Randomized Phase II Trial Comparing Twice-daily Hyperfractionated With Once Daily Hypofractionated Thoracic Radiotherapy in Limited Disease Small-Cell Lung Cancer

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Running title
Phase II trial comparing once and twice daily TRT in LD SCLC

Abstract

Background

Concurrent chemotherapy and thoracic radiotherapy (TRT) is recommended for limited disease small-cell lung cancer (LD SCLC). Twice daily TRT is well documented, but not universally implemented – probably mainly due to inconvenience and concerns about toxicity. A schedule of 3-week hypofractionated TRT is a commonly used alternative. This is the first randomized trial comparing twice-daily and hypofractionated TRT in LD SCLC.

Materials and Methods

Patients received four courses of cisplatin/etoposide (PE) and were randomized to TRT of 42 Gy in 15 fractions (once daily - OD) or 45 Gy in 30 fractions (twice-daily - BID) between the second and third PE-course. Good responders received prophylactic cranial irradiation of 30 Gy in 15 fractions.

Results

157 patients were enrolled between May 2005 and January 2011 (OD: n=84, BID: n=73). Median age was 63 years, 52% were men, 84% had performance status 0-1, 72% had stage III disease and 11% non-malignant pleural effusion. The treatment arms were well balanced. The response rates were similar (OD: 92%, BID: 88%; p=.41), but more BID-patients achieved a complete response (OD: 13%, BID: 33%; p=.003). There was no difference in 1-year PFS (OD: 45%, BID: 49%; p=.61) or median PFS (OD: 10.2 months, BID: 11.4 months; p=.93). The median overall survival in the BID arm was 6.3 months longer (OD: 18.8 months, BID: 25.1 months; p=.61). There were no differences

in grade 3-4 esophagitis (OD: 31%, BID: 33%, p=.80) or pneumonitis (OD: 2%, BID: 3%, p=1.0). Patients on the BID arm reported slightly more dysphagia at the end of the TRT.

Conclusion

There was no difference in severe toxicity between the two TRT-schedules. The twice-daily schedule resulted in significantly more complete responses and a numerically longer median overall survival, but no firm conclusions about efficacy could be drawn from this phase II trial.

Introduction

Small-cell lung cancer (SCLC) accounts for up to 16% of lung cancer cases [1]. The main treatment is chemotherapy, and cisplatin plus etoposide is the standard regimen [2, 3]. Concurrent thoracic radiotherapy (TRT) improves overall survival (OS) if all lesions can be included in one radiotherapy field ("limited disease" - LD SCLC) [4]. Prophylactic cranial irradiation (PCI) reduces the risk of brain metastases and prolongs survival in those who respond to chemo-radiotherapy [5]. Up to 90% of patients respond to the treatment, but most relapse and die from this disease [2, 6].

Several schedules of TRT are being used in LD SCLC, but few comparative trials have been conducted. The most known study, by Turrisi et al., compared twice-daily TRT (45 Gy/30 fractions, 3 weeks) with once-daily TRT (45 Gy/25 fractions, 5 weeks). Response rates were equal (87%), but twice-daily TRT significantly prolonged median OS (23.0 months vs. 19.0 months; p=0.04) [6]. Thus, twice-daily TRT is the most recommended schedule, but not universally adopted [7-11]. Inconvenience of this schedule and concerns about esophagitis are probably the main explanations [10]. Furthermore, the different duration of the schedules (3 vs. 5 weeks) and dissimilar biologically effective doses might have contributed to the OS-difference [6]; a systematic overview concluded that shortening the treatment time from start of chemotherapy until completion of TRT was associated with a prolonged OS [12].

A three-week schedule of once-daily hypofractionated TRT (40 Gy in 15 fractions) was one of the schedules included in the meta-analysis establishing TRT in LD SCLC [4]. Similar schedules have been used in Norway and other countries [2, 9, 11, 13], but have never been compared with twice-daily TRT in a randomized trial. The aims of this study were to compare 45 Gy/30 fractions (twice daily - BID) with 42

Gy/15 fractions (once daily – OD) TRT in LD SCLC with respect to progression free survival (PFS), overall survival (OS), toxicity and health related quality of life (HRQoL). The hypothesis was that BID-regimen would be feasible and improve efficacy without severely increase toxicity.

Material and Methods

Design and approvals

This randomized phase II trial was approved by the Regional Committee for Medical Research Ethics, Central Norway; the Norwegian Social Science Data Services; and the Norwegian Directorate for Health and Social Affairs.

