Tumour size reduction after the first chemotherapy-course and outcomes of chemoradiotherapy in limited disease small-cell lung cancer

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Abstract

Objectives

Concurrent chemotherapy and thoracic radiotherapy (TRT) is recommended for limited disease small-cell lung cancer (LD SCLC). TRT should start as early as possible, often meaning with the second course due to patient referral time and the fact that TRT planning takes time. Early assessment of response to the first course of chemotherapy may be a useful way to individualise treatment. The aims of this study were to assess tumour size reduction after the first chemotherapy-course, and whether this reduction was associated with outcomes in LD SCLC.

Material and methods

A randomised trial comparing twice-daily (45Gy/30 fractions) with once-daily (42 Gy/15 fractions) TRT, given concurrently with four courses of cisplatin/etoposide (n=157) was the basis for this study. Tumour size was assessed on CT scans at baseline and planning scans for TRT according to RECIST 1.0.

Results

CT scans were available for 135 patients (86%). Ninety-four percent had a reduction in tumour size after the first chemotherapy-course. The median reduction in sum of diameters (SOD) of measurable lesions was ÷16 mm (÷84 to +10 mm), corresponding to ÷18% (÷51 to +12%). Eighty-two percent had stable disease, 18% partial response. Reduction in SOD was significantly associated with complete response at first follow-up (OR: 1.05, 95% CI 1.01-1.09; p=.013)**,** PFS (HR: 0.97, 95% CI 0.96-0.99; p=.001), and overall survival (HR: 0.98, 95% CI 0.96–1.00; p=.010).

Conclusion

Response from the first course of chemotherapy had a significant positive association with outcomes from chemoradiotherapy, and might be used to stratify and randomise patients in future studies.

1. **Introduction**

Concurrent chemotherapy and thoracic radiotherapy (TRT) is the recommended treatment for LD SCLC [1-7]. Cisplatin plus etoposide constitutes the standard chemotherapy regimen [2, 8], and should commence as soon as possible due to the potentially rapid progress of SCLC [9]. Guidelines recommend that radiotherapy should be administered along with the first or second course of chemotherapy [1-4], since meta-analyses have shown improved survival when TRT starts within 30 days after start of chemotherapy, and when the time from start of any treatment until the end of radiotherapy (SER) is short [6, 7]. Although starting TRT concomitant with the first course results in the lowest SER, TRT is often administered concomitant with the second chemotherapy course due to time-delay in the referral and TRT planning process [10-13].

There is often a tumour response between the first and second chemotherapy-course, allowing for smaller radiotherapy fields and less toxicity than when TRT starts along with the first course. But little is known about the extent of the response. Most patients (80-90%) with LD SCLC respond to chemoradiotherapy, but the 5-year survival is only 25% [14]. Studies indicate that early response to treatment is associated with better outcomes [15-17], and might be a method for identifying patients who do not benefit from TRT.

We analysed LD SCLC patients enrolled in a randomised trial comparing two three-week schedules of TRT, administered concurrently with cisplatin plus etoposide. The aim was to assess the reduction in tumour size after the first chemotherapy course, and to investigate whether this tumour size reduction was associated with outcomes of therapy.

2. Material and methods

2.1 Design and approvals

The trial was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs.

2.2 Patients

Eligible patients had SCLC confined to one hemithorax, the mediastinum, the contralateral hilus and the supraclavicular regions; WHO performance status (PS) 0-2; and adequate kidney and bone marrow function. Pleural effusion was allowed if cytological negative. Four courses of cisplatin plus etoposide (PE1-4) were planned for all patients, and they were randomly allocated to receive TRT of 45 Gy in 30 fractions (twice daily; BID) or 42 Gy in 15 fractions (once daily; OD). Good responders were offered prophylactic cranial irradiation (PCI) of 30 Gy in 15 fractions.

Patients who completed at least two PE-courses and TRT were eligible for the present study, provided that the baseline CT scan and CT planning scan for TRT were available. Patients with a baseline scan more than two months prior to, or a planning scan more than one month later than start of treatment were excluded. Since there were no significant differences in toxicity, response-rates, progression free survival (PFS), or overall survival (OS) between the treatment arms in the main trial [18], we analysed all patients as one cohort in the present study.

