Comorbidity and outcomes of concurrent chemo- and radiotherapy in limited disease small-cell lung cancer

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Abstract

Background

Many patients with limited disease small-cell lung cancer (LD SCLC) suffer from comorbidity. Not all patients with comorbidity are offered standard treatment, though there is little evidence for such a policy. The aim of this study was to investigate whether patients with comorbidity had inferior outcomes in a LD SCLC cohort.

Material and methods

We analysed patients from a randomized study comparing two 3-week schedules of thoracic radiotherapy (TRT) plus standard chemotherapy in LD SCLC. Patients were to receive four courses of cisplatin/etoposide and TRT of 45 Gy/30 fractions (twice daily) or 42 Gy/15 fractions (once daily). Responders received prophylactic cranial irradiation (PCI). Comorbidity was assessed using the Charlson Comorbidity Index (CCI), which rates conditions with increased 1-year mortality.

Results

157 patients were enrolled between May 2005 and January 2011. Median age was 63 years, 52% were men, 16% had performance status 2, and 72% stage III disease. Forty percent had no comorbidity; 34% had CCI-score 1; 15% CCI 2; and 11% CCI 3-5. There were no significant differences in completion rates of chemotherapy, TRT or PCI across CCI-scores; or any significant differences in the frequency of grade 3-5 toxicity (p=.49), treatment related deaths (p=.36), response rates (p=.20), progression-free survival (p=.18) or overall survival (p=.09) between the CCI-categories.

Conclusion

Patients with comorbidity completed and tolerated chemo-radiotherapy as well as other patients. There were no significant differences in RR, PFS or OS - suggesting that comorbidity alone is not a reason to withhold standard therapy in LD SCLC.

Keywords:

Prognostic factor; predictive factor; survival; toxicity; elderly

Introduction

Concurrent chemotherapy and thoracic radiotherapy (TRT) is the recommended treatment for limited disease small-cell lung cancer (LD SCLC). Cisplatin plus etoposide is the standard chemotherapy-regimen [1]. Several schedules of TRT are being used. Many administer doses of 40-45 Gy, and twice-daily TRT of 45 Gy in 30 fractions is one of the recommended schedules [2]. Almost all patients respond to the treatment, and the 5-year survival is up to 25%. However, the treatment often causes severe and sometimes fatal toxicity.

There are concerns about treatment related toxicity, especially from the twice-daily TRT-schedule. Some recommend this treatment to “fit” patients – though there is no clear definition of "fit" in this setting [2]. A large proportion of patients with LD SCLC suffer from co-existing diseases – mainly due to old age and a long history of tobacco smoking [3]. Unfortunately, patients with severe comorbidity are often underrepresented in clinical trials, and comorbidity is seldom systematically assessed [4, 5]. Thus, there is a need to better understand how these patients should be treated.

Population-based studies have shown that LD SCLC patients with comorbidity are less likely to receive standard chemo-radiotherapy [6-8]. Several studies have demonstrated that comorbidity is an independent prognostic factor for survival in cancer. However, the effect on survival in SCLC is unclear as some studies have reported negative effects [3, 9-13], while others did not find an influence on survival [7, 14, 15]. Furthermore, it is not known whether the inferior survival observed in these patients is due to less aggressive treatment or whether comorbidity is an independent negative prognostic factor. Few have assessed whether patients with comorbidity experience more severe toxicity [16].

The aims of this study were to investigate whether LD SCLC patients with co-existing conditions completed chemo-radiotherapy to the same extent as those without comorbidity; and whether they experienced more severe toxicity or inferior treatment outcomes compared to those without comorbidity. We analysed patients enrolled in a randomized clinical trial comparing two schedules of TRT in LD SCLC [17].

Material and methods

Approvals

The study 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.

