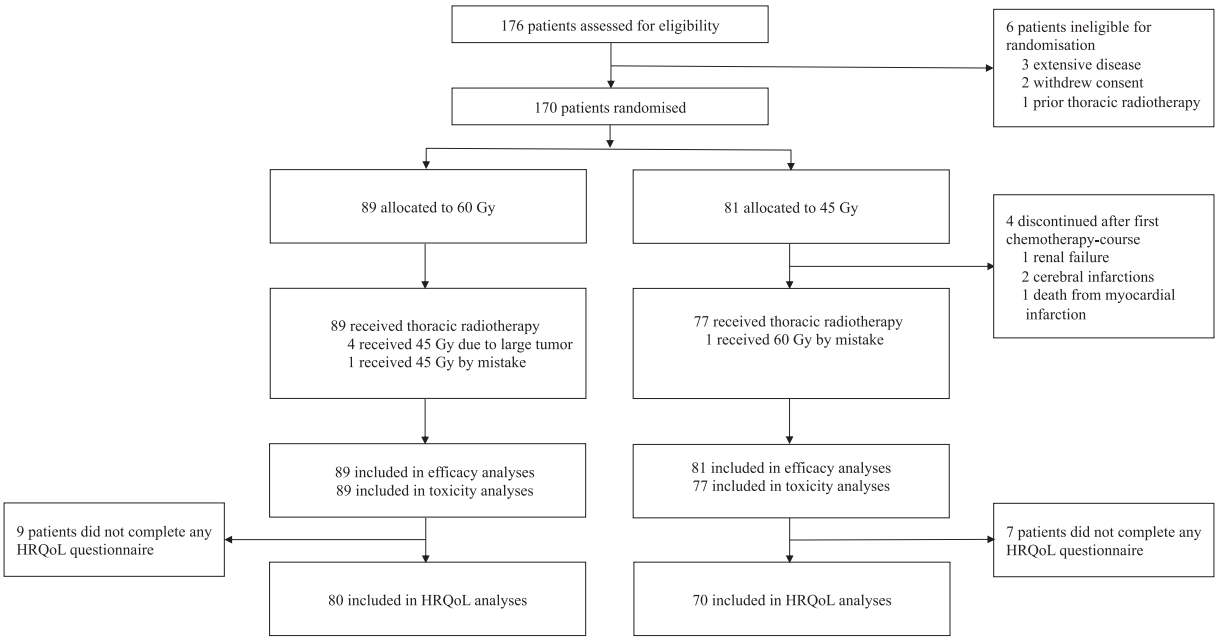

Fig. 1. Consort diagram.

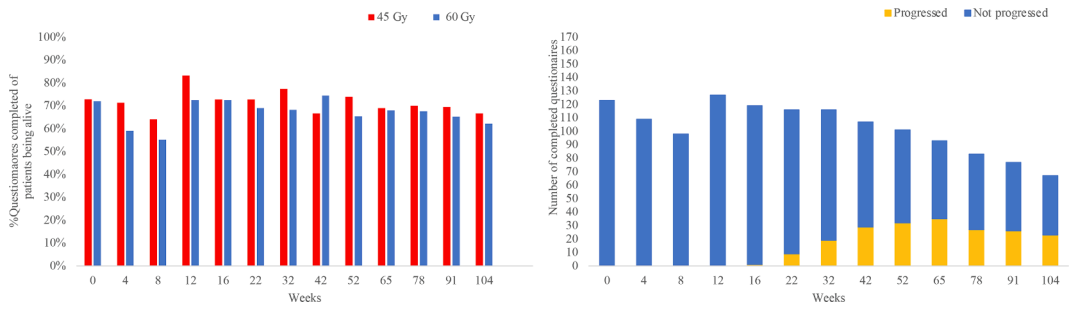

Fig. 2. A) Completion rate of HRQoL questionnaires of patients (intention-to-treat population) being alive at each timepoint split for treatment arm and B) Number of HRQoL questionnaires completed at each timepoint including disease status.