2.3 Response evaluations

Timing of treatment and response evaluation are presented in Figure 1. A baseline CT scan for staging (CT1) was obtained before PE1. Response to the first course (RE1) was assessed by comparing CT1 with the CT planning scan for TRT (CT2) obtained 2-3 weeks after PE1. A CT scan for response evaluation after completion of study treatment (RE2) was conducted 2-3 weeks after PE4 (CT3).

Response to overall therapy (RE2) was evaluated according to the RECIST 1.0 criteria [19]. Measurable lesions were defined as lesions ≥ 10 mm. Up to 10 target lesions (maximum 5 per organ) were measured. Sum of largest diameter (SOD) of target lesions at CT1 was compared with SOD of these lesions at CT2. Complete response (CR): Disappearance of all measurable lesions. Partial response (PR): A reduction in SOD of ≥ 30%. Progressive disease (PD): An increase in SOD of ≥ 20%. Stable disease (SD): A change in SOD between +20% and -30% [19].

A central review of RE1 was conducted by a radiologist (MH) and an oncologist (TH). Since staging of disease was based on CT alone, using the RECIST 1.0 criteria for response evaluation, we additionally performed all analyses evaluating only the change in size of the primary tumours. Not all lymph nodes considered pathological according to RECIST 1.0 are defined as pathological according to RECIST 1.1.

2.4 Other assessments

Stage of disease was assessed according to TNM v6 [20]. PFS was defined as time from randomisation until progression or death; OS as time from randomisation until death of any cause. Median follow-up for PFS was 58 months (range: 30 - 97); 31 patients were progression free when this follow-up ended (July, 2013). Median follow-up time for survival was 89 months (range: 61 - 128); 30 patients were alive when survival follow-up ended (February, 2016).

2.5 Statistical considerations

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 survival analyses, and binomial logistic regression for the other multivariate analyses. Multivariate models were adjusted for baseline characteristics and TRT schedule. Associations between reduction in tumour size and outcomes of therapy were analysed using percent reduction of SOD as a continuous variable and according to RECIST categories. The significance level was defined as $p<0.05$.

3. Results

3.1 Patients and treatment completion

Complete descriptive and clinical data are presented in Table 1. We enrolled 157 patients at 18 hospitals in Norway between May 2005 and January 2011 [18]. Twenty-two patients were excluded from these analyses due to missing baseline (n=5) or planning (n=11) CT scan; baseline CT scan more than two months prior (n=1) or planning CT scan one month later (n=2) than start of

chemotherapy; and TRT not completed (n=3). Thus, 135/157 patients (86%) were eligible for the present study. Median age was 64 years; 53% were men; 15% had PS 2 and 74% stage III disease. Mean number of PE-courses was 3.86, 118 patients (87%) completed four courses. Sixty patients (44%) received TRT as 45 Gy in 30 fractions. One hundred and fifteen patients (85%) received PCI, and 64 (47%) received second-line chemotherapy.

3.2 Time between CT scans

Median time from CT1 until start of PE1 was 17 days (range: 0-60). Median time from start of PE1 until CT2 was 18 days (range: 6-30). Median time from CT1 until CT2 was 35 days (range: 14-85).

3.3 Tumour size reduction after the first chemotherapy-course

Median SOD on CT1 was 96 mm (range: 14 to 260 mm); on CT2 76 mm (range: 14 to 196 mm). One-hundred and twenty-seven patients (94%) had a reduction in tumour size. Median change in SOD from CT1 until CT2 was ÷16 mm (range: ÷84 to +10 mm), corresponding to a median change of ÷18% (range ÷51 to +12%) in SOD. Besides, 111 patients (82%) had stable disease, and 24 (18%) achieved a partial response (Figure 2).

Regarding the proportion of patients completing four PE-courses (p=.31); receiving 45 Gy (p=.29) or second-line chemotherapy (p=.78), there was no significant difference between patients with partial response and those with stable disease at RE1. Although patients with a PR were more likely to receive PCI (PR: 100%, SD: 82%; p=.024, Table 1).

