Chapter 4

Outcomes of concurrent chemoradiotherapy in patients with stage III non-small-cell lung cancer and significant comorbidity

ECJ Phernambucq
FOB Spoelstra
WFAR Verbakel
PE Postmus
CF Melissant
KI Maassen van den Brink
V Frings
PM van de Ven
EF Smit
S Senan

Annals of Oncology 2011; Vol 22, No 1, pp. 132-138

Abstract

Background: Published trials of concurrent chemoradiotherapy (CCRT) in stage III non-small-cell lung cancer (NSCLC) generally excluded patients with significant comorbidity. We evaluated outcomes in patients who were selected by using radiation planning parameters and were considered, despite comorbidity, fit enough to receive cisplatin-based chemotherapy.

Patients and methods: From 2003 to 2008, 89 patients with stage III NSCLC fit to receive cisplatin-based chemotherapy and a V_{20} <42% underwent CCRT at one center outside clinical trials. Most received one cycle of cisplatin–gemcitabine, followed by two to three cycles of cisplatin–etoposide concurrent with involved-field thoracic radiotherapy between 46 and 66 Gy.

Results: Median age was 64 years; performance status (PS) of zero, one or two in 20/64/5 patients; one or more comorbidities in 41.6%; 14% were treated previously for NSCLC. Median V_{20} was 26.6% (range 4%–39.4%). Grade III esophagitis and pneumonitis occurred in 28.1% and 7.9% of patients, respectively, while 4.5% died during treatment. Median overall survival was 18.2 months [95% confidence interval (CI) 13.1–23.3 months]. Independent prognostic factors for overall survival were PS (0 versus ≥1, P = 0.041) and planning target volume (P = 0.022).

Conclusions: Patients with significant comorbidity who are fit to undergo cisplatin-based CCRT achieve median survivals similar to that reported in phase III trials and with relatively few late toxic effects.

Introduction

The 5-year overall survival for patients presenting with stage III non-small-cell lung cancer (NSCLC) is poor, of clinically staged IIIA and IIIB NSCLC only 18% and 8%, respectively, and pathologically staged IIIA and IIIB disease between 25% and 19%, respectively [1]. The rates of locoregional failure are between 30% and 55%, with distant failure rates in the range of ≥50% [2–4]. Recent large phase III trials using carbo- or cisplatin-based combination chemotherapy achieved survival rates ranging from 12 to 22 months [2, 5, 6]. A meta-analysis by the NSCLC Collaborative Group evaluated the effect of either concurrent administration of chemotherapy and radiation (CCRT) or sequential chemotherapy and radiotherapy [7] and found improved overall survival for CCRT [hazard ratio (HR) = 0.84, 95% confidence interval (CI) 0.74–0.95, P = 0.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. For progression-free survival, the HR was 0.90 (95% CI 0.79–1.01, P = 0.07). The survival benefits of CCRT were due to less locoregional progression (HR = 0.77, 95% CI 0.62–0.95, P = 0.01) as its effect on distant progression was not significantly different from that of sequential treatment (HR = 1.04, 95% CI 0.86–1.25, P = 0.69).

However, concerns about both toxicity and modest survival benefits have contributed to the slow implementation of CCRT in some European countries [8]. CCRT increases acute grade III/IV esophageal toxicity from 4% to 18% [7], but esophagitis is largely reversible. The absence of a significant increase in radiation pneumonitis and late toxicity after CCRT was considered, in part, due to incompleteness of data. Another point of concern was the fact that patients included in the meta-analysis were not representative of the typical patients with this disease. For example, only 13% receiving CCRT were aged ≥70 years and 45% of patients included were <60 years [7]. A recent population-based analysis applied the inclusion criteria used for key phase III trials involving CCRT, as well as the ongoing phase III trial RTOG 0617/NCCTG N0628/CALGB 3060, and concluded that >50% of patients with stage III lung cancer in a Dutch population were ‘theoretically ineligible’ for CCRT [9]. Since 2003, we implemented a treatment approach for CCRT at our center for patients with stage III NSCLC treated outside clinical trials, which was based on (i) patients fitness to undergo treatment with systemic doses of cisplatin-based chemotherapy and (ii) use of radiation planning parameters predicting pulmonary toxicity to determine eligibility for high-dose radiotherapy (**Figure 1**). Our approach was based on the fact that pulmonary oncologists had become much more experienced in safely administering cisplatin-based chemotherapy to patients