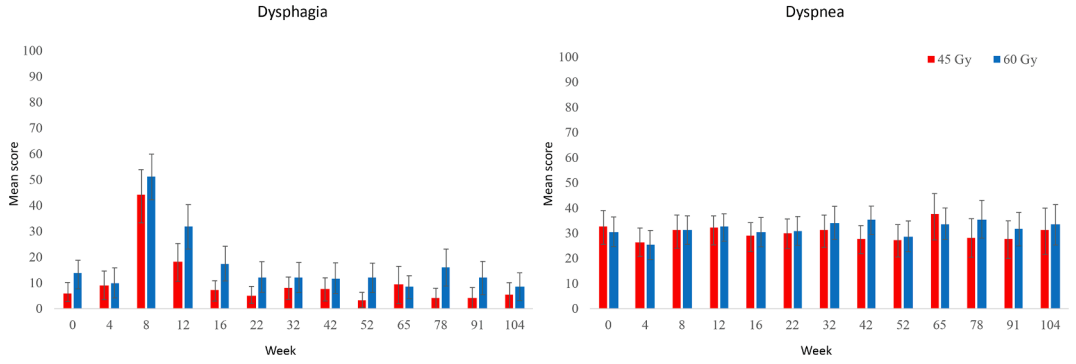

Fig. 3. Mean scores for A) dysphagia and B) dyspnea as reported on the LC-13 questionnaire split for treatment arms. The error bars show the 95% confidence intervals for the mean scores. A higher score represents more symptoms.

The proportions of patients reporting any dysphagia (score > 0) at week 8 or 12 were 44 of 71 (62%) and 52 of 67 (77%) for patients receiving 45 Gy and 60 Gy respectively. The proportions reporting maximum (score of 100) dysphagia week 8 or 12 were 12 of 71 (17%) and 10 of 67 (15%) for patients receiving 45 Gy and 60 Gy, respectively.

Mean score for dyspnea did not change significantly during the study period, and there were no differences between the study arms (Fig. 3).

3.5. Remaining HRQoL scales

For all other HRQoL scales there were no clinically significant differences between treatment arms. There were, however, some clinically significant changes during the study periods for some scales. Patients developed alopecia during the chemotherapy. Overall, there was a decline in cognitive functioning and an increase in neuropathy that exceeded 10 points during the study period. Patients reported more chest-pain at the end of TRT (week 8). After TRT ended (week 8 and 12) there was a transient lower score for role- and social functioning as well as a higher score of fatigue. Emotional functioning increased from baseline and remained stable throughout the study period (Fig. 4).

4. Discussion

In this first trial comparing high-dose with standard-dose twice-daily thoracic radiotherapy in LS SCLC, patients reported an increase in mean scores of dysphagia from 10 points at baseline to 47 points at the end of TRT. Interestingly, there was no significant difference in maximum mean scores between the treatment arms, and no difference in the proportion of patients who reported maximal score of 100 for dysphagia at the end of TRT. Patients receiving the high-dose reported more dysphagia at week 12 and 16 compared to patients receiving the standard-dose, though at week 16, the differences in mean scores from baseline levels were less than 10 points in both treatment arms. There were no significant differences in any of the other HRQoL-scales between the treatment arms.

We are only aware of one other randomized controlled trial of TRT in LS SCLC that included patient reported HRQoL. In this previous randomized phase II trial by our group, we compared hypo-fractionated once-daily TRT of 42 Gy in 15 fractions with 45 Gy twice daily in 30 fractions [8]. The design was similar to the present study, and patients reported HRQoL on the same questionnaires and at similar timepoints. Patients reported significantly higher mean scores for dysphagia after TRT (42 OD: 61, 45 BID: 72) than in the present study (45 Gy: 44.2, 60 Gy: 51.1) [7,8]. In both studies, patients recovered from dysphagia during the 8 weeks after completing TRT. This difference in maximum mean scores for dysphagia between our former and the present trial, corresponds well to the difference in physician reported severe esophagitis, which was observed in 30% of participants in the former trial vs. 20% in the present trial [7,8]. The lower frequency of dysphagia is probably explained by the fact that the former study included elective nodal irradiation, while we limited radiotherapy fields to FDG PET CT positive lesions in the recent trial [6,22–24].

Few studies of LS SCLC have included patient reported HRQoL. In a systematic review of RCT on lung cancer from 2012 to 2018, only 10 out of 122 studies included patients with SCLC [25]. Of these, only two reported HRQoL-data, but the study participants had extensive stage SCLC [26,27]. There were no comparable studies included in a systematic review of HRQoL-data in SCLC [28]. We are aware of three other randomized trials of high-dose TRT in LS SCLC and hitherto, none have reported patient reported outcomes [6,9,10].

