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Impact of comorbidity and age on the outcome of patients with inoperable NSCLC treated with concurrent chemoradiotherapy

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Summary
Background: The value of concurrent chemoradiotherapy (CRT) for treatment of locally advanced non-small cell lung cancer (NSCLC) in elderly and multimorbid patients is generally disputed due to the assumed lack of toxicity compensation or the limited prognosis of the accompanying morbidity.
Aim: We investigated correlation between impaired organ function, age, tumor-associated symptoms, social factors and acute toxicity as well as survival following CRT.
Patients and methods: Retrospective data collection and analysis were performed on the variables age, functional parameters: FEV_1, VC, DLCO, LVEF, creatinine clearance, age, several categories of comorbidities, WHO performance status, alcohol and nicotine habits, toxicity according CTC-criteria and survival of all patients ($n = 66$) with inoperable NSCLC suffering substantial comorbidities or advanced age (>70 years) treated with an CRT consisting of two cycles cisplatin or carboplatin plus vinorelbine and a conventionally fractionated radiotherapy up to 63 Gy.
Results: Median survival of all patients was 13 months (10.6–15.4 months, 95% confidence interval). Univariate analyses showed significantly poorer survival (12 months vs. 15 months) in patients with LVEF $<50\%$ compared with LVEF $\geqslant 50\%$ ($P = 0.022$, in log-rank test). All other variables did not exhibit any significant correlation to survival. Multivariate analyses revealed significantly inferior survival in patients suffering from cardiac or pulmonary dysfunction ($P = 0.039$, hazard ratio [HR]: 2.18; 95% CI of HR [1.04–4.59]). Elderly patients (>70 years) had a higher prevalence of hematotoxicity of higher degree than younger patients ($\leqslant 70$ years), but without significant impact on the feasibility of both treatment modalities.

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Conclusion: Our results suggest that cardiac and pulmonary dysfunction may be associated with a reduced survival in elderly or poor-risk patients with inoperable NSCLC after CRT.

Introduction

Intensification of treatment through concurrent chemoradiotherapy (CRT) has improved the survival of patients with inoperable non-small cell lung cancer (NSCLC) without distant metastases. This was unequivocally demonstrated in four randomized clinical trials.[1–4] These findings are also reflected in the treatment recommendations of medical societies.[5] However, patients with advanced age, various concomitant diseases or a low Karnofsky performance status were excluded from many of these studies while in others they represented only a small minority or were not included because they were considered to be incapable of tolerating cisplatin. Consequently, the mean age of patients in the cited trials and other lung cancer trials is between 54 and 63 years.[6]

Only few authors have investigated the feasibility of intensive treatment, i.e., concurrent CRT, in elderly and poor-risk patients.[7–10] These investigators have found that individual combination chemotherapy with a platinum salt and a new generation cytostatic agent resulted in a good side effects profile. Still, overall survival in these patients was lower than the rates achieved in other randomized trials: median survival 10–13 months vs. 16–17 months (see Fietkau[11] for overview). The obvious questions, however, which comorbidities or general risk profiles do impact on the survival of patients with inoperable NSCLC and which prognostic criteria such as general state of health, age and pretreatment weight loss predict response to treatment and/or survival have not been addressed.

We therefore conducted a retrospective analysis of all 66 NSCLC patients with at least one type of organ dysfunction or old age, who had received platinum-based concurrent CRT with carboplatin or cisplatin plus vinorelbine to determine how these objective patient- and tumor-related factors would correlate with survival and toxicity.

Patients and methods

Patient selection, classification of morbidity, classification of acute toxicity and causes of death

The population contains all patients, who received concurrent CRT with vinorelbine and carboplatin or cisplatin according to the scheme outlined in Figure 1[8,10] at the Department of Radiotherapy at the University of Rostock, Germany in the period from November 1998 to June 2005, had stage I to IIIB (UICC classification) NSCLC that was clinically inoperable but without evidence of distant metastases. Results of the feasibility study were published in 2003.[8] All patients except for two had at least one of the risk factors listed in Table 1. Patients treated within other studies (e.g. Chartwell protocol; a phase II study with cisplatin/CPT—11) were excluded to have a homogenous treatment of the patients.