Eligibility criteria and random assignment

A CT of the chest/upper abdomen, brain MRI and bone scan were conducted within three weeks prior to inclusion. Eligible patients gave written informed consent; were ≥ 18 years old (no upper limit); had SCLC ineligible for surgery and confined to one hemithorax and the mediastinum, contralateral hilus and supraclavicular regions; measurable disease according to RECIST v1.0 [14]; no other active cancer; no prior chest-radiotherapy; WHO performance status (PS) 0-2; leukocytes $\geq 3.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, bilirubin <1.5 x ULN and creatinine <125 μmol/l. One negative cytology was required if pleural effusion was present.

Patients were randomized to receive TRT of 42 Gy/15 fractions (OD) or 45 Gy/30 fractions (BID) in blocks of eight and stratified for the five Norwegian health care regions.

Chemotherapy

Patients were to receive four courses of cisplatin 75 mg/m^2 IV day 1 and etoposide 100 mg/m^2 IV days 1-3 every 3 weeks (PE). A full dose was administered if leukocytes were ≥3.0 x 10^9/l and platelets ≥100 x 10^9/l on day 22. Doses were reduced by 25% if leukocytes were 2.5-2.99 x 10^9/l or platelets 75-99 x 10^9/l on day 22. At lower leukocyte- or platelet counts, courses were postponed. Dose-reductions were maintained for subsequent cycles. Use of G-CSF was not recommended. Chemotherapy was discontinued if a course was delayed more than three weeks or a third dose-reduction was warranted. Carboplatin was allowed if cisplatin was not tolerated. The use of other agents was not addressed in the protocol.

Radiotherapy

All patients received 3D conformal TRT five days a week starting between three and four weeks after day 1 of the first PE-course. The targets of the TRT were all known pathological lesions plus elective nodal irradiation of lymph node stations 4-7 (bilateral). A planning CT scan was performed within one week prior to TRT. The gross tumor volume (GTV) included all pathological lesions on the baseline scan delineated according to the size on the planning CT scan. The clinical target volume (CTV) included GTV with a 1 cm margin in all directions (CTV_{tumor}) plus the central part of the mediastinum comprising lymph node stations 4-7 ($CTV_{mediastinum}$). An internal margin (IM) of 1.0 cm was added to the CTV_{tumor} in the transverse plane and 1.0-1.5 cm in the cranio-caudal direction. An IM of 0.5 cm was added to the $CTV_{mediastinum}$ in all directions. Finally, a setup margin was added according to each hospitals routine. Less than 50% of the normal lung tissue should receive more than 20 Gy ($V20_{lung}$ <50%).

Other normal tissue constraints were defined and treatment verification was done according to local routines.

A CT response evaluation was conducted three weeks after the last PE-course. Patients with a complete or near complete response were offered prophylactic cranial irradiation (PCI) of 30 Gy/15 fractions starting within six weeks after the CT evaluation.

Endpoints

Primary endpoint was 1-year PFS. Secondary endpoints were OS, toxicity and HRQoL (global quality of life, dysphagia and dyspnea).

Evaluation and follow up

All patients were clinically examined and assessed for toxicity before each PE-course and weekly during TRT. Response evaluation was performed three weeks after the last PE. Confirmation of response was not required. Post-therapy, patients were followed every eight weeks year 1, every four months year 2-3, and every six months year 4-5. A CT of the chest/upper abdomen was done at each evaluation year 1. Later, a chest x-ray or CT scan (optional) was performed. Progressive disease (PD) was to be confirmed with a CT scan.

Stage of disease was assessed according to TNM v6, response according to RECIST v1.0, and toxicity according to CTCAE v3.0 . PFS was defined as time from randomization until PD or death; OS as time from randomization until death.

Patients reported HRQoL using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the lung

cancer specific module LC13. Patients completed the questionnaires at inclusion and at weeks 3, 6, 12, 20, 28 and 52.

Statistical considerations

To detect a 30% improvement in 1 year PFS (from 70% to 91%) from BID TRT with a two-sided alpha of 0.05 and a beta of 0.20, 75 patients were required in each arm. We expected a loss to follow-up of <10% and aimed at enrolling 83 patients in each arm. Patients who received at least one PE-course and one fraction of TRT were included in the analyses.

HRQoL-scores were calculated according to the QLQ-C30 scoring-manual . The clinically relevant minimum difference in mean scores was defined as 10 (on a scale from 0 to 100) [15].

Survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Pearson's Chi-square and Fisher's exact tests were used for group comparisons. The Cox proportional hazard method was used for multivariate analyses. The level of significance was defined as $p<.05$.

Results

Patients

171 patients were enrolled between May 2005 and January 2011 at 18 hospitals in Norway. Fourteen patients were excluded: extensive disease (n=9), withdrawn consent (n=2), carcinoid tumour (n= 2), and prior chest radiotherapy (n=1). Thus, 157 were analysed (OD: 84 patients, BID: 73) (Figure 1). The imbalance in number of patients in each arm was partly due to the block randomization.

Median age was 63 years, 26% were ≥70 years, 52% were men, 84% had PS 0-1, 72% had stage III disease and 11% had cytologically negative pleural fluid. Baseline characteristics were balanced between the arms (Table 1).

Median follow-up for PFS was 59 months (range: 29-97); 34 patients were progression free when the analyses were performed (July, 2013). Median follow-up for OS was 81 months (range: 52-119); 34 patients were alive at the time of the analyses (April, 2015).

Study therapy

More OD-patients completed chemotherapy without delays (OD: 42%, BID: 26%; p=.04). There were no other differences in chemotherapy. Fourteen patients received other chemotherapy due to cisplatin toxicity (OD: n=10, BID: n=4) (Table 2).

The completion rate of TRT was similar (OD: 96%, BID: 97%). Mean doses were OD: 41.8 Gy (range: 34-45) and BID: 44.7 Gy (range: 30-46). 82% of OD patients and 84% of BID patients received PCI. PCI was omitted in 27 patients due to poor response (n=21), poor PS (n=3), patients' decision (n=3) and death (n=1) (Table 2).

Response to therapy, PFS and OS

There was no difference in response rates (OD: 92% [95% CI: 86-98], BID: 88% [95% CI: 80-95]; p=.41), but more patients on the BID arm achieved a complete response (OD: 13% [95% CI: 6-20], BID: 33% [95% CI: 22-44]; p=.003) (Table 3).

There were no differences in 1-year PFS (OD: 45% [95% CI: 34-56], BID: 49% [95% CI: 38-61]; p=.61) or median PFS (OD: 10.2 months [95% CI: 7.4-13.0], BID: 11.4 months [95% CI: 8.2-14.7]; p=.93) (Figure 2). There were no significant

differences in location of first relapse: distant failures (OD: 47%, BID: 38%; p=.33), local failures (OD: 34%, BID: 50%; p=.10) or synchronous distant and local failures (OD: 19%, BID: 13%; p=.38).

There were no statistically significant differences in 1-year OS (OD: 76% [95% CI: 67-85], BID: 77% [95% CI: 67-87]; p=.94), 2-year OS (OD: 42% [95% CI: 31-52], BID: 53% [95% CI: 42-65]; p=.14), 4-year OS (OD: 25% [95% CI: 16-34], BID: 25% [95% CI: 15-35]; p=.96) or median OS (OD: 18.8 months [95% CI: 13.6-23.9], BID: 25.1 months [95% CI: 16.9-33.3]; p=.61) (Figure 2). The difference in median disease-specific survival was of similar magnitude (OD: 20.9 months, BID: 29.5 months; p=.56).

Toxicity

There were no differences in grade 3-4 neutropenic infections (OD: 44%, BID: 37%; p=.37), grade 3-4 esophagitis (OD: 31%, BID: 33%; p=.80) or grade 3-4 pneumonitis (OD: 2%, BID: 3%; p=1.0) (Table 3). There was no difference in treatment-related deaths (OD: n=4, BID: n=3; p=1.0). Four patients died from radiation pneumonitis (OD: n=3, BID: n=1). Three patients died within 30 days of chemoradiotherapy: hemoptysis (n=1), coronary disease (n=1) and respiratory failure (n=1).

HRQoL

The completion rate of the questionnaires was 85-97% of patients alive at each time point and similar in both arms. Patients in the BID-arm experienced more dysphagia at the end of TRT (mean score OD: 61, BID: 72) (Figure 3). There were no other differences in global QoL, dysphagia, dyspnea or in any other HRQoL-domain.

Post-study treatment

Seventy-five patients received second line chemotherapy (OD: 51%, BID: 44%; p=.36) (Table 2). Re-induction with etoposide plus cisplatin or carboplatin was the most common regimen (37/75 patients; 49%).