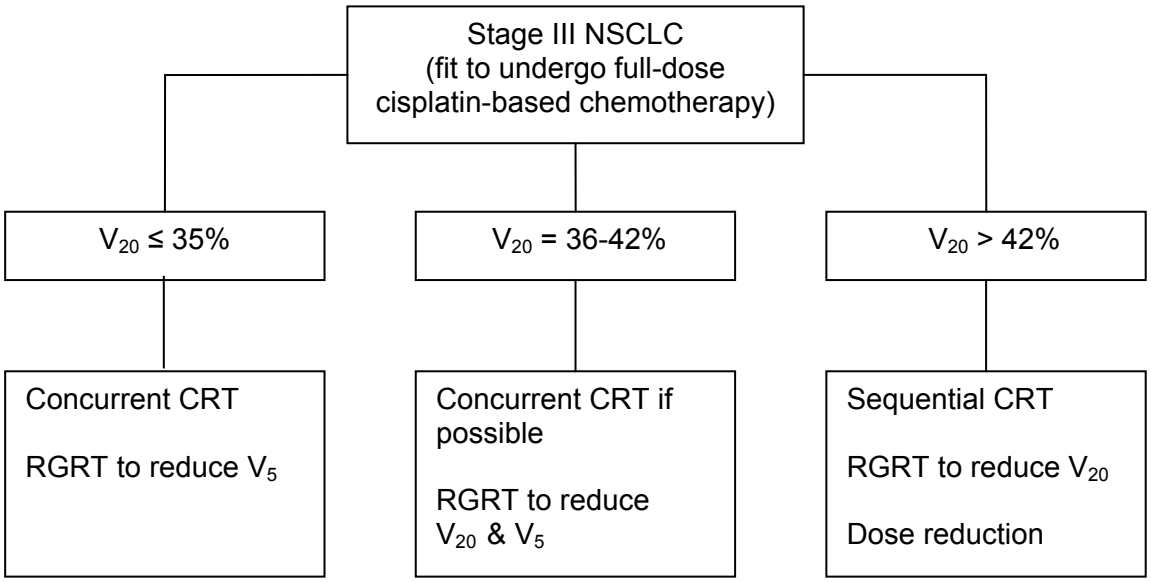
with significant comorbidities, as well as elderly, during the last decade [10]. Furthermore, improved imaging and radiotherapy delivery techniques have enabled greater reductions in toxicity in recent times [11, 12]. Outcomes of this treatment paradigm are reported here.

Patients and methods

Treatment paradigm

CCRT using cisplatin–etoposide was implemented into routine care at our departments in 2003, and details of all treated patients were entered into a prospective database. All patients were discussed within a multidisciplinary thoracic oncology workgroup before commencing treatment. However, (sequential) treatment policy for referred patients was often decided and initiated at the referring center. A performance status (PS) of zero, one or two was necessary to undergo systemic chemotherapy. Patients were eligible for CCRT when at least 46 Gy could be administered based on the INT 0139 phase III trial [5], while respecting dose constraints to organs at risk, i.e. the percentage volume of lung tissue outside the planning target volume (PTV) receiving a threshold dose of ≥20 Gy was limited to 42% (V_{20} ≤ 42%) (**Figure 1**) and the maximum spinal cord dose was limited to 50 Gy. If the patient had a V_{20} between 36% and 42% and a mobile tumor on four-dimensional computed tomography (4D-CT) (motion of ≥7.5 mm), respiration-gated radiotherapy (RGRT), where the tumor is irradiated only in a selected phase of the respiratory cycle where it is relatively immobile, was used [13]. In patients in whom a preoperative 'downstaging' strategy was considered, effort was made to maximally spare the contralateral lung by minimizing the volume receiving a dose of 5 Gy (V_5). These 'potentially resectable' patients underwent surgery dependent on results of restaging procedures after induction CCRT. Patients were treated using sequential chemoradiotherapy or radiotherapy alone in case of refusal to accept CCRT, when the PS was poor and when V_{20} >42%. Other (standard) treatment criteria as well as clinical and pathological staging were applied according to Dutch practice guidelines for NSCLC [14]. All patients had a whole-body fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) before treatment. Finally, routine brain imaging was not implemented in our staging work-up until 2009.

Figure 1. Treatment paradigm for stage III non-small-cell lung cancer (NSCLC) patients.



CRT, chemoradiotherapy; RGRT, respiration-gated radiotherapy; V_5, V_{20}, percentage volume of lung tissue outside the planning target volume receiving indicated threshold dose or more.