Patients

From May 2005 until January 2011, 157 patients were enrolled at 18 Norwegian hospitals in a randomized phase II trial comparing TRT of 45 Gy in 30 fractions (two fractions per day - BID) with 42 Gy in 15 fractions (once daily – OD) in LD SCLC. Eligible patients had SCLC confined to one hemithorax, the mediastinum, contralateral hilus and supraclavicular regions; WHO performance status (PS) 0-2; and adequate kidney and bone marrow function (leukocytes ≥3.0 x 10^9/L, platelets ≥100 x 10^9/L, bilirubin <1.5 x ULN and creatinine <125 μmol/L). Other active cancers were not allowed. There were no other restrictions with respect to comorbidity and no upper age limit. All patients were to receive four courses of cisplatin and etoposide (PE). TRT was administered along with the second course of PE. Those with a complete or near complete response were offered prophylactic cranial irradiation of 30 Gy in 15 fractions.

In the overall study cohort, there were no significant differences between the treatment arms in toxicity; treatment related deaths; response rates (OD: 92%, BID: 88%; p=.41), median progression free survival (PFS) (OD: 10.2 months, BID: 11.4 months; p=.93), median overall survival (OS) (OD: 18.8 months, BID: 25.1 months; p=.61) or 5-year survival (OD: 25%, BID: 23%, p=.80) [17]. Thus, all patients were analysed as one cohort in the present study.

Assessments

Comorbidity was assessed using the Charlson Comorbidity Index (CCI), the most commonly used comorbidity index in cancer studies - including many studies of comorbidity in SCLC [6, 10, 11, 13, 14]. The CCI was developed in 1987 by identifying conditions with a negative influence on 1-year survival in a cohort of 559 hospitalized patients. Conditions are given a value of 1, 2, 3 or 6 representing each conditions relative risk of death. These values are summarized to a total score ("CCI-score") [18]. After training, the first author scored comorbidity retrospectively from hospital medical records of the three-month period prior to enrolment.

Stage of disease was assessed according to TNM v6. Toxicity was assessed according to the CTCAE v3.0. Response to treatment was assessed according to RECIST v1.0.

Statistical considerations

Progression free survival was defined as time from randomization until progression or death, and overall survival as time from randomization until death. 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, adjusting for

study treatment and baseline prognostic factors (age, gender, performance status and stage of disease). The level of significance was defined as two-sided $p<0.05$.

Results

Patients

All 157 patients enrolled in the randomized trial were included in the present study. Baseline characteristics are presented in Table 1. The median age was 63 years; 26% were ≥70 years; 52% were men; 84% had PS 0-1 and 72% stage III disease; and 46% received twice-daily thoracic radiotherapy. Median age was 8-10 years higher and there were more men among those with the highest CCI. Otherwise, the baseline characteristics were balanced between the CCI-categories (Table 1).

Median follow-up for progression free survival (PFS) was 59 months (range: 29-97); 34 patients were progression-free when the analyses were performed (July 2013). Median follow-up for survival was 90 months (range: 60-129); 31 patients were alive at the time of the survival analyses (February 2016).

Comorbidity

Sixty-three patients (40%) had no comorbidity (CCI 0): 54 patients (34%) had CCI 1; 23 (15%) had CCI 2; 13 (8%) CCI 3; 3 (2%) CCI 4 and 1 (1%) CCI 5. Mean CCI-score was 0.99. Due to the low numbers, patients with CCI 3, 4 and 5 were analysed as one category.

The most common comorbidities were chronic obstructive pulmonary disease (38%), peptic ulcer disease (12%), myocardial infarction (11%), diabetes mellitus (11%), peripheral vascular disease (8%), and cerebrovascular disease (8%) (Table 2).

Significantly more elderly patients had comorbidity (<70 years: 53%, ≥70 years: 78%, p=.006) and they had a significantly higher mean CCI-score (<70 years: 0.78, ≥70 years: 1.59, p<.001).

Study treatment

There were no significant differences across CCI-scores in the proportion who received four courses of cisplatin plus etoposide (p=.09); completed chemotherapy without dose-reductions (p=.07); completed TRT as planned (p=.54); or received PCI (p=.30). The overall dose-intensity of the chemotherapy was 92%, and there were no significant differences across CCI-scores (p=.25). Patients with CCI 3-5 received significantly less second-line chemotherapy (p=.010) (Table 3).

Toxicity

Grade 3-5 toxicity occurred in 141 patients (92%) in the overall population, 136 patients (89%) experienced grade 3-5 haematological and 106 patients (69%) grade 3-5 non-haematological toxicity. The most common non-haematological toxicities were neutropenic infections (41%), radiation esophagitis (32%) and infections without neutropenia (10%). Radiation pneumonitis was observed in eight patients (5%). Grade 5 toxicity was only observed from radiation pneumonitis (n=4, 3%) (Table 4).