3.4 Response evaluation at treatment completion (RE2)

The overall response rate was 90%, of which 23% achieved CR, 67% PR, 1% SD and 5% PD. Four patients (3%) were not evaluable at RE2. There was a non-significant association between percent reduction in SOD and the response rate to chemoradiotherapy (OR: 1.04, 95% CI 0.99-1.09; p=.15), but a significant association with CR (OR: 1.04, 95% CI 1.00-1.07; p=.025). Patients with an increase in SOD did not have a significantly different response rates than other patients (increase: 100%, decrease: 90%; p=1.00)

There was a trend towards higher final response rates at RE2 for those with PR (100%) at RE1 compared with those with SD (88%) (p=.08). Furthermore, patients with a PR at RE1 were more likely to achieve a complete response at RE2 (42% vs. 19%; p=.016) (Table 2). The only other variable significantly associated with response at RE2 was treatment arm: Among those patients receiving twice-daily radiotherapy, more patients had CR at RE2 (BID: 37%, OD: 12%; p=.001).

Multivariate analyses showed a trend towards increased response rate (OR: 1.06, 95% CI 0.99-1.12; p=.08) and significantly more CR (OR: 1.05, 95% CI 1.01-1.09; p=.013) with increasing SOD reduction. There was a significant association between PR at RE1 and CR at RE2 (OR: 3.72, 95% CI 1.26-11.02; p=.018).

3.5 Progression free survival

Median PFS was 11.4 months (95% CI 8.5-14.4 months) in the overall population. PFS improved with increasing percent reduction in SOD at RE1 (HR: 0.99, 95% CI 0.97-1.00; p=.043). Patients with an increase in SOD did not have a significantly different PFS than other patients (increase: 8.5 months, decrease: 11.6 months; p=.47). Patients with a PR at RE1 had a numerically, but not significantly, longer median overall PFS (PR: 19.5 months, SD: 9.9 months; p=.20) (Table 2).

Multivariate analyses showed that overall PFS significantly improved with increasing percent reduction in SOD (HR: 0.97, 95% CI 0.96-0.99; p=.001), and there was a trend towards improved PFS for those with PR compared with those with SD at RE1 (HR: 0.63, 95% CI 0.36-1.10; p=.10).

3.6 Overall survival (OS)

The median overall survival in the whole study cohort was 23.6 months (95% CI: 17.1-30.0 months) with 25% 5-year survival. There was a trend towards improved overall survival with increasing percent reduction of SOD at RE1 (HR: 0.99, 95% CI 0.97-1.00; p=.07); a significantly improved 2-year survival (OR: 1.03, 95% CI 1.00-1.06; p=.026), but no improvement in 5-year survival (OR: 1.02, 95% CI 0.99-1.05, p=.19). Patients with an increase in SOD did not have a significantly different OS than other patients (increase: 19.9 months, decrease: 23.6 months; p=.43).

The difference in median overall survival between those with PR and SD at RE1 was not statistically significant (PR: 33.3 months, SD: 22.6 months; p=.14). There was a trend towards improved 2-year (PR: 67%, SD: 46%; p=.07), but not for 5-year survival (PR: 33%, SD: 23%; p=.31) (Table 2).

The multivariate analyses showed significantly improved overall survival (HR: 0.98, 95% CI 0.96–1.00; p=.010), 2-year survival (OR: 1.04, 95% CI 1.01–1.08; p=.011), and a trend towards improved 5-year survival (OR: 1.05, 95% CI 1.01–1.09; p=.07) with increasing percent reduction in SOD (Table 3). The association was not significant when comparing PR with SD: overall survival (HR: 0.68, 95% CI 0.39-1.18; p=.17), 2-year survival (OR: 2.19, 95% CI 0.82–5.82; p=.12) and 5-year survival (OR: 1.58, 95% CI 0.54–4.64, p=.41).

3.7 Change in primary tumour size and outcomes of therapy

The median primary tumour diameter (PTD) at CT1 was 62 mm (range: 12 to 137 mm); the median PTD at CT2 was 49 mm (range: 10 to 134 mm). Median change in PTD was ÷11 mm (range: ÷44 to +11 mm) corresponding to a median change of ÷18% (range: ÷71 to +24%).

There was no significant association between percentage change in PTD and response rate (OR: 1.02, 95% CI 0.98-1.06; p=.26); but the association with CR was significant (OR: 1.03, 95% CI 1.00-1.06; p=.029). Furthermore, there were significant associations with improved PFS (HR: 0.98, 95% CI 0.97-0.99; p=.004); overall survival (HR: 0.98, 95% CI 0.97-0.99; p=.001), 2-year survival (OR: 1.04, 95% CI 1.01–1.07, p=.003) and 5-year survival (OR: 1.05, 95% CI 1.01–1.08, p=.008).