Selection of study cohort

All 241 patients with stage III NSCLC who underwent radiotherapy outside clinical trials at our center in the period from 2003 to end of 2008 were identified from multidisciplinary meeting and departmental records (**Table 1**). During this period, doses of ≥50 Gy were not routinely administered to patients with bulky tumors and/or those with supraclavicular nodal metastases as the more conformal technique of intensity-modulated radiotherapy (IMRT) was not yet available at our center. Before the availability of IMRT, sequential chemoradiotherapy was preferred to CCRT in specified patient groups where high V_{20} values were anticipated [15]. The latter included patients with metastases to the contralateral hilus, peripheral lower lobe tumors with contralateral upper mediastinal nodes and large retrocardiac tumors with mediastinal nodal metastases. After exclusion of patients treated with sequential chemoradiotherapy (n = 68), radiotherapy alone (n = 33) or other (n = 1), a total of 139 patients receiving CCRT (with the intention to administer at least 46 Gy in daily fractions of 2 Gy) were identified (**Table 1**). Of these patients, 50 had limited-volume, potentially operable N2 disease and underwent surgery, of which 24 have been described previously [16]. Consequently, the subjects of the present analysis are 89 stage III NSCLC patients who did not qualify for surgery due to reasons including extensive comorbidity, bulky disease, postsurgical recurrences and those with no downstaging after prior induction CCRT. Comorbidity of all patients was scored using the Charlson comorbidity index (CCI) [17], which in this study defines weighted number and seriousness of diseases next to NSCLC, without taking into account the age. In order to compare characteristics of our patients with published CCRT eligibility criteria used by De Ruysscher et al. [9], we also applied the adapted CCI described in that article which classified selected diseases (other malignancies, hypertension, diabetes mellitus and some autoimmune diseases) as non-severe comorbidities.

Table 1. Treatment details of all stage III NSCLC patients who were eligible for radiotherapy in the period 2003-2008 (n = 241)

Characteristics	No. of patients
CCRT (daily fractions of 2 Gy)	**89**
Newly diagnosed stage III	76
Mediastinal recurrence	7
Ipsilateral lung recurrence	5
Following R1 resection	1
CCRT followed by planned surgery	50
Sequential CRT	**68**
Treatment policy decided and initiated at referring center	36
PS ≥2	9
Planned for surgery but found to be ineligible post-chemotherapy	6
Cardiac dysfunction	2
Large radiation field as previously defined [15]:	
Supraclavicular nodal metastases	6
Poorly demarcated tumor due to extensive atelectasis	5
Contralateral mediastinal lymph nodes involved	3
Three separate tumor lesions in one lobe	1
Radiotherapy only	**33**
PS ≥2 and/or extensive comorbidity	18
Age related concerns (≥82 years)	7
Following R1 (n=3) or R2 (n=1) resection	4
Patient refused chemotherapy	4
Other	
CCRT using daily fractions of 3 Gy to 39 Gy (physician's choice)	**1**

NSCLC, non-small-cell lung cancer; CCRT, concurrent chemoradiotherapy; R1, microscopic residual disease; CRT, chemoradiotherapy; PS, performance status; R2, macroscopic residual disease.

Details of radiotherapy planning

In order to permit the planning of image-guided involved-field radiotherapy (IFRT), treatment commenced with one cycle of induction chemotherapy and a 4D-CT scan was carried out for radiotherapy planning either before or during this first course. During 4D-CT scan, spatial and temporal information on organ mobility are generated while synchronously recording respiration waveforms. The tumor delineation encompassed all motion for patients not

treated with RGRT. Treatment plans were generated using Eclipse version 8.1 (Varian Medical Systems, Palo Alto, CA) and generally consisted of two to six fields using 6 and/or 15 MV photons, with heterogeneity corrections. For the present analysis, all plans were recalculated using the analytical anisotropic algorithm, which allows for a more accurate calculation of the delivered dose [18]. Planning parameters for radiotherapy were derived from the dose–volume histograms of the original treatment plans. All initial treatment plans aimed to achieve International Commission on Radiation Units objectives by having the 95% isodose volume (at a minimum) conformed as tightly as possible to the PTV, while respecting dose constraints to organs at risk as described earlier.

Chemo(radio)therapy schedules

Our routine treatment sequence consisted of one cycle of induction chemotherapy consisting of cisplatin 80 mg/m^2 on day 1 and gemcitabin 1250 mg/m^2 on days 1 and 8. Thoracic radiotherapy started concurrently with cisplatin 80 mg/m^2 (days 21 and 42) and etoposide 100 mg/m^2 (days 21–23 and 42–44) on day 22, 5 days/week to a minimum dose of 46 Gy and up to 66 Gy when feasible, depending on the dose to critical organs. A fourth course of (adjuvant) cisplatin–etoposide was administered in patients who received their chemotherapy at one of the referring peripheral hospitals. Hematological toxicity, radiation esophagitis and pneumonitis were graded according to the National Cancer Institute Common Toxicity Criteria grading system v3.0.