There were no statistically significant differences in the frequency of any grade 3-5 toxicity (p=.49), grade 3-5 haematological toxicity (p=.23), or grade 3-5 non-haematological toxicity (p=.98) across CCI-scores. CCI-scores were not significantly associated with neutropenic infections (p=.86), radiation esophagitis (p=.36) or radiation pneumonitis (p=.76) (Table 4).

There were seven treatment related deaths (Table 4): Radiation pneumonitis (n=4), coronary disease (n=1), haemoptysis (n=1) and respiratory failure (n=1). There were no significant associations with CCI-scores: One patient had CCI 0; four patients had CCI I; one patient CCI 2; and one patient CCI 3 (p=.36).

Response rates and progression free survival (PFS)

Overall, 90% of patients had an objective response at CT evaluation within three weeks after completing study treatment (Table 5). There were no significant differences in response rates across CCI-scores (CCI 0: 95%, CCI 1: 87%, CCI 2: 87%, CCI 3-5: 82%; p=.20).

Median progression-free survival for the whole population was 10.6 months, the 1-year PFS was 47%. There was no significant difference in median PFS between CCI categories (p=.18), but patients with CCI 1 (31%) had a lower 1-year PFS than other patients (52%-65%) (p=.032) (Figure 1).

Survival

Median overall survival was 22.7 months, 2-year survival was 47% and the 5-year survival was 24% in the whole cohort (Figure 1). Patients with CCI 1 had the lowest 2-year survival (CCI 0: 56%, CCI 1: 37%, CCI 2: 48%, CCI 3-5: 47%; p=.26), 5-year survival (CCI 0: 27%, CCI 1: 19%, CCI 2: 26%, CCI 3-5: 29%; p=.67) and median overall survival (CCI 0: 30.6 months, CCI 1: 15.1 months, CCI 2: 23.0 months and CCI 3-5: 23.0 months; p=.09); but the difference was not statistically significant (Figure 1).

Neither CCI-score (p=.23), nor any of the baseline characteristics were independent prognostic factors in multivariate analyses: Age (p=.27), gender (p=.82), TRT-schedule (p=.45), disease stage (p=.10) and performance status (p=.52) (Table 6).

Discussion

In our cohort of patients with LD SCLC receiving concurrent chemo- and radiotherapy, we found that the majority (60%) had co-existing diseases associated with increased 1-year mortality according to the Charlson Comorbidity Index. Patients aged 70 years or older had more comorbidity than younger patients. There were no differences in completion of study treatment, and there were no significant differences in the frequency of severe toxicity, response rates, progression free survival or survival across CCI-categories.

Interestingly, we did not find any differences in completion of study treatment between those with comorbidity and other patients. In population-based studies, patients with comorbidity received less treatment, but it is not clear whether this was due to more toxicity or concerns about toxicity [11, 16]. In contrast to our study, comorbidity was associated with more toxicity in one population-based study of 368 LD SCLC patients ≥75 years [16]. Otherwise, there is little evidence for withholding standard therapy from these patients due to concerns about tolerability.

There were numerical differences in median PFS and overall survival, mainly because the values for patients with CCI 1 were lower than for the other patients. Thus, we did not find a uniform trend towards decreasing PFS or survival time with increasing CCI-scores, and all CCI-categories had longer median overall survival than in studies of extensive disease SCLC [1, 19]. The lack of prognostic impact of comorbidity has also been observed in several other studies of SCLC [7, 14, 15, 20]. However, the literature is not consistent since others have demonstrated an inferior survival among patients with comorbidity [3, 9-13]. The studies are, however, not necessarily comparable. Three of the studies reporting that comorbidity was a negative prognostic factor, were population-based studies, and not studies of patients receiving specific therapy [3, 11, 12]. There were variations in age distribution, extent of disease and treatment administered, and data on important prognostic factors such as performance status were not available in all studies [12]. Furthermore, comorbidity was assessed using different methods. The choice of index might influence the results - as illustrated by two studies who demonstrated different prognostic impact of comorbidity when several methods for comorbidity-assessment were compared [10, 13]. No standard method for measuring comorbidity in cancer studies has been established, but CCI is the most widely used [21].