There was no significant association between reduction in PTD and total response rate in multivariate analyses (OR: 1.04, 95% CI 0.99-1.09; p=.13), whereas the association with CR remained significant (OR: 1.05, 95% CI 1.01-1.08; p=.006). The associations also remained significant for PFS (HR: 0.97, 95% CI 0.96-0.99; p<.001), overall survival (HR: 0.98, 95% CI 0.97-0.99; p=.001), 2-year

survival (OR: 1.04, 95% CI 1.01-1.07; p=.003), and 5-year survival (OR: 1.04, 95% CI 1.01-1.08; p=.008).

4. Discussion

In this study of patients with LD SCLC receiving concurrent chemoradiotherapy, 94% had a reduction in tumour size after the first course of chemotherapy. The median reduction in SOD of target lesions was ÷18%, and 18% of patients had a partial response according to RECIST 1.0 [19]. Furthermore, there were significant, positive associations between reduction in SOD and complete response after completion of chemoradiotherapy, progression free survival and overall survival.

Three other studies indicate that early treatment-response is associated with better outcomes of chemoradiotherapy in LD SCLC, though there are differences in patient selection, treatment administered, study design, methods for assessment of early response and sample size (n=15-70). Fuji et al. reviewed patients with objective response after chemoradiotherapy, and showed that patients who achieved a PR or CR after the first chemotherapy-course had longer PFS and overall survival than those who responded later [17]. Lee et al. found that those with >45 % tumour volume reduction after 1-2 courses of chemotherapy and 36 Gy of TRT had significantly longer overall survival than other patients [16]. van Loon et al. observed that patients with a reduction in metabolic volume on PET-CT or tumour volume reduction on CT after the first chemotherapy-course had significantly longer overall survival [15].

Though our study is the largest of its kind, the sample size is still a limitation, and the level of significance was not adjusted to account for multiple testing in this explorative study. Exploratory ROC analyses did not reveal any cut-off values that strongly discriminated PFS or OS on an individual basis. Thus, we have chosen to only present the results of the analyses using SOD as a continuous variable, and according to the established RECIST-criteria. We did not perform a central review of CT scans obtained for response-evaluation after completion of chemotherapy (RE2), and distinguishing between radiation fibrosis and viable tumour is difficult, which might have influenced the assessment of response rates after completion of chemoradiotherapy and PFS. We present robust survival data collected from a validated national registry.

There was a variation in the time from the baseline CT scan until treatment commenced, and from treatment start until the CT planning scan. Thus, the reduction in SOD might have been underestimated in some cases. Extent of disease in SCLC is assessed more accurately with PET-CT than CT alone, but PET-CT was not generally available when we conducted the study and we are not aware of any of our patients being staged using PET-CT. Furthermore, we used the RECIST 1.0 criteria for definition of pathological lesions and response evaluation (RECIST 1.1 was published in 2010). The main difference in this setting is that RECIST 1.0 defines lesions with a diameter ≥10 mm as pathological, while the RECIST 1.1 criteria defines lymph nodes as pathological if the short axis diameter is ≥15 mm [21]. Thus, not all lymph nodes considered measurable, pathological lesions in our study were necessarily metastases. However, the results were similar when we ran all the analyses using only the change in diameter of the primary tumours.

In the trial establishing the twice-daily TRT schedule, TRT started concurrently with the first chemotherapy course [14]. However, many start TRT after the second course due to the delay caused by time needed for referral to and planning of TRT. The reduction in tumour size 3-4 weeks after the first course allows - in many cases - for smaller radiotherapy fields than if TRT starts concurrently with the first course. This will potentially reduce TRT toxicity and may be a requirement for offering TRT for those with widespread thoracic disease at baseline due to normal tissue constraints. In others, this reduction can facilitate dose escalation with acceptable toxicity.