All other patients (⩽70 years), in WHO PS 0 and 1, medically fit for receiving cisplatin by cardiac and renal function were treated with a different schedule and excluded from this analyses due to the different inclusion criteria, the rareness of risk factors and the potentially

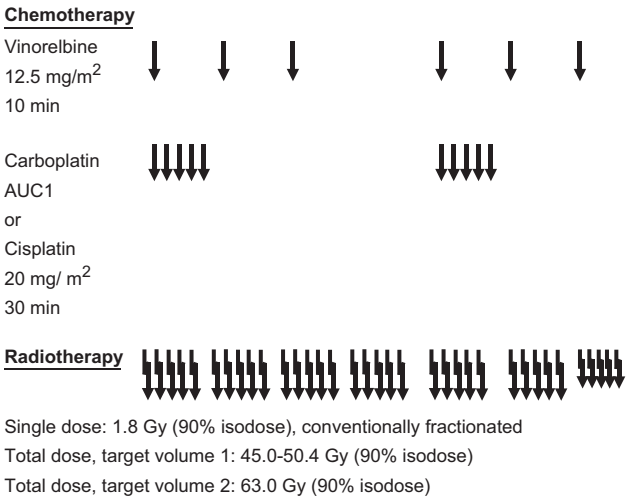

Figure 1 Treatment protocol. Single dose: 1.8 Gy (90% isodose), conventionally fractionated. Total dose, target volume 1: 45.0–50.4 Gy (90% isodose). Total dose, target volume 2: 63.0 Gy (90% isodose).

Table 1 Inclusion criteria.

Poor general health (WHO-PS 2; WHO-PS 3 at patient's request)
OR: Significant pretreatment weight loss: 5% three months prior or 10% six months prior
OR: Compensated renal failure (creatinine clearance 30–60 ml/min)
OR: Prior cardiac disease that inhibits a volume load of more than 2 l (confirmed by a cardiologist), e.g., LVEF <50%, atrial fibrillation, prior myocardial infarction, CHD confirmed by coronary angiography, left or right ventricular dilatation confirmed by echocardiography or grade >1 heart valve defect
OR: Pulmonary dysfunction (FEV_1: <60%, >30%, or VC: <60%, >30%, DLCO <60%, >30% of age-matched normal values)
OR: Age 71–78 years

CHD: coronary heart disease; FEV_1: forced expiratory volume in 1 s; LVEF: left ventricular ejection fraction; DLCO: lung transfer factor for diffusion impairment; VC: vital capacity; WHO-PS: World Health Organization performance status.

different toxicity profile of other concurrent RCT protocols. All cases investigated in this study had been rejected by thoracic surgeons or aesthesiologists as inoperable.

The minimum requirements for lung function, kidney function, WHO performance status and age included: creatinine clearance >30 ml/min, forced expiratory volume in 1 s (FEV_1) $>30\%$, VC $>30\%$, DLCO (lung transfer factor, regarding gas diffusion capacity) $>30\%$ of age-matched normal value, WHO-PS $\geqslant 4$; age <78 years and the usual laboratory parameters. Patients who did not meet these requirements were excluded from any CRT.

All patients were assessed by thoracic and abdominal computed tomography and/or abdominal ultrasound and by bone scintigraphy prior to treatment. Spirometry was performed in 56/66 (85%) of cases, measurement of baseline diffusion capacity in 51/66 (77%), and echocardiography in 54/66 (81%).

Left ventricular ejection fraction (LVEF) was the only parameter of cardiac function used for the analysis. The following parameters of pulmonary function were assessed: vital capacity (VC), FEV_1, and diffusing capacity represented by the lung transfer factor (DLCO) using bodypletysmography (Jaeger-Viasys, Hoechberg, Germany). These variables were measured as values relative to the age-matched normal values for the respective age group, and they were weighted as a correlate of pulmonary function. Cardiac/pulmonary dysfunction was defined using the following threshold values: LVEF $<50\%$ and FEV_1 $<60\%$, VC $<60\%$ or DLCO $<60\%$. Reduced kidney function was defined as creatinine clearance of less than 60 ml/min.

Additional retrospective data on comorbidities were also gathered from available referral letters and medical reports. Comorbidities of interest were diabetes, psychiatric or neurological disorders, and prior incidences of cancer. The patient records were also searched for information regarding alcohol or nicotine abuse. When such information was found, the patient was classified as having a past or present history of alcohol use, when consumption was described as ''daily'' or ''regular'' or ''occasional'' with more than one drink. Smoking abuse was defined in pack years, if any present or former use was mentioned. If no such information was found in the records, the patient's smoking/alcohol abuse status was defined as ''not specified''.