A possible explanation for the lack of influence on prognosis from comorbidity might be that the impact on survival of the conditions listed in the CCI has changed over time. The CCI was developed in 1987, and improved classification and treatment may have changed the prognosis of conditions specified in the index. Furthermore, the CCI does not take into account the severity of all conditions (e.g. COPD and ischemic heart disease). Another possible explanation is the relatively short median survival time in the overall study population. Read et al. found that the influence of comorbidity on prognosis in cancer patients depends on the overall survival time and that it is less important in cancers with a short expected survival time such as lung cancer [22].

A potential limitation of our study is the retrospective assessment of comorbidity, and that most of the comorbidity assessment was done by one author - although CCI is know to have a high inter-rater-reliability [23]. All co-existing conditions may not be accurately described or mentioned at all in the medical records. However, in a previous study, by carefully checking the medical records and lists of medication, trained oncologists registered more comorbidity from hospital medical records than what attending physicians recorded at inclusion in a study of advanced non-small-cell lung cancer [24].

The most important limitation to this study is the sample size. Due to the low numbers, patients with CCI-scores 3-5 were analysed as one category, but the results did not change when these CCI-categories were analysed separately (data not shown). Strengths of the study include a higher proportion of PS 2 patients than in other studies of LD SCLC [4, 5], and all patients received standard, concurrent chemo-radiotherapy.

There were few restrictions with respect to comorbidity in the eligibility criteria, but it is still possible that some patients have been considered ineligible for the study due to co-existing conditions. This is not possible to assess accurately since we did not collect data on patients with LD SCLC who were not enrolled in the main trial, and the Norwegian Cancer Registry does not contain detailed information about disease stage or comorbidity. The prevalence of comorbidity (60%) in our cohort was similar to former, population-based studies of all stages SCLC (range: 56%-67%) [3, 7, 11]. The proportion of patients with CCI ≥2 in our cohort (26%) was higher than in a study of 174 patients with LD SCLC (12%) [6], but only three percent of our patients had a CCI ≥4. In a population-based study 23% of patients (n=7845), and 18% of those receiving chemotherapy (n=4820), had a CCI ≥4 [11]. However, patients with extensive disease SCLC were included in that study and 8% had PS 3-4. In the only other study of LD SCLC patients receiving concurrent chemo- and radiotherapy (n=73), 15% of patients had a CCI of 5-8 [13]. The studies are not necessarily comparable since the methods for assessing comorbidity varied. In studies using CCI, different cutoff-values

and categorizations of CCI-scores have been applied, and there is no established definition of “severe” comorbidity with respect to CCI-scores in cancer studies. Furthermore, there is limited information about what treatment patients received in these studies, and only one, small study (n=73) reported frequency and severity of comorbidity in LD SCLC patients receiving concurrent chemo- and radiotherapy.[13]

There have been concerns about toxicity from concurrent chemo- and radiotherapy, especially from the twice-daily schedule of thoracic radiotherapy. The European Society of Medical Oncology recommends that patients in a good performance status are treated with concurrent chemo-radiotherapy. Thus, we did not include PS 3-4 patients. Furthermore, ESMO recommends that twice-daily TRT is offered fit patients, although "fit" has not been defined in this setting [2]. It has been reported that physicians offer alternative treatment schedules to patients with severe comorbidity [6-8]. Our study suggests that patients with performance status 0-2 and organ function adequate for standard chemotherapy tolerate standard concurrent chemo- and radiotherapy even if they suffer from co-existing diseases. Interestingly, the proportion of long-time survivors in our study was similar for all CCI-categories. However, only limited evidence can be obtained from a small study assessing comorbidity retrospectively, and our results are not necessarily generalizable to all patients with LD SCLC due to the possible exclusion of patients with comorbidity despite wide eligibility criteria. Systematic, prospective assessment of comorbidity should be conducted prospectively in future trials before treatment strategies can be outlined for patients with comorbidity. Building on the experience from this randomized trial, we are currently running a Nordic randomized trial comparing twice-daily TRT of 45 Gy/30 fractions and 60 Gy/40 fractions. In this trial, a prospective, comprehensive geriatric assessment is performed on all patients including measuring comorbidity on the CCI; patient reported frailty (G8); nutritional status (PG SGA); timed-up-and-go and 5 meter walk test; patient reported health-related quality of life (EORTC QLQ C30); and assessment of lean body muscle mass (protocol available on nlcg.no/node/113). A comprehensive Geriatric Assessment appears to provide more prognostic and predictive information than comorbidity assessment alone [20, 25].