Due to the high response rate and chances for cure, most patients with LD SCLC are offered chemoradiotherapy. The 5-year survival of 25% is encouraging, but also demonstrates that better treatment is needed for the majority. Several new cytotoxic compounds have shown efficacy in LD SCLC, and some studies suggest that higher doses of TRT can improve the outcome [22, 23]. However, no other chemotherapy regimen has shown to be superior to cisplatin/etoposide. Besides, no randomised studies has to date demonstrated improved survival from high-dose versus standard dose TRT [24]. Moreover, there are concerns about more toxicity from higher TRT-doses.

Little is known about how to individualize treatment of LD SCLC. Some prognostic factors have been identified [25, 26], but none are currently used to guide treatment for the individual patient. One hypothesis for our study was that there might be a subgroup of patients with survival as short as patients with extended disease. In case, one might question whether these patients benefit from TRT. However, even those with an increase in tumour size after the first course had a median overall survival of 19.9 months, which is much longer than in extended disease (typically 8-12 months) [27, 28]. It is, however, possible that an early response assessment as described herein might be used for randomisation or stratification in future studies. One might, for example, hypothesise that patients with a poor response after the first course would benefit from switching to another chemotherapy-regimen or higher TRT-doses, but this needs to be explored in future studies.

5. Conclusion

We found that 94% of patients with LD SCLC had a reduction in tumour size after the first chemotherapy course, and 18% achieved a partial response. Response to the first course of chemotherapy was an independent positive prognostic factor for complete response after chemoradiotherapy, progression free survival and overall survival.

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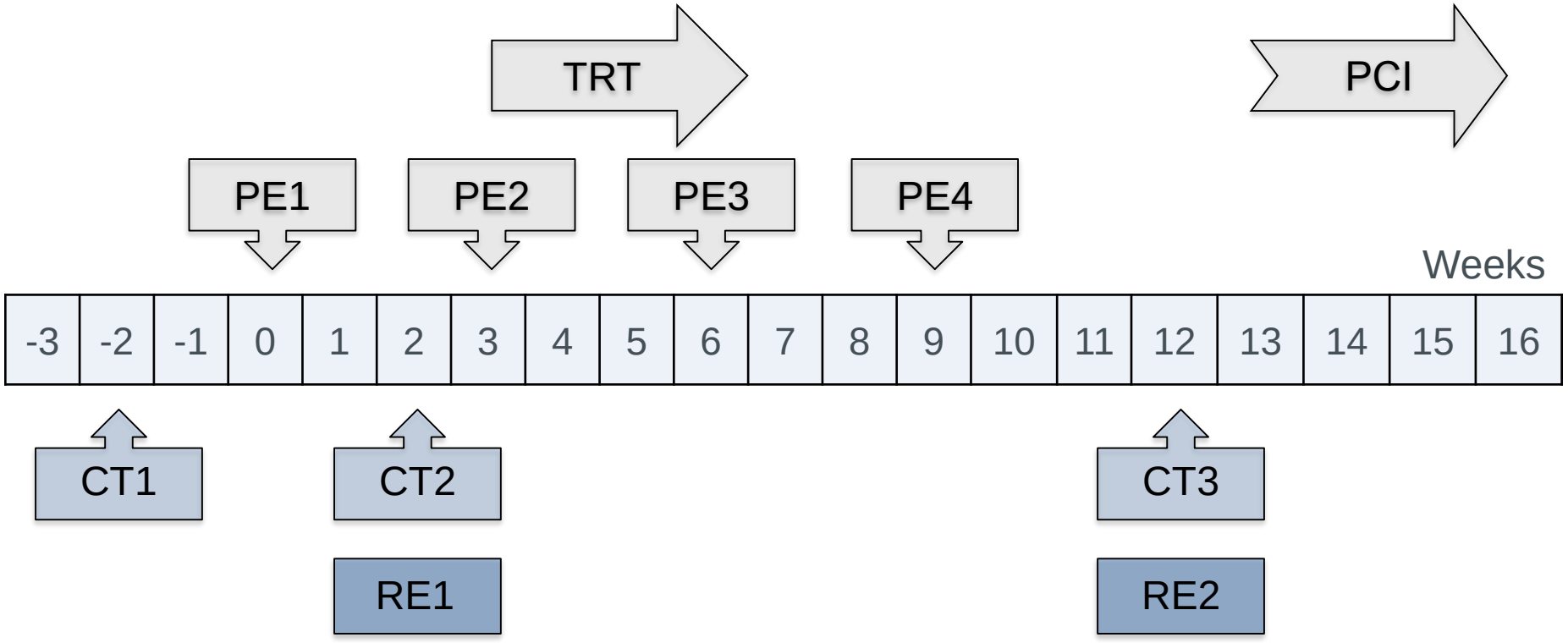
Figure 1 Timing of treatment and evaluation of response on CT