PS and stage of disease

All patients were analyzed as one cohort in these explorative analyses. There was no PS-related influence on response rates (PS 0-1: 89%, PS 2: 92%; p=1.0) or median OS (PS 0-1: 23.0 months, PS 2: 18.8 months; p=.32). Patients with stage I-II disease had similar response rates as stage III patients (stage I-II: 86%, stage III: 90%; p=.51), but longer median OS (stage I-II: 33.3 months, stage III: 20.4 months; p=.024). Elderly patients had similar response rates (< 70 years: 91%, ≥ 70 years: 88%; p=.76) and there were no significant differences in median OS (< 70 years: 24.6 months, ≥ 70 years: 14.6 months; p=.28). Across genders, there were no differences in response rates (men: 89%, women: 91%; p=.69) or median OS (men: 21.7 months, women: 24.7 months; p=.53). There were no differences in grade 3-5 esophagitis or pneumonitis across PS, disease stage, age or gender.

The multivariate analysis revealed that stage I-II patients had significantly longer survival than those with stage III (p=.026). No other characteristics were significantly associated with PFS or OS.

Discussion

In this RCT comparing two 3-week schedules, the twice-daily TRT-schedule provided significantly more complete responses, but not higher response-rates. There were no

statistically significant differences in PFS or OS, though the median OS (25.1 vs. 18.8 months) and disease-specific survival (29.5 vs. 20.9 months) were more than 6 months longer on the BID-arm. The BID-patients reported slightly more dysphagia immediately after radiotherapy, but a difference in mean score of 10 to 20 is considered a "moderate change" [15]; they had slightly more dysphagia also before radiotherapy; and patients on both arms regained similar, pre-treatment levels of dysphagia soon after therapy. Thus, there were no differences in severe toxicity or treatment related deaths. We used a wide definition of limited disease, had no restrictions regarding comorbidity or age and 16% of the patients had PS 2. Approximately 17% of all patients diagnosed with LD SCLC in Norway during the enrolment period participated in the trial.

We are aware of two other prospective RCTs comparing one and two daily fractions of TRT in LD-SCLC. The split course used by Schild et al. [16] causes longer treatment duration and might enhance repopulation of cancer cells [12]. Thus, it is most relevant to compare our results with the study by Turrisi et al. In this study, TRT of 45 Gy in 30 fractions (BID) was compared with 45 Gy in 25 fractions (OD). All patients received cisplatin plus etoposide. Patients on the BID arm had significantly longer median OS (23.0 vs. 19.0 months; p=.04) [6]. The survival difference is of similar magnitude in our smaller study, though not statistically significant. Furthermore, the difference in median OS in our study did not result in a higher proportion of long-term survivors.

Results from other studies might indicate that twice-daily regimens are superior to hypo-fractionated 3-week schedules. In two studies, patients on the control arms receiving four courses of cisplatin plus etoposide and TRT of 45 Gy/30 fractions

achieved response rates of 95-97%, median PFS of approximately 13 months, and median OS of 25-38 months [17, 18]. In studies administering TRT with 40-42 Gy/15 fractions, response rates were 81-85%, median PFS 10.6 months and median OS 13.7-21.2 months [2, 11, 13]. However, these studies are not necessarily comparable due to differences in patient selection, staging procedures, chemotherapy, timing and schedules of TRT, response-evaluation and follow-up.

Turrisi et al. reported more esophagitis grade 3 (27% vs. 11%) but not more grade 4 (5% both arms) in the BID group. We found a similar proportion of grade 3-4 esophagitis in the BID arm (33%), but a higher proportion in our OD arm (31%) – probably due to the higher daily dose. The percentage of deaths from radiation pneumonitis (4%) in the OD-arm is higher than in other reports [6, 13], but the number was low (n=3).

PFS was chosen as the primary endpoint since it correlates well with OS in several studies of SCLC and is less influenced by relapse treatment and death of other causes [6, 19]. However, using PFS as the primary endpoint can be debated. Distinguishing between relapse and radiation fibrosis in lung tissue is challenging, there was a large number of radiologists involved in this study, and no central review of CT images. On the other hand, assessment of progression was done equally in both arms. The assumptions for our sample size calculation were incorrect. The delta value in the calculation was rather large, but we considered the sample size adequate to guide directions for future research. Other reasons for limiting the sample size were concerns about toxicity of the BID-schedule, as well as concerns about inferiority of the OD-schedule.