Conclusion

Patients with comorbidity completed and tolerated concurrent chemo- and radiotherapy for limited-disease small-cell lung cancer as well as other patients. There were no significant differences in response rates, progression free survival or overall survival - suggesting that comorbidity alone is not a reason to withhold standard, concurrent chemo- and radiotherapy in LD SCLC.

Acknowledgements

The study was supported by the Central Norway Regional Health Authority (RHA), the Norwegian University of Science and Technology (NTNU) and the Norwegian Cancer Society.

Conflicts of interest: None to declare.

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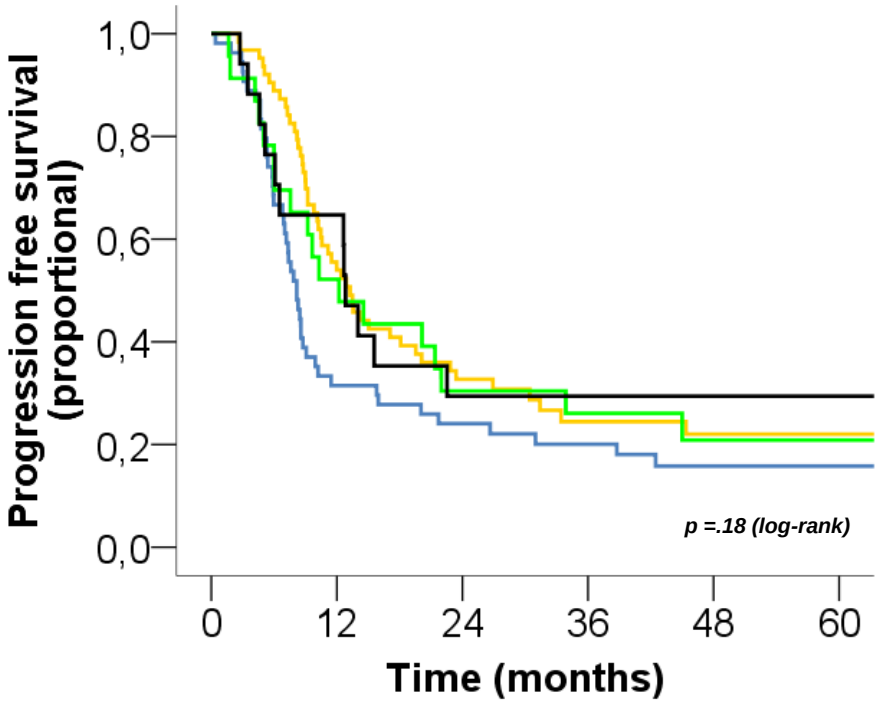
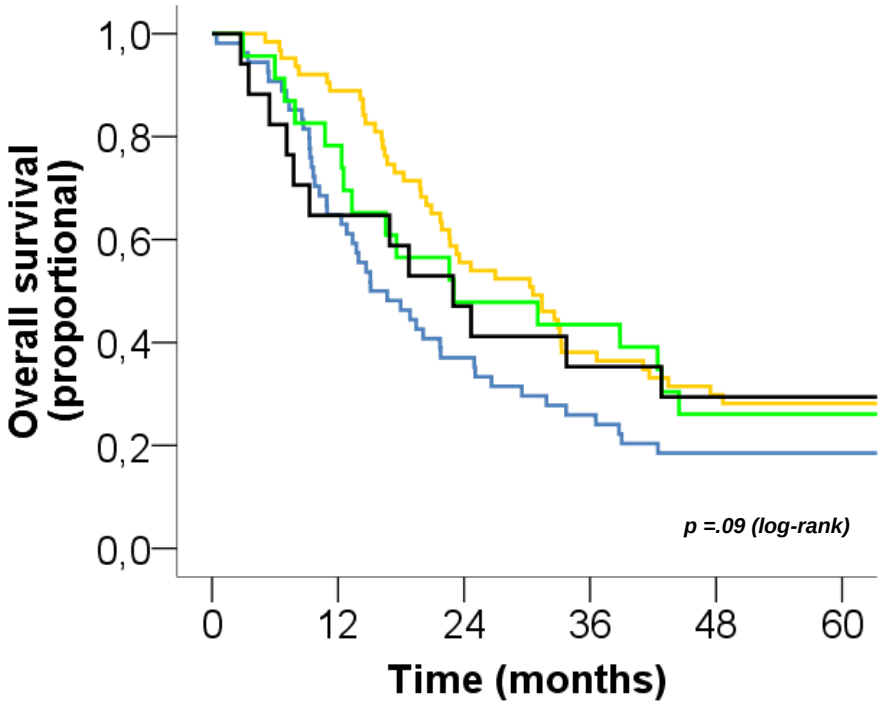
Figure 1 Progression free survival and overall survival according to CCI-scores