Patients had a baseline CT scan (CT1) prior to chemotherapy. PE = cisplatin/etoposide. Early response (RE1) was evaluated on planning CT scans (CT2) before thoracic radiotherapy (TRT). Response to chemo-radiotherapy (RE2) was evaluated on a CT scan (CT3) obtained 2-3 weeks after the last chemotherapy-course. Patients with a good PR or CR at RE2 were offered prophylactic cranial irradiation (PCI).

Figure 2 Percent tumour reduction after the first chemotherapy-course. Median and 5-year survival according to response category

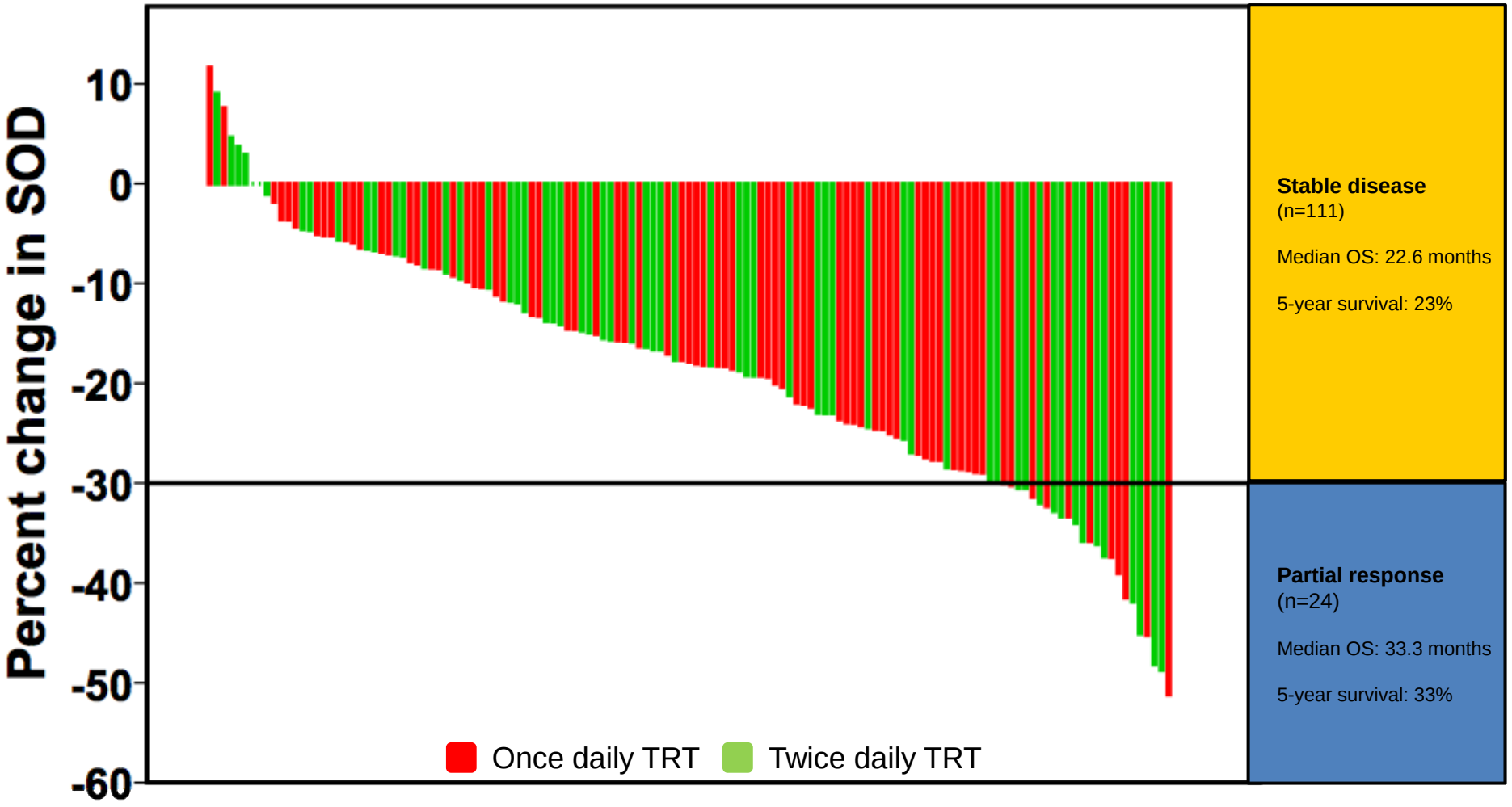
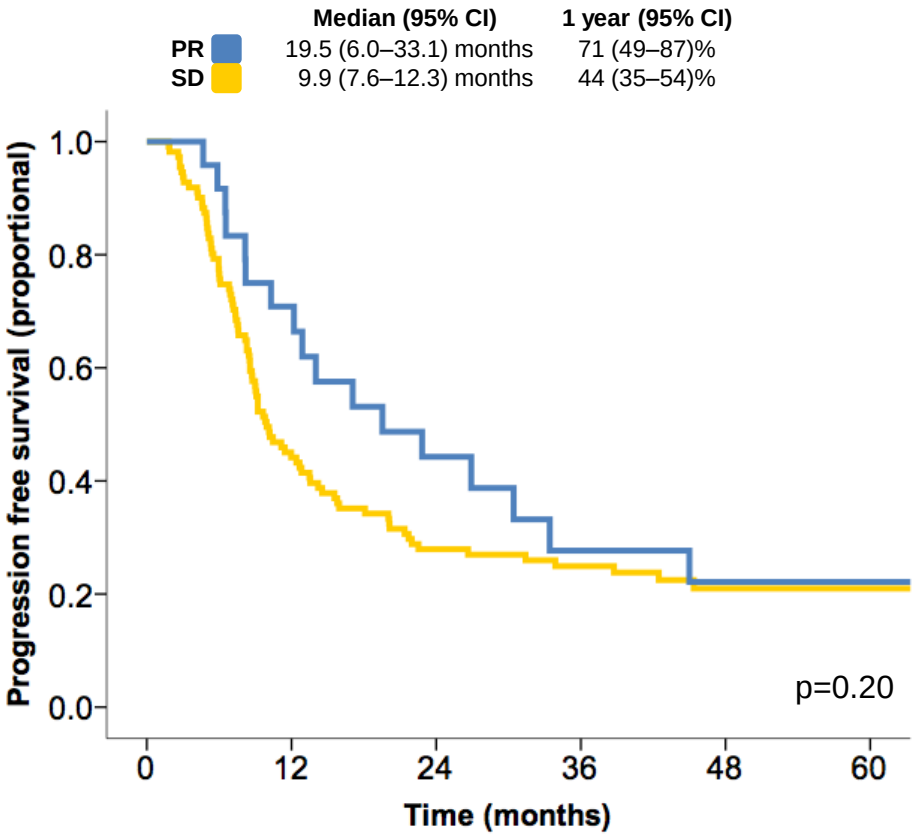