A limitation of the study is the lack of PET/CT for staging of disease. PET/CT identifies pathological lesions better than CT- and bone-scans [20], allowing for more accurate staging and definition of radiotherapy fields for TRT [21]. However, PET/CT was not generally available in Norway at the time when this study was conducted. The use of elective nodal irradiation could have been avoided if PET/CT was used for staging.

Further, there may have been some technical development in radiotherapy during the six year inclusion period. The annual number of patients per hospital was low, and we had no central quality assurance of radiotherapy. We have no information on patients not included into the trial. It is difficult to draw any firm conclusions about efficacy from this phase II trial. The higher rate of complete responses and the longer median overall survival may indicate superiority of the BID-schedule. But no corresponding difference in PFS was observed, and there was a trend towards more local relapses at first recurrence in the BID-arm. Besides, the difference in median overall survival was not statistically significant, and there were no differences in 4-year survival rates. Thus, a phase III study is needed before one can conclude whether the BID-schedule is more effective than the OD-schedule. Considering the results of the present study, the hypothesis of such a trial should be that BID is superior to OD. A large number of patients would be required, and by conducting such a study, many patients might receive an inferior treatment - which would probably be equally toxic as the BID-schedule. Thus, we assume that the relevance of such a trial is limited.

By using PET/CT for target volume definition and advanced radiotherapy techniques, higher TRT doses can be delivered and there are indications that 60-70 Gy in 6-7 weeks may be superior to 45 Gy/30 fractions [22-24]. In line with this, we have

initiated a Nordic, randomized phase II trial comparing 45 Gy/30 fractions with 60 Gy/40 fractions. All patients receive two fractions per day. The primary endpoint is 2-year survival.

Despite improvements in radiotherapy-techniques it may not be possible to deliver 60-70 Gy to all patients with disseminated intra-thoracic disease, severe comorbidity or poor PS. Thus, some patients might receive TRT doses of 40-45 Gy also in the future. Our study indicates that concerns about toxicity should not be a reason for choosing hypo-fractionated instead of twice-daily TRT.

In conclusion, there was no difference in toxicity between the two TRT-schedules. The twice-daily schedule was feasible and resulted in more complete responses and a numerically longer median overall survival. There was no difference in progression free survival, and the survival-difference was not statistically significant. Thus, no firm conclusions about efficacy could be drawn from this phase II trial.

Conflicts of interest

None to declare.

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Legends

Figure 1 Patient selection

Figure 2 Progression free survival and overall survival

Figure 3 Mean HRQoL-scores. A higher score on the global QoL-scale represents a better HRQOL, a higher score on the symptom-scales is associated with a worse HRQoL. A difference in mean scores of 10 points was considered clinically relevant.

Table 1 Baseline characteristics. Stage of disease was assessed according to TNM v6.

Table 2 Treatment administered

Table 3 Response evaluation three weeks after the last chemotherapy-course according to the RECIST-criteria (v 1.0) and toxicity