	Median (95% CI) PFS	1-year (95% CI) PFS
Overall	10.6 (8.1–13.0) months	47 (39–55) %
CCI 0	13.3 (10.3–16.2) months	54 (41–67) %
CCI 1	8.2 (6.9–9.5) months	31 (20–46) %
CCI 2	12.2 (4.5–19.9) months	52 (31–73) %
CCI 3-5	12.8 (11.0–14.7) months	65 (38–86) %

	Median (95% CI) OS	2-year (95% CI) OS	5-year (95% CI) OS
Overall	22.7 (19.1–26.3) months	47 (39–55) %	24 (18–32) %
CCI 0	30.6 (20.5–40.6) months	56 (42–68) %	27 (17–40) %
CCI 1	15.1 (9.2–21.0) months	37 (24–51) %	19 (9–31) %
CCI 2	23.0 (2.0–44.1) months	48 (27–69) %	26 (10–48) %
CCI 3-5	23.0 (12.5–33.4) months	47 (23–72) %	29 (10–56) %

Table 1 Baseline characteristics

		Overall (n=157)		CCI 0 (n=63)		CCI 1 (n=54)		CCI 2 (n=23)		CCI 3-5 (n=17)	
		n	%	n	%	n	%	n	%	n	%
Age	Median (range)	63 (40-85)		62 (40-79)		64 (41-79)		64 (51-85)		72 (56-79)	
	<70	116	74%	54	86%	39	72%	17	74%	6	35%
	≥70	41	26%	9	14%	15	28%	6	26%	11	65%
Gender	Women	76	48%	34	54%	28	52%	9	39%	5	29%
	Men	81	52%	29	46%	26	48%	14	61%	12	71%
Performance status	0	51	32%	19	30%	20	37%	9	39%	3	18%
	1	81	52%	35	56%	26	48%	10	44%	10	59%
	2	25	16%	9	14%	8	15%	4	17%	4	24%
Stage	I	13	8%	4	6%	5	9%	2	9%	2	12%
	II	16	10%	9	14%	2	4%	4	17%	1	6%
	III	113	72%	45	71%	45	83%	10	43%	13	76%
	Unknown	15	10%	5	8%	2	4%	7	30%	1	6%
Thoracic radiotherapy	Once daily:	84	54%	29	46%	33	61%	14	61%	8	47%
	Twice daily:	73	46%	34	54%	21	39%	9	39%	9	53%

Table 2 Comorbidity scores specified in the Charlson Comorbidity Index – and the frequency of each condition in our study population

Condition	CCI-score	n	%
Chronic obstructive pulmonary disease	1	60	38%
Peptic ulcer disease	1	19	12%
Myocardial infarction (MI)	1	17	11%
Diabetes	1	17	11%
Peripheral vascular disease (PVD)	1	12	8%
Cerebrovascular disease (CVD)	1	12	8%
Connective tissue disease	1	8	5%
Congestive heart failure (CHF)	1	2	1%
Dementia	1	1	1%
Mild liver disease	1	1	1%
Tumour last 5 years	2	3	2%
Hemiplegia	2	-	-
Moderate severe renal disease	2	-	-
Diabetes with organ damage	2	-	-
Lymphoma	2	-	-
Leukaemia	2	-	-
Moderate-severe liver disease	3	-	-
Metastatic solid tumour	6	-	-
AIDS	6	-	-