Figure 3 Progression free survival and overall survival



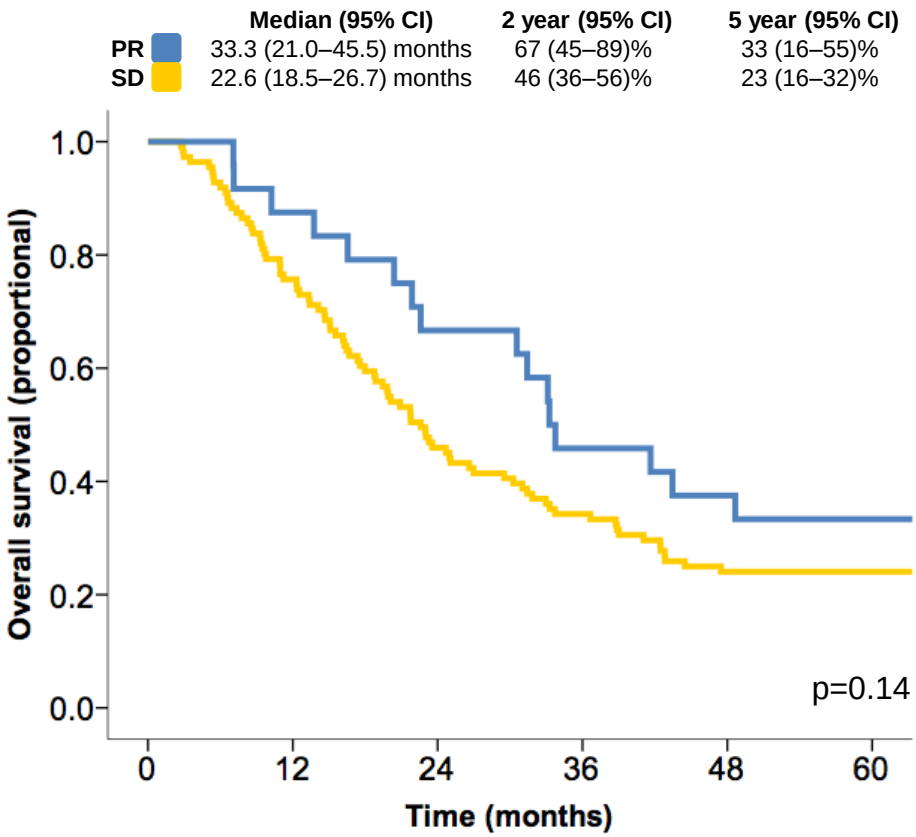


Table 1 Baseline characteristics and treatment completion

		All patients (n=135)		Partial response after first course (n=24)		Stable disease after first course (n=111)	
Age	Median (range)	64 (40-85) years		64 (49-76) years		63 (40-85) years	
	<70	97	72%	17	71%	80	72%
	≥70	38	28%	7	29%	31	28%
Gender	Female	64	47%	11	46%	53	48%
	Male	71	53%	13	54%	58	52%
PS	0	45	33%	9	38%	36	32%
	1	70	52%	11	46%	59	53%
	2	20	15%	4	17%	16	14%
Stage	I	11	8%	2	8%	9	8%
	II	12	9%	5	21%	7	6%
	III	100	74%	16	67%	84	76%
	Unknown	12	9%	1	4%	11	10%
Thoracic radiotherapy	Once daily	75	56%	11	46%	64	58%
	Twice daily	60	44%	13	54%	47	42%
Four courses cisplatin/etoposide		118	87%	23	96%	95	86%
Prophylactic cranial irradiation		115	85%	24	100%	91	82%
Received 2. line chemotherapy		64	47%	12	50%	52	47%

Table 2 Outcomes of chemo-radiotherapy in patients with SD or PR after the first course of cisplatin/etoposide

		All patients (n=135)		Partial response after first course (n=24)		Stable disease after first course (n=111)		p
Response after chemo-	CR	31	23%	10	42%	21	19%	.016
radiotherapy	PR	91	67%	4	56%	77	69%	
	SD	2	1%	-	-	2	2%	
	PD	7	5%	-	-	7	6%	
	NE	4	3%	-	-	4	4%	
Progression-free survival	Median (95% CI) months	11.4 (8.5 – 14.4)		19.5 (6.0 – 33.1)		9.9 (7.6 – 12.3)		.20
	1-year	66	49%	17	71%	49	44%	.018
Overall survival	Median (95% CI) months	23.6 (17.1 – 30.0)		33.3 (21.0 - 45.5)		22.6 (18.5 – 26.7)		.14
	2-year	67	50%	16	67%	51	46%	.07
	5-year	34	25%	8	33%	26	23%	.31

Table 3 Multivariate survival analyses. Overall p-value is presented for variables with more than two categories

		HR	95 % CI		p
Age*		1.01	.99	1.04	.43
Gender	Female	1			
	Male	.87	.58	1.33	.53
PS	0	1			
	1	1.09	.69	1.73	
	2	1.74	.94	3.21	.18
Stage	I	1			
	II	.43	.14	1.30	
	III	1.31	.65	2.63	.051
Treatment	Once daily	1			
	Twice daily	1.19	.79	1.79	.42
Percent SOD reduction*		.98	.96	1.00	.010

** Age and percent SOD reduction after first chemotherapy-course was entered as continuous variables. Female gender, PS 0, stage I and once-daily radiotherapy were defined as reference categories for categorical variables.*