Figure 1 Patient selection

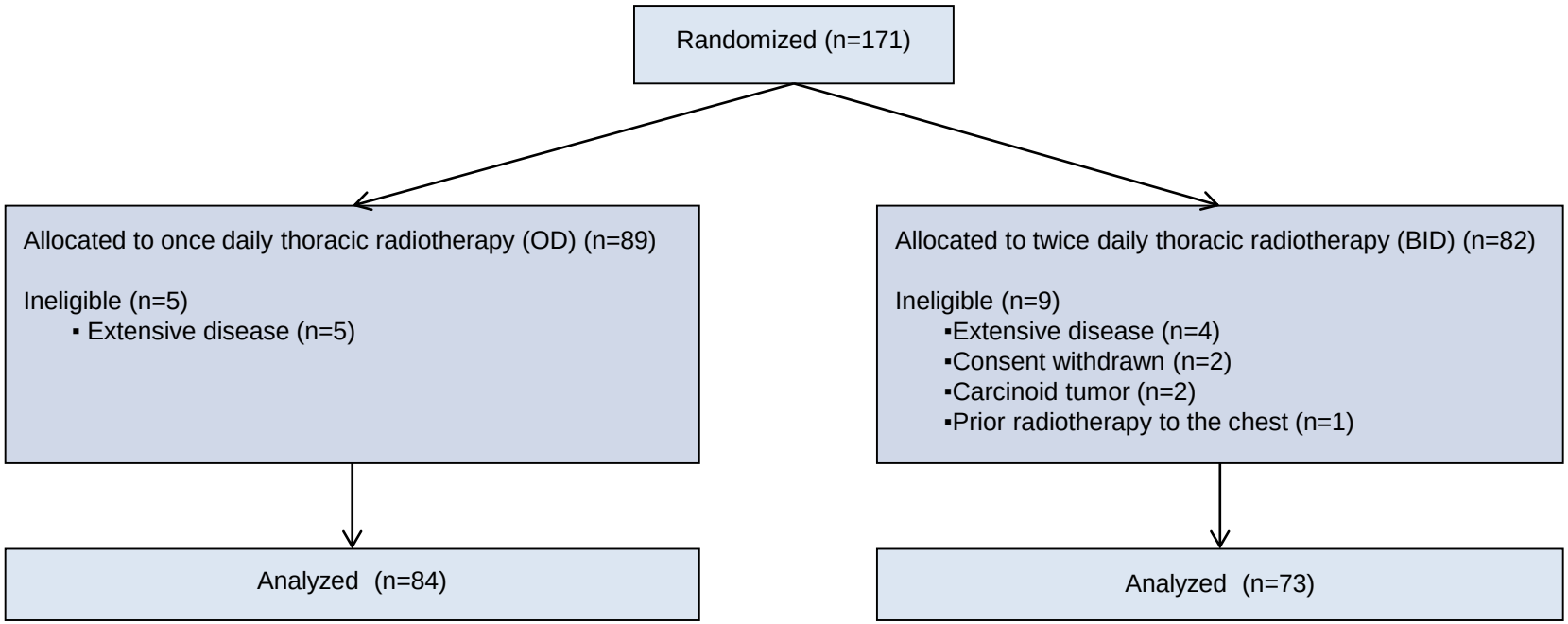
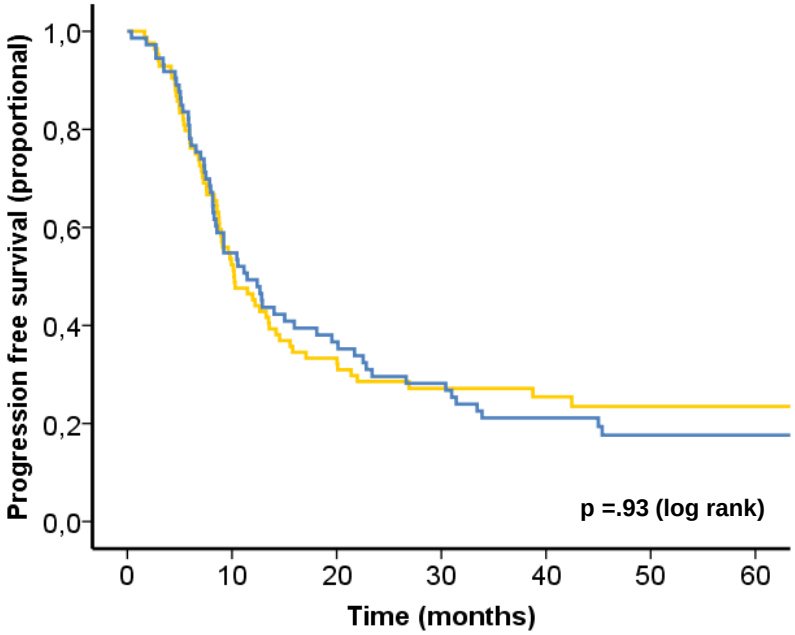


Figure 2 Progression free survival and overall survival

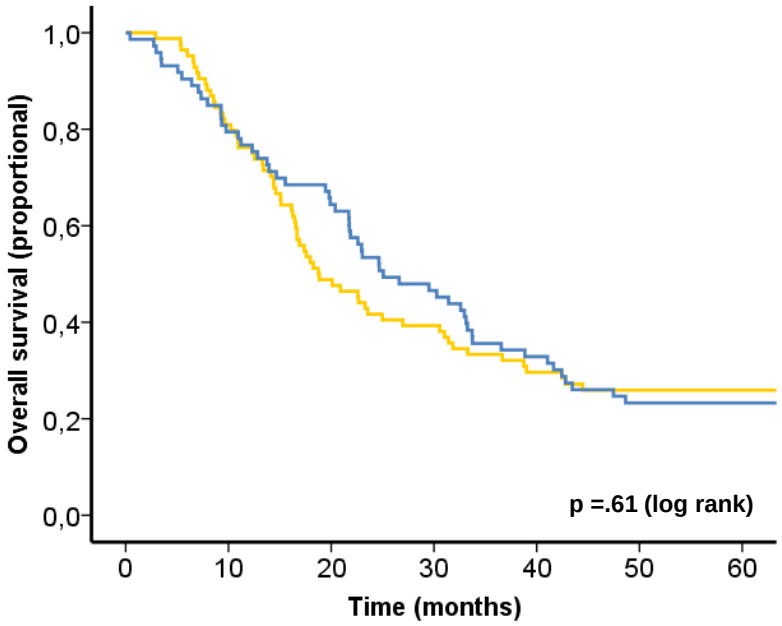
	Median (95% CI) PFS	1 year (95% CI) PFS	2 year (95% CI) PFS
Twice daily	11.4 (8.2-14.7) months	49 (38-61)%	29 (18-39)%
Once daily	10.2 (7.4-13.0) months	45 (34-56)%	26 (17-36)%