Follow-up and statistical analysis

Post-treatment follow-up generally consisted of outpatient visits including CT thorax every 3 months until 2 years and every 6 months after that. Survival is calculated from day 1 of the first course of chemotherapy (start treatment) until death or 1 February 2010 (date of last visit). Progression-free survival is defined as the period from start treatment to the date of disease progression, relapse or death. Survival distributions were estimated with the Kaplan–Meier method. The relationship between survival and categorical variables was analyzed using the log-rank test. Finally, Cox proportional hazard regression analysis was used to assess the effect of continuous variables on survival, to assess the independent effect of several variables (continuous and categorical) on survival in a multivariate model and to estimate the HRs.

Results

Patient characteristics

All 89 patients had pathologically proven NSCLC, and **Table 2** shows patient characteristics and specifies tumor sites. Stage IIIA disease was diagnosed in 45 patients and stage IIIB in 44, and 12 of the total were treated for recurrent NSCLC (specification in **Appendix 1**). In six stage IIIB patients in whom T4N0–XM0 was based on a radiological diagnosis only, the T4 status was agreed upon at a multidisciplinary thoracic oncology workgroup. In addition, 13 patients were considered to have N2/N3 disease without pathological confirmation. However, mediastinal lymph node involvement was highly suspected on the basis of FDG-PET and CT imaging (regarding nodal size, necrosis, etc.). Comorbidity was present in 37 patients (41.6%) according to CCI and according to the adapted version applied by De Ruysscher et al. [9].

Toxicity

Seventy-five patients (84.3%) commenced treatment with one induction chemotherapy cycle consisting of cisplatin–gemcitabine, while remaining 14 patients received induction carboplatin–gemcitabine (n = 5), cisplatin–etoposide (n = 5) or other platinum-based combination (n = 4), of which one had three induction courses of cisplatin–vinorelbine. A median of three courses of chemotherapy were administered in the whole study group, whereas 37 patients (41.6%) received one additional (fourth) cycle. Hematological toxic effects grade III/IV occurred in 76 patients (85.4%) and consisted of anemia (16.9%), leukocytopenia (75.3%) and thrombocytopenia (48.3%). Two patients died of neutropenic sepsis after the third chemotherapy course (grade V). Three patients had a cerebrovascular event during treatment, of which one was fatal. Because of acute myocardial infarction (n = 1) and arterial thrombosis (n = 1), two patients did not receive their third chemotherapy cycle. Eighty-five patients (95.5%) completed their radiation treatment to ≥46 Gy in an overall treatment time of 41 days (range 30–64 days). Of four remainders, discontinuation of radiation treatment before reaching 46 Gy was caused by persisting grade IV hematological toxicity after 40 Gy (n = 1), disease progression after 14 Gy (n = 1), fatal lung bleeding after 6 Gy (n = 1) and the earlier mentioned fatal cerebrovascular event after 8 Gy. Overall, four patients (4.5%) died during treatment and six patients (6.7%) were not able to complete CCRT for reasons of toxicity and/or progression.

Acute radiation esophagitis requiring tube feeding was observed in 25 patients (28.1%) but never exceeded this grade III. Esophagitis generally resolved soon after completion of CCRT; two patients had persistent dysphagia due to stenosis of the esophagus. One patient with a paraesophageal tumor developed a bronchoesophageal fistula, while no acute esophagitis was observed. Grade III radiation pneumonitis occurred in seven patients (7.9%), all of whom were hospitalized and treated with prednisolone. Higher grades of pneumonitis were not observed.

Radiotherapy planning results

Radiotherapy was delivered conventionally (3D) in 49 patients, and respiration-gated delivery was carried out in 40 patients (45%). Planning parameters of patients receiving a dose of <46 Gy (n = 4) were not evaluated. Three additional patients/treatment plans could not be evaluated due to calculation problems. Of the remaining 82, planning parameters are summarized in **Table 3**.