The varying completion rate of the questionnaires at different timepoints is a potential limitation of our study. However, the overall completion rate was similar to other studies on HRQoL in lung cancer [29,30]. The lowest completion rate was at the end of TRT at week 8. The most likely explanation is that study personnel forgot to hand out the questionnaire at this timepoint, but we cannot rule out that the lower completion rate was related to treatment toxicity [31]. Furthermore, patients completed HRQoL questionnaires also after progression, and

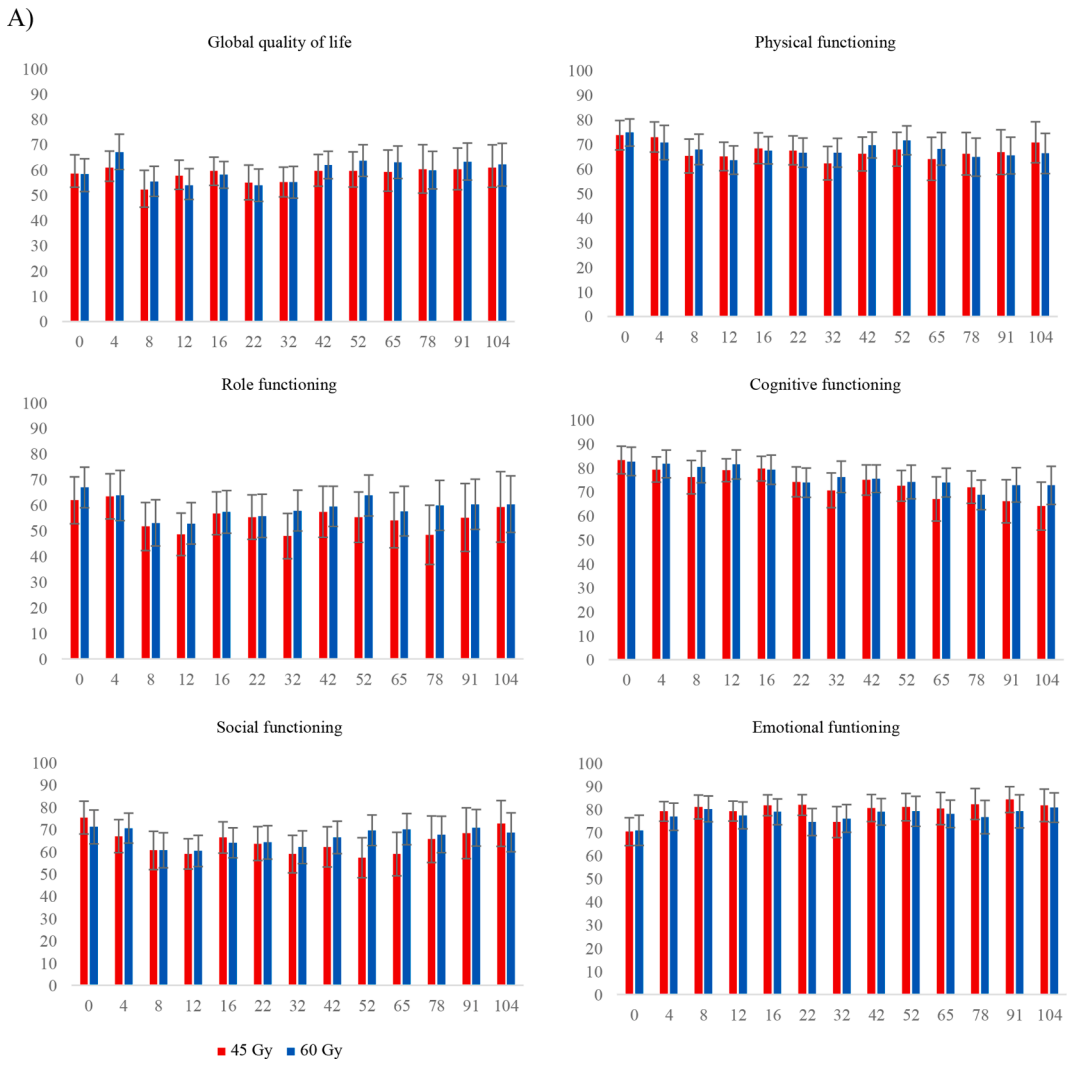

Fig. 4. Mean scores for the remaining scales on the EORTC C30 and LC-13 quality of life questionnaires split for treatment arms. The error bars represent 95% confidence intervals. A) Global quality of life and functional scales on the C30; B) Symptom scales on the C30; C) LC-13 scales. A higher score on the symptom scales reflects more symptoms, while a higher score on the functional scales indicates a better function. The last plot shows proportions of patients using pain medication.