Table 3 Study treatment completed for each CCI-score

		Overall population (n=157)	CCI 0 (n=63)	CCI 1 (n=54)	CCI 2 (n=23)	CCI 3-5 (n=17)	p
Chemotherapy	Completed all four courses	86%	94%	82%	83%	77%	.09
	No dose reduction	44%	52%	33%	57%	29%	.07
	Mean dose-intensity	92%	93%	91%	94%	89%	.25
	Received second-line chemotherapy	48%	57%	50%	44%	12%	.010
Radiotherapy	Thoracic radiotherapy completed as planned	97%	98%	94%	96%	100%	.54
	Received prophylactic cranial irradiation	83%	89%	76%	83%	82%	.30

Table 4 Treatment toxicity and treatment-related deaths

Toxicity	Overall population (n=157)	CCI 0 (n=63)	CCI 1 (n=54)	CCI 2 (n=23)	CCI 3-5 (n=17)	p
Any grade 3-5 haematological	89%	87%	88%	100%	82%	.23
Anaemia	18%	19%	17%	22%	12%	.86
Neutropenia	83%	87%	82%	91%	65%	.13
Thrombocytopenia	41%	40%	44%	39%	35%	.94
Any grade 3-5 non-haematological	69%	68%	69%	74%	69%	.98
Neutropenic infections	41%	41%	39%	48%	35%	.86
Radiation esophagitis	32%	38%	28%	35%	18%	.36
Radiation pneumonitis	5%	5%	4%	9%	6%	.76
Any grade 3-5 toxicity*	92%	89%	92%	100%	94%	.49

Treatment related deaths	CCI	Co-existing conditions	Age
Coronary heart disease	3	Myocardial infarction, congestive heart failure and chronic obstructive pulmonary disease (COPD)	62
Radiation pneumonitis	2	Cerebrovascular disease and COPD	75
Haemoptysis	1	COPD	69
Radiation pneumonitis	1	COPD	62
Respiratory failure	1	Peripheral vascular disease	76
Radiation pneumonitis	1	Peripheral vascular disease	73
Radiation pneumonitis	0	-	65

** Grade 5 toxicity was observed in 4 patients with pneumonitis (CCI 0: n=1, CCI 1: n=2, CCI 2: n=1; p=.70)*

Table 5 Response rates according to RECIST 1.0 three weeks after completion of chemo-radiotherapy

	Overall population		CCI 0 (n=63)		CCI=1 (n=54)		CCI=2 (n=23)		CCI=3-5 (n=17)		p
	n	%	n	%	n	%	n	%	n	%	
Complete response	35	22%	13	21%	9	17%	6	26%	7	41%	
Partial response	106	68%	47	75%	38	70%	14	61%	7	42%	
Stable disease	2	1%	1	2%	1	2%	-	-	-	-	
Progressive disease	8	5%	2	3%	3	6%	3	13%	-	-	
Not evaluable	6	4%	-	-	3	6%	-	-	3	18%	.026
Overall response rate	141	90%	60	95%	47	87%	20	87%	10	77%	.20

Table 6 Multivariate survival analysis

Variables*		Hazard ratio	95% CI		p
Age		1.01	0.99	1.04	.27
Gender	Female	1			
	Male	0.96	0.65	1.41	.82
Thoracic radiotherapy	OD	1			
	BID	1.16	0.79	1.71	.45
Stage	I	1			
	II	0.48	0.19	1.22	
	III	1.10	0.58	2.09	.10
PS	0	1			
	1	1.09	0.71	1.66	
	2	1.39	0.79	2.45	.52
CCI	0	1			
	1	1.43	0.93	2.20	
	2	1.04	0.55	1.98	
	3-5	0.77	0.38	1.59	.23

**Age was entered as a continuous variable. Female sex, once daily radiotherapy, stage I, PS 0 and CCI 0 were reference categories for categorical variables. Overall p-value is presented for variables with more than two categories.*