Survival and statistical analysis

At the present analysis after an overall median follow-up of 16.8 months, 31 patients (34.8%) were still alive with a median follow-up of 31.5 months. Overall median survival was 18.2 months (95% CI 13.1–23.3 months) (**Figure 2A**) and progression-free survival 11.2 months (95% CI 8.9–13.6 months). Locoregional progression (n = 17), distant failure (n = 32) or a combination of both (n = 5) was the first site of relapse in patients with disease progression. Locoregional progression was diagnosed after a median of 10.0 months (range 1.2–54.8 months). Seventeen patients (19.1%) have developed brain metastases during follow-up, with median time to diagnosis of 10.1 months (range 3.5–54.9 months). Kaplan–Meier survival curves were used to compare overall survival in patients with different PS (0 versus ≥1) and PTV above or below mean value (748 cm^3). A nonzero PS and high PTV were associated with shorter survival (**Figure 2B and C**). Multivariate Cox regression identified that PS and PTV independently influenced survival. The HR for the PS in the model was 2.206 (95% CI 1.031–4.719, Wald statistic = 4.157, P = 0.041). The HR for PTV per 100 cm^3 increase was 1.074 (95% CI 1.010–1.143, Wald statistic = 5.255, P value = 0.022). No other categorical variables had a significant relation with survival. In this study, the presence or absence of comorbidities as scored by the method of De Ruysscher et al. [9] was not significantly different in terms of overall survival (P = 0.803) (**Figure 2D**).

Table 2. Patient characteristics

Characteristics	No. of patients	%
Sex		
Male	53	59.6
Female	36	40.4
Age (years)		
Median	64 (range 42-82)	
≥70 years	25	28.1
ECOG performance status		
0	20	22.5
1	64	71.9
2	5	5.6
Comorbidities (according to CCI)		
None	52	58.4
1	26	29.2
≥2	11	12.4
Common comorbidities		
COPD	15	16.9
Myocardial infarction	9	10.1
Peripheral vascular disease	9	10.1
Diabetes	7	7.9
Cerebrovascular disease	6	6.7
Location		
Right upper lobe	36	40.4
Middle lobe	4	4.5
Right lower lobe	11	12.4
Left upper lobe	18	20.2
Left lower lobe	5	5.6
Mediastinum	1	1.1
Recurrent cancer	12 (**Appendix 1**)	13.5
Clinical stage		
IIIA	45	50.6
IIIB	44	49.4
Histology		
Squamous cell carcinoma	32	36
Adenocarcinoma	30	33.7
Large cell carcinoma	27	30.3

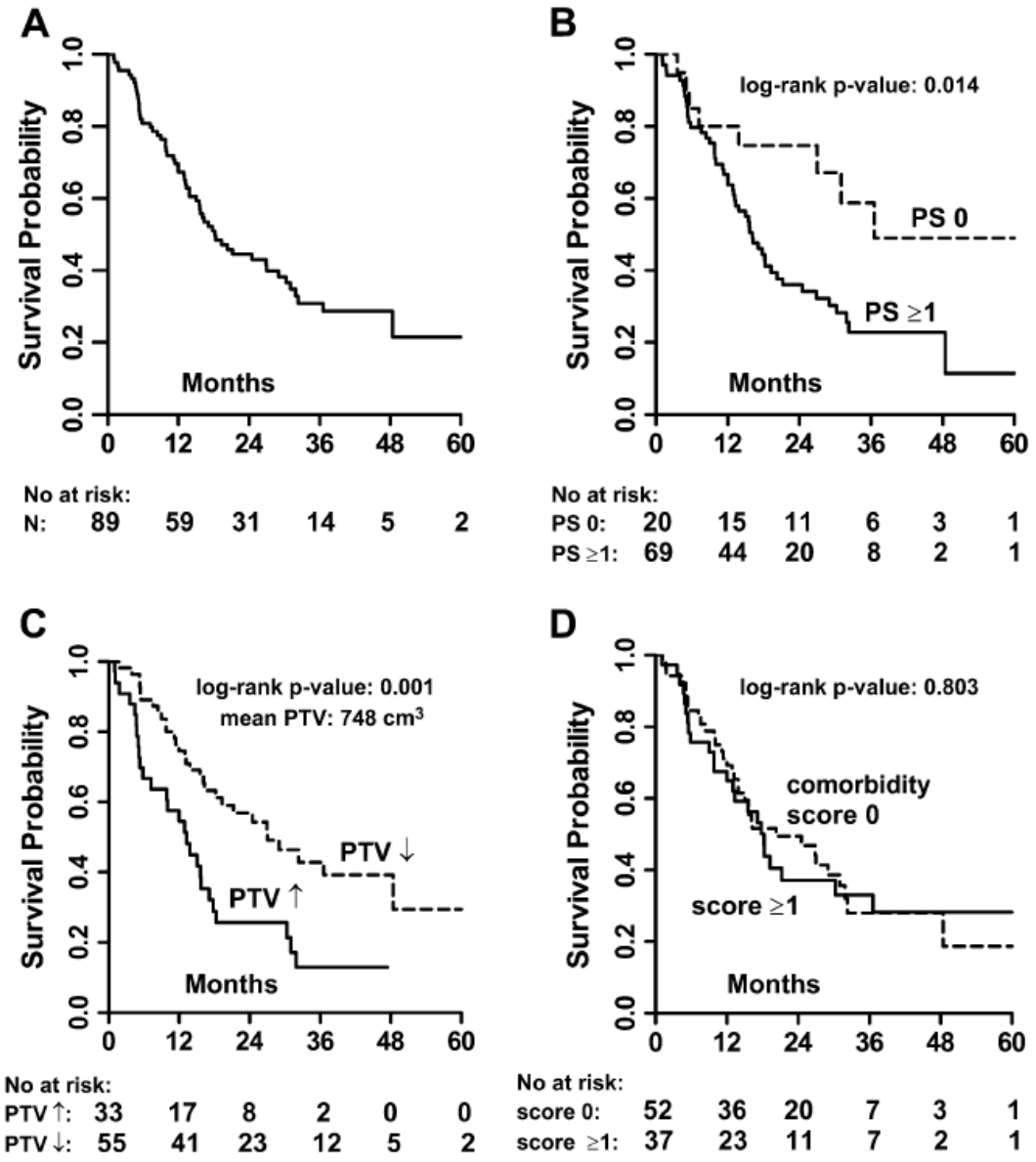
ECOG, Eastern Cooperative Oncology Group; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease.