Number at risk

	0	10	20	30	40	50	60
	73	40	26	20	13	8	6
	84	44	28	18	15	8	5

	Median (95% CI) OS	1 year (95% CI) OS	2 year (95% CI) OS
Twice daily	25.1 (16.9-33.3) months	77 (67-87)%	53 (42-65)%
Once daily	18.8 (13.6-23.9) months	76 (67-85)%	42 (31-52)%



Number at risk

	0	10	20	30	40	50	60
	73	58	47	34	24	17	17
	84	68	41	33	24	21	17

Figure 3 Mean HRQoL-scores. A higher score on the global QoL-scale represents a better HRQOL, a higher score on the symptom-scales is associated with a worse HRQoL. A difference in mean scores of 10 points was considered clinically relevant.

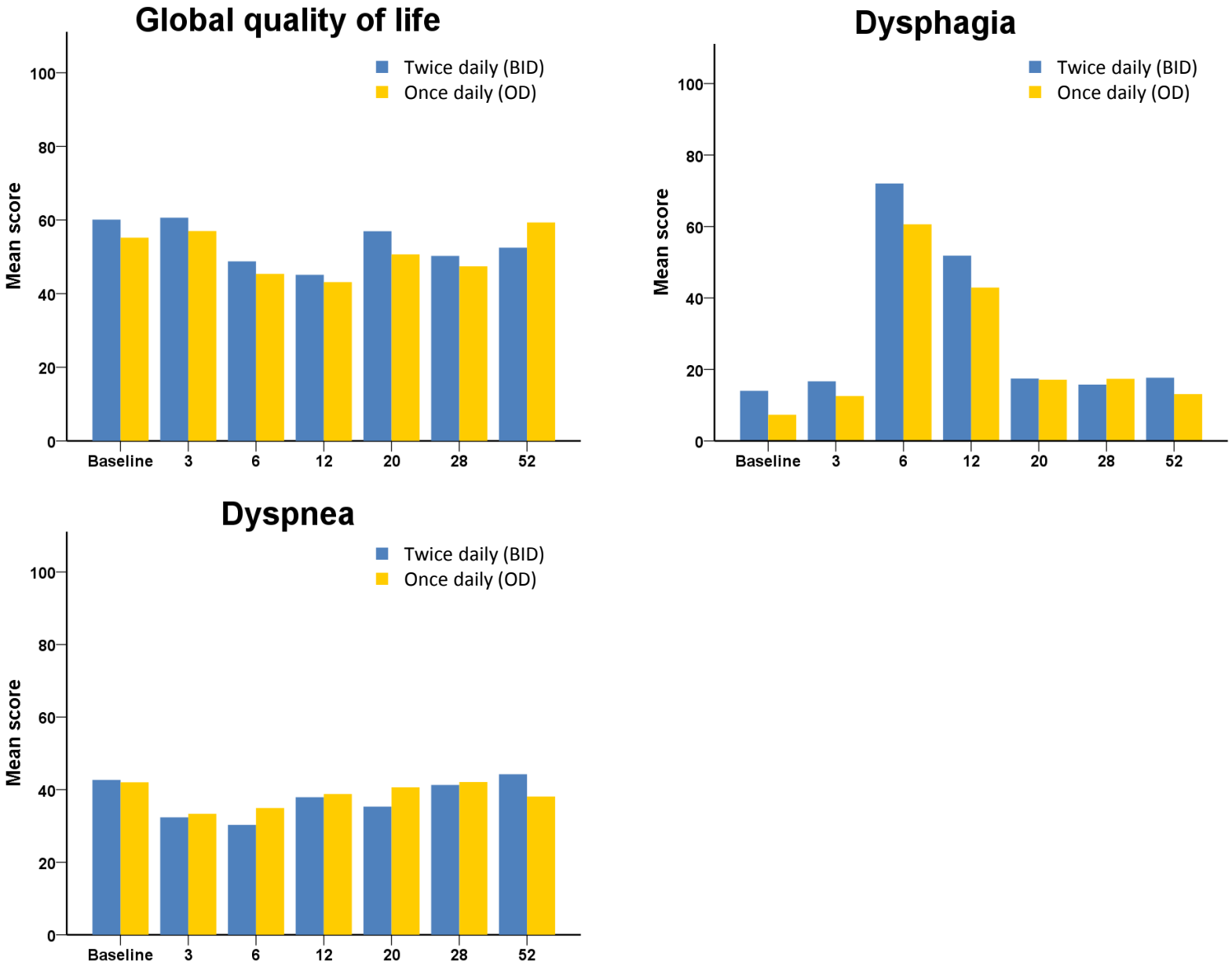


Table 1 Baseline characteristics. Stage of disease was assessed according to TNM v6.

		Once daily (OD) (n=84)		Twice daily (BID) (n=73)	
Age	Median (range)	63 (40-85)		63 (44-79)	
	≥ 70 years	26	31 %	15	21 %
Sex	Women	39	46 %	37	51 %
	Men	45	54 %	36	49 %
PS	0	31	37 %	20	27 %
	1	42	50 %	39	53 %
	2	11	13 %	14	19 %
Pleural fluid	Present	11	13 %	7	10 %
Stage	I	7	8 %	6	8 %
	II	7	8 %	9	12 %
	IIIA	34	40 %	21	29 %
	IIIB	30	36 %	28	38 %
	Unknown	6	7 %	9	12 %

Table 2 Treatment administered

		Once daily (OD) (n=84)		Twice daily (BID) (n=73)		p
Chemotherapy	1 course	-	-	1	1 %	-
	2 courses	3	4 %	1	1 %	-
	3 courses	6	7 %	11	15 %	-
	4 courses	75	89 %	60	82 %	.20
	Mean no. of course	3.86		3.78		.33
	4 courses without delay	35	42 %	19	26 %	0.04