quality of life scores might be influenced by progressive disease and relapse treatment. However, as few patients progressed the first months, results mainly reflects discomfort from chemoradiotherapy.

Differences in radiotherapy technique, anatomical distribution and extent of disease might have influenced our results. However, there was no difference in TNM (version 7) stage between the treatment arms. All radiotherapy plans are currently being reviewed and we will publish comprehensive data on distribution and localization of lesions and normal tissue irradiation separately.

Despite evidence of improved survival, twice daily thoracic radiotherapy has not been widely implemented in clinical practice, mainly due to fear of severe esophagitis [14,32]. Our study shows that there are no longer reasons for such concerns since dysphagia caused by twice daily TRT is transient. This was also observed in our previous study, in which patients reported significantly more esophageal toxicity than in the present study [8]. Thus, the clinical impact of dysphagia is limited, and should not prevent patients from receiving BID TRT.

It has been stated that BID TRT is inconvenient for the patients and that it might impact their quality of life [33]. Our study was not designed to clarify whether twice daily TRT impacts quality of life more than once daily TRT, but the transient and modest change in role- and social functioning and fatigue indicates that the impact on quality of life of twice daily TRT was minimal. The increase in reported chest pain after radiotherapy is most likely due to esophagitis. Alopecia and neuropathy are well known side-effects of platinum/etoposide chemotherapy [34,35]. Emotional functioning improved from baseline, possibly because of the strong association between emotional burden and symptom burden. It is well known that many SCLC patients respond rapidly to chemotherapy and such response might relieve both symptoms and emotional burden [36,37].

There was also a steady, but modest decline in cognitive functioning. There are concerns that PCI cause cognitive deficits [38,39], but on the other hand, it has repeatedly been shown that PCI improves survival [40,41]. It is not possible to accurately assess the causes of the cognitive decline. We did not perform more comprehensive, objective tests of cognitive function, and our study was not designed to thoroughly assess associations between comorbidity, treatment toxicity, disease development, brain metastases and cognitive function. Studies show that chemotherapy might also affect cognitive functioning [42]. Furthermore, most patients have a history of tobacco smoking, and many suffer from cardiovascular comorbid conditions that might negatively affects cognitive functioning [43].

The present study adds further evidence on how BID TRT is perceived by patients. The maximum dysphagia is much lower compared to our