Table 3. Radiotherapy (planning) parameters

Characteristics	Result	Range	%
Delivery			
Conformal 3D	49		55
Respiration gated	40		45
Total dose delivered, Gy			
<46	4		4.5
≥46	85		95.5
≥60	54		60.7
Volume (mean), cm^3			
Total lung volume (n=87)	3843	2079 – 7447	
PTV (n=88)	748	169 – 1982	
Median toxicity parameters (n=82), Gy			
Mean lung dose	15.8	4.1 – 23.7	
Mean dose to PTV	59.5	44.3 – 69.2	
Maximum spinal cord dose	47.8	28.1 – 56.6	
V_{20} (%)	26.6	4 – 39.4	
V_{20} contralateral lung only (%)	6.8	0 – 29.7	
V_5 (%)	54.8	22.7 – 90.7	
V_5 controlateral lung only (%)	44.1	6.5 – 87.5	
V_{13} (%)	34.1	5.5 – 60.6	
V_{13} controlateral lung only (%)	13.9	0.1 – 51.5	

V_5, V_{13}, V_{20}, percentage volume of lung tissue outside the planning target volume (PTV) receiving indicated threshold dose or more.

Figure 2. Survival curves



(A) Overall survival (median 18.2 months). **(B)** PS of zero versus one or more (median 36.6 vs 16.1 months, P value = 0.014). **(C)** PTV above versus below mean value of 748 cm^3 (median 13.3 vs 27 months, P value = 0.001). **(D)** Comorbidity score as calculated by method of De Ruysscher et al. [9], meaning no comorbidity (0) versus one or more 'significant' comorbidities (≥1) (20.3 vs 18.2 months, P value = 0.803). PS, performance status; PTV, planning target volume.

Discussion

Patients included in clinical trials do not reflect the overall stage III NSCLC population [9]. In particular, those with significant comorbidity and the elderly were underrepresented in previous clinical trials. As stage III NSCLC patients represent a heterogeneous population in terms of presentation and outcomes [19], the selection criteria used for CCRT outside clinical trials are important.

Since 2003, our treatment paradigm in stage III disease has been based on two factors, namely the fitness to receive full-dose cisplatin-based chemotherapy and the radiation planning parameter V_{20}. In our patient cohort, only 23% had a PS of 0, 28% were aged ≥70 years, 42% had one or more comorbidities and 14% had prior treatment of NSCLC. Nevertheless, a median overall survival of 18.2 months was achieved with modest toxicity. These findings compare favorably with an overall median survival of ~18 months reported in the latest meta-analysis on CCRT, encompassing six phase III studies with patient enrollment from 1988 to 2003 [7]. Our findings strongly argue for the use of less restrictive criteria concerning patient inclusion in routine practice of CCRT.

The suggestion that up to 59% of patients with stage III NSCLC are theoretically ineligible for CCRT based on inclusion criteria for previous and ongoing trials [9] is clearly inappropriate as this would have excluded at least 42% of our patients due to comorbidity. In particular, we observed no difference in survival of our patients with one or more important comorbidities versus those without comorbidity. Independent prognostic factors for overall survival on multivariate analysis were PS and the PTV.