	4 courses without dose reduction	33	39 %	24	33 %	0.41
	Carboplatin instead of cisplatin in ≥ 1 course	9	11 %	3	4 %	-
	Adriamysin (or epirubicin) /cyclophosphamid/vincristine instead of cisplatin/etoposide in ≥ 1 course	1	1%	1	1 %	-
Radiotherapy	Thoracic radiotherapy completed as planned	81	96 %	71	97 %	1.0
	Prophylactic cranial irradiation received	69	82 %	61	84 %	.81
Second line chemotherapy	Received	43	51%	32	44%	.36
	cis or carboplatin/etoposide	18	42%	19	59%	.13
	adriamysin/cyclophosphamid/vincristine	18	42%	8	25%	.13
	Other and unknown	7	16%	5	16%	.94

Table 3 Response evaluation three weeks after the last chemotherapy-course according to the RECIST-criteria (v 1.0) and toxicity

		CTCAE grade	Once daily (OD) (n=84)		Twice daily (BID) (n=73)		p
Response	Complete response	-	11	13%	24	33%	.003
	Partial response	-	66	79%	40	55%	.002
	Stable disease	-	1	1%	1	1%	1.0
	Progressive disease	-	5	6%	3	4%	.73
	Not evaluable	-	1	1%	5	7%	.10
Toxicity	Esophagitis	0-2	58	69 %	49	67 %	0.80
		3-4	26	31 %	24	33 %	0.80
		5	-	-	-	-	-
	Pneumonitis	0-2	79	94 %	70	96 %	0.73
		3-4	2	2 %	2	3 %	1.0
		5	3	4 %	1	1 %	0.62
	Anemia	3-4	9	11 %	16	22 %	0.06
	Leukopenia	3-4	58	69 %	57	68 %	0.20
	Thrombocytopenia	3-4	29	35 %	28	38 %	0.62
	Neturopenia	3-4	72	86 %	59	81 %	0.41
	Neutropenic infections	3-4	37	44 %	27	37 %	0.37
	Infection without neutropenia	3-4	8	10 %	7	10 %	.99