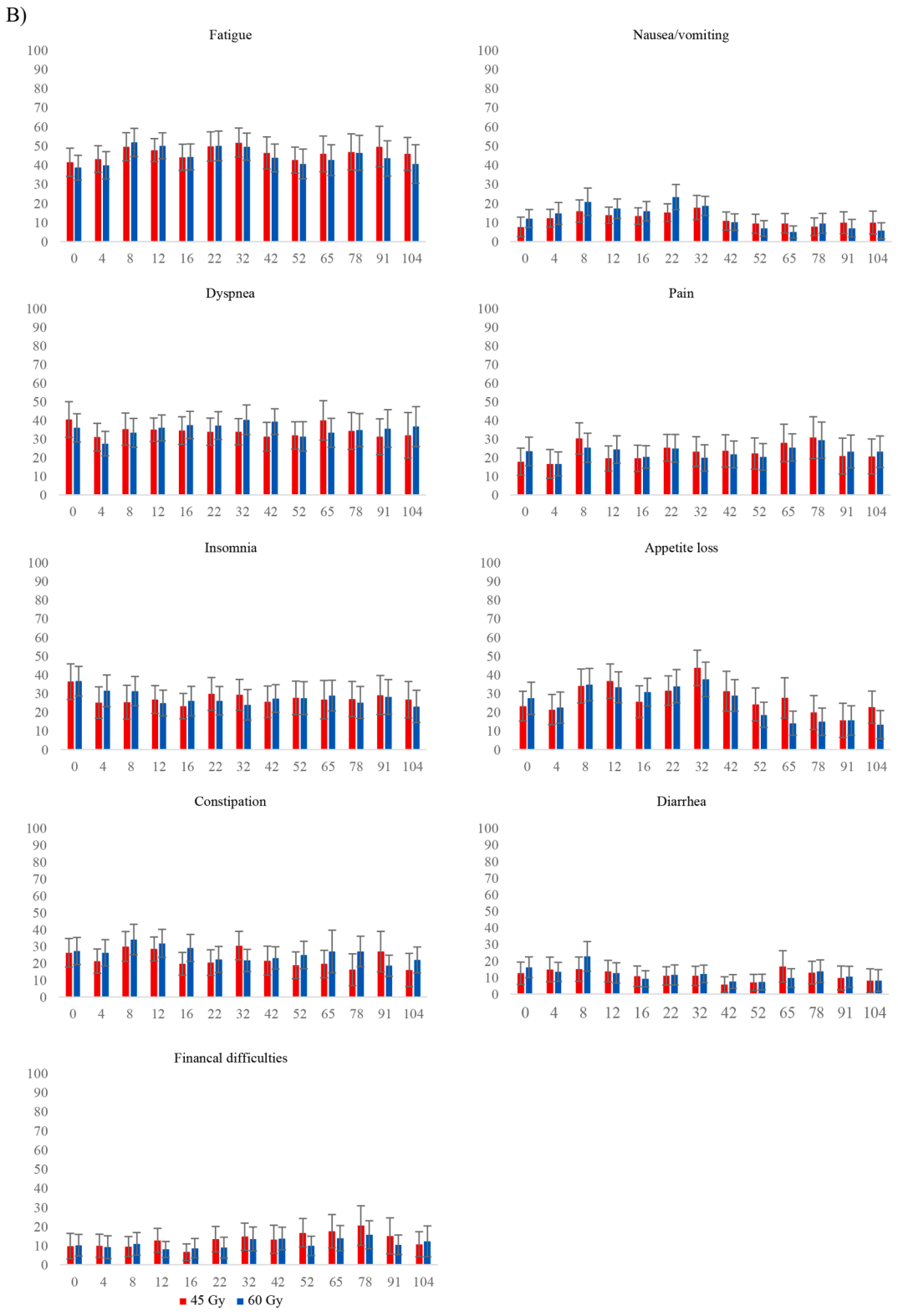

Fig. 4. (*continued*).

previous study, even though half of the patients received a higher TRT dose, since we limited the radiotherapy fields to PET CT positive lesions, while all patients in our former trial received elective nodal irradiation [8]. In our opinion, the transient impact of the higher dose with respect to dysphagia, is acceptable considering the large survival benefit of the higher dose. The normal tissue constraints in our trial were based on accepted norms for conventional, once-daily, TRT schedules [44], and our study results indicate that these constraints are relevant and acceptable also for BID TRT.

5. Conclusion

In conclusion, there was no difference in maximum mean dysphagia between the treatment arms, but patients in the 60 Gy arm reported a