Some aspects of our results merit further comment. A higher median survival of 21.7 months was reported in a recent phase III trial (HOG-LUN 01-24) investigating cisplatin-based CCRT with or without consolidation docetaxel [6]. However, patients in our report represent a less fit subgroup with more extensive tumors as CCRT followed by resection had been our policy for patients with limited-volume stage III disease who were treated during the same period [16]. Despite the comorbidities, our treatment dropout rate of 11.2% compares favorably with a 20%–23% incidence reported in the recent literature [5, 20]. It should be noted that our patients routinely underwent staging FDG-PET scans and IFRT based on 4D-CT scans. The relatively low median radiotherapy dose of 59.5 Gy to the PTV (range 44.3–69.2 Gy) reflects the fact that we did not have access to the technique of IMRT during the period in question. At present, most of the patients in this category receive a minimum dose of 60 Gy with the use of IMRT approaches. Acute radiation esophagitis continues to be an

important cause of morbidity with CCRT, and despite our use of IFRT, a grade III esophagitis occurred in 23.8% of patients. However, no grade IV toxicity was seen and late toxicity is uncommon. Incidence of esophagitis grade III or higher in other recent phase III trials ranges from 23% [5] to 34% [2].

Despite including patients with a V_{20} of up to 39.4%, grade III or higher pneumonitis was observed in only 8% of our cohort. Although earlier recommendations had suggested caution when using CCRT in patients with V_{20} values >35% [11], more recent prospective data led to our acceptance of a V_{20} of 36%–42%. Grade II–V radiation pneumonitis was only observed in 7% of patients in the HOG-LUN 01-24 study [21], despite V_{20} values ranging from 5% to 74% (median 35%). Similarly, the phase III SWOG 0023 trial reported grade III or higher pneumonitis in only 10% of patients with V_{20} >35% [22].

Another potential option to allow safe implementation of CCRT is individualizing radiation doses based on normal tissue dose constraints [23]. Van Baardwijk et al. [24] recently reported on a prospective study with sequential chemoradiotherapy in NSCLC using these 'biologically optimized' radiotherapy doses (hyperfractionated) up to 79.2 Gy. Median survival rates in this study were only 16.2 months for stage IIIA and 17.2 months for stage IIIB disease. These authors reported acceptable acute and late toxicity; mean lung dose was 19 Gy compared with 15.8 Gy in our study. Only 55% of patients treated with this sequential 'biologically optimized' radiotherapy received induction chemotherapy, and the 67% incidence of distant disease as the first site of recurrence emphasizes the need for incorporating adequate systemic doses of chemotherapy. Another example is the EORTC 08972 study of Belderbos et al. [4], where daily low-dose cisplatin (6 mg/m^2) was administered concurrent with radiotherapy to 66 Gy and where the median survival was only 16.5 months. The use of daily low-dose cisplatin has not been shown to influence systemic relapses [25].

Nearly 20% of our patients developed brain metastases, with most being diagnosed within 1 year after start of treatment. The high incidence and early manifestation of brain metastases in stage III NSCLC is well recognized and we now follow the recommendation for routine pretreatment brain imaging (CT/magnetic resonance imaging) before CCRT [26]. The retrospective nature of our analysis is a limitation but the follow-up of our patients for both toxicity and progression was nearly complete. The very fact that these patients were either ineligible or had declined participation in studies suggests that our conclusions are a better reflection of CCRT outcomes in the community. We report that both PS ≥1 and high PTV had a significantly negative impact on survival. However, new radiotherapy techniques are

available now (including IMRT) that can potentially increase local control rate [27], especially for large tumors, but this will have to be validated in prospective randomized trials.

In conclusion, our data indicate that concerns about comorbidities should not be a reason for not applying CCRT in patients with a PS of zero or one, who are otherwise fit to receive systemic doses of chemotherapy.

Appendix 1. Study patients with recurrent NSCLC (n=12)

Patient	PS	Site of recurrence	Clinical TNM	Stage	Time to recurrence (years)	Previous treatment	Site of previous treatment
1	1	Ipsilateral lung	T4N2M0	IIIB	0.9	Wedge resection + chemotherapy	LUL
2	1	Ipsilateral lung	T2N2M0	IIIA	24.3	Bilobectomy	RUL + ML
3	1	Ipsilateral lung	T4N0M0	IIIB	2.1	Pneumonectomy	Left lung
4	0	Ipsilateral lung	T1N2M0	IIIA	0.5	Stereotactic radiotherapy	RUL
5	1	Ipsilateral lung	T4NxM0	IIIB	4.8	Lobectomy	RUL
6	2	Mediastinal	TxN2M0	IIIA	7.0	Lobectomy	LUL
7	0	Mediastinal	TxN2M0	IIIA	5.2	Lobectomy	RUL
8	1	Mediastinal	TxN3M0	IIIB	6.6	Lobectomy	LUL
9	1	Mediastinal	TxN2M0	IIIA	4.3	Chemotherapy + lobectomy	LUL
10	1	Mediastinal	TxN2M0	IIIA	1.2	Lobectomy	RUL
11	0	Mediastinal	TxN3M0	IIIB	0.9	Lobectomy	RLL
12	0	Mediastinal	TxN3M0	IIIB	1.4	Chemotherapy + lobectomy	RLL

PS, performance status; LUL, left upper lobe; RLL, right lower lobe; RUL, right upper lobe; ML, middle lobe.

References

1. Goldstraw P, Crowley J, Chansky K et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007; 2: 706–714.

2. Vokes EE, Herndon JE II, Kelley MJ et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007; 25: 1698–1704.

3. Van Meerbeeck JP, Kramer GW, Van Schil PE et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007; 99: 442–450.

4. Belderbos J, Uitterhoeve L, Van Zandwijk N et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). Eur J Cancer 2007; 43: 114–121.

5. Albain KS, Swann RS, Rusch VW et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009; 374: 379–386.

6. Hanna N, Neubauer M, Yiannoutsos C et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 2008; 26: 5755–5760.

7. Auperin A, Le Pechoux C, Rolland E et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010; 28: 2181–2190.

8. Rowell NP, O'rourke NP. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2004; 4: CD002140.

9. De Ruysscher D, Botterweck A, Dirx M et al. Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study. Ann Oncol 2009; 20: 98–102.

10. Simon GR. Treatment of older patients with non-small-cell lung cancer: walking the therapeutic tightrope. J Clin Oncol 2010; 28: 523–526.

11. Senan S, De Ruysscher D, Giraud P et al. Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol 2004; 71: 139–146.

12. Haasbeek CJ, Slotman BJ, Senan S. Radiotherapy for lung cancer: clinical impact of recent technical advances. Lung Cancer 2009; 64: 1–8.

13. Spoelstra FO, Van Sörnsen de Koste JR, Cuijpers JP et al. Analysis of reproducibility of respiration-triggered gated radiotherapy for lung tumors. Radiother Oncol 2008; 87: 59–64.

14. Landelijke Werkgroep Longtumoren. Niet-kleincellig longcarcinoom, landelijke richtlijn. VIKC 2004. URL: http://www.cbo.nl/Downloads/318/lonc-rl-2004.pdf (2 March 2010, date last accessed).

15. Senan S, Lagerwaard FJ. The role of radiotherapy in non-small-cell lung cancer. Ann Oncol 2005; 16 (Suppl 2): ii223–ii228.

16. Phernambucq EC, Spoelstra FO, Paul MA et al. Evaluation of a treatment strategy for optimising preoperative chemoradiotherapy in stage III non-small-cell lung cancer. Eur J Cardiothorac Surg 2009; 36: 1052–1057.

17. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47: 1245–1251.

18. Hasenbalg F, Neuenschwander H, Mini R, Born EJ. Collapsed cone convolution and analytical anisotropic algorithm dose calculations compared to VMC++ Monte Carlo simulations in clinical cases. Phys Med Biol 2007; 52: 3679–3691.

19. Robinson LA, Ruckdeschel JC, Wagner H Jr, Stevens CW. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132: 243S–265S.

20. Fournel P, Robinet G, Thomas P et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. J Clin Oncol 2005; 23: 5910–5917.

21. Barriger RB, Aseneau JC, Yu M et al. Rates and risk of pneumonitis in non-small cell lung carcinoma (NSCLC) patients (pts) treated with concurrent chemoradiation. Int J Radiat Oncol Biol Phys 2008; 72: S117–S118 (Abstr 1011).

22. Kelly K, Chansky K, Gaspar LE et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 2008; 26: 2450–2456.

23. Van Baardwijk A, Bosmans G, Boersma L et al. Individualized radical radiotherapy of non-small-cell lung cancer based on normal tissue dose constraints: a feasibility study. Int J Radiat Oncol Biol Phys 2008; 71: 1394–1401.

24. Van Baardwijk A, Wanders S, Boersma L et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. J Clin Oncol 2010; 28: 1380–1386.

25. Schaake-Koning C, Van den Bogaert W, Dalesio O et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 1992; 326: 524–530.

26. Silvestri GA, Gould MK, Margolis ML et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007; 132: 178S–201S.

27. Liao ZX, Komaki RR, Thames HD Jr et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010; 76: 775–781.