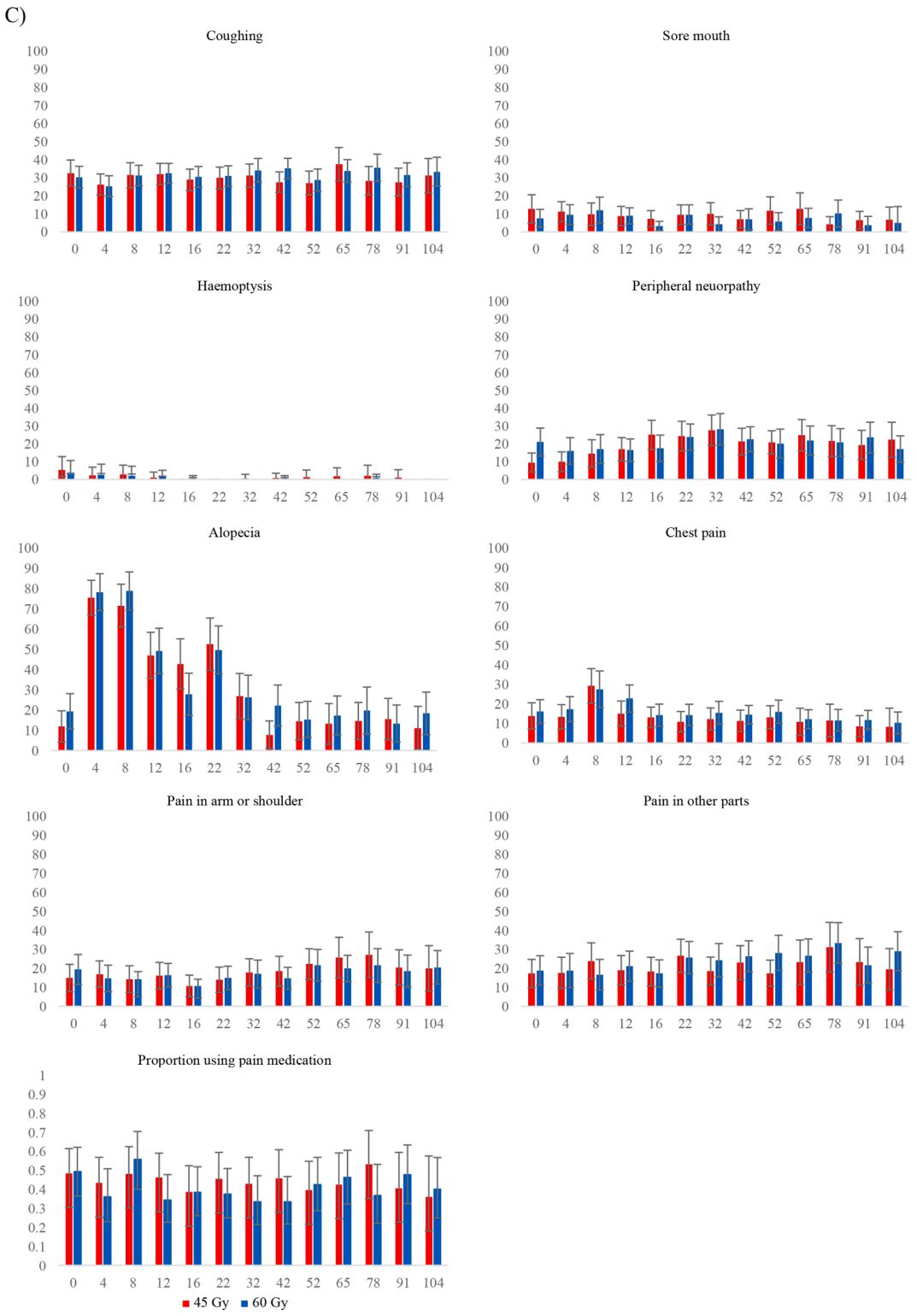

Fig. 4. (*continued*).

higher level of dysphagia compared to patients in the 45 Gy arm during the convalescence period. There were no significant differences between treatment arms in other HRQoL-scales, and overall, patients reported small changes in HRQoL during the first two years. These patient-reported data support the conclusion from our main report, that 60 Gy BID is well tolerated, and given the large survival benefit, an alternative to current TRT schedules in LS SCLC.

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CRediT authorship contribution statement

Kristin Toftaker Killingberg: Project administration, Data curation, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Tarje Onsøien Halvorsen:** Project administration, Methodology, Formal analysis, Writing – review & editing, Supervision, Validation. **Øystein Fløtten:** Data curation, Writing – review & editing. **Odd Terje Brustugun:** Conceptualization, Data curation, Writing – review & editing. **Seppo W. Langer:** Conceptualization, Data curation, Writing – review & editing. **Jan Nyman:** Conceptualization, Project administration, Data curation, Writing – review & editing. **Kjersti Hornslien:** Data curation, Writing – review & editing. **Tesfaye Madebo:** Data curation, Writing – review & editing. **Tine Schytte:** Project administration, Data curation, Writing – review & editing. **Signe Risum:** Data curation, Writing – review & editing. **Georgios Tsakonas:** Data curation, Writing – review & editing. **Jens Engleson:** Data curation, Writing – review & editing. **Bjørn Henning Grønberg:** Conceptualization, Funding acquisition, Project administration, Methodology, Data curation, Writing – review & editing, Supervision.

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.

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