Data on the acute toxicity were collected retrospectively and classified according to CTC-criteria.

The cause of death was ascertained in 49 of 61 (80%) patients who had died by 6/2006 by locating the data in the tumor register or by asking the last attending physician or family doctor by phone. The causes of death could be classified in the following broad etiological categories only: intrathoracic tumor with or without pneumonia or heart failure; metastasis-related, non-tumor-related.

Concurrent chemoradiotherapy

Radiotherapy consisted of conventionally fractionated radiotherapy of the primary tumor and suspicious lymph nodes (>1 cm) at a dose of up to 63 Gy (90% isodose envelope equals ca. 66 Gy reference point dose) and elective irradiation of mediastinal nodes ipsi—and contralateral with up to 45 Gy/50.4 Gy. In patients with upper lobe tumors, the supraclavicular fossa was electively irradiated with up to 45 Gy, or with up to 50.4 Gy in some cases (48 Gy/54 Gy reference point dose). CT planning was performed prior to treatment and was repeated after delivery of 20 Gy in cases of atelectasis or large tumors and after 45 Gy routinely. Three and four-field technique using a 15 MV linac was performed in each case. The mean dose in both lungs was no more than 20 Gy, and the maximum dose to the spinal cord was 44 Gy.

Chemotherapy consisted of two cycles of either carboplatin AUC 1 (up to the year 2000: 70 mg/m^2) or cisplatin 20 mg/m^2 on days 1–5 plus 12.5 mg/m^2 vinorelbine on days 1, 8, 15 in 28-day cycles. Dose modification was accomplished by shifting the time of application (vinorelbine: by a few days, maximum: 7 days; cisplatin/carboplatin: by a whole week). Up to the year 2001, the choice between carboplatin and cisplatin was based on cardiac and renal function reserve parameters; all later patients received carboplatin/vinorelbine, due to the survival data of patients with stage III NSCLC (unpublished data, with a trend of better survival with vinorelbine/carbplatin of 21 months vs. 15 months for vinorelbine/cisplatin). To be eligible to receive the chemotherapy drugs, the patients had to have adequate bone marrow function, which was defined as a peripheral leukocyte count of $>3000\,\mu l^{-1}$ and a peripheral platelet count of $>100{,}000\,\mu l^{-1}$.

In order to compare the intensity and feasibility of chemotherapy and radiotherapy in the different patient subgroups, values were calculated using 90% of the prescribed radiation dose (57 Gy) and 50% of the prescribed cisplatin/carboplatin dose (equals one cycle) plus 60% of the prescribed vinorelbine dose (four vinorelbine infusions) as threshold values.

Statistical analysis

The variables ''organ dysfunction'' and ''age'' were analyzed for the subgroups delineated by the threshold values specified above. Survival was a continuous variable defined as the interval, in months, between the time of diagnosis and the date of death. Survival curves were calculated according to the method of Kaplan–Meier. Log-rank tests were used to compare the curves and test for differences in effects of the individual category variables. Variables that tended to have a one-dimensional effect on survival ($P<0.2$) were analyzed using a multivariate model. Hazard ratios and the 95% confidence interval (CI) were also calculated. The χ^2 test was used to test for differences in the frequency of individual variables between groups.

Results

Demographics and morbidity

The median age of the population was 68 years (range 39–77). Because of the nature of the primary disease and comorbidities, the majority of the patients ($39/66 = 60\%$) were in a poor state of health (WHO performance status 2–3), and many had a history of nicotine/alcohol abuse. Nearly all of the patients had a past or present history of

smoking (58/61 = 95%; not specified: 5), and 27/56 (48%) had a past or present history of regular alcohol consumption (not specified: 10). Significant pretreatment weight loss occurred in 22/66 (33%) of the patients. The predominant types of tumors in the population were locally advanced tumors with mediastinal lymph node involvement, especially stage IIIb tumors (46/66 = 70% of patients). Further patient-related information and data on tumor stage distribution and histological classification are presented in Table 2.

The most common functional organ disorders and concomitant diseases were: pulmonary dysfunction: 25/51 (49%; missing data: 15), myocardial dysfunction (LVEF < 50%): 17/54 (31%, missing data: 12), combined cardiac/pulmonary dysfunction 36/50 (72%, missing data: 16), coronary artery disease with a history of prior infarction or relevant coronary artery stenosis: 17/66 (26%), diabetes mellitus: 13/66 (20%), mild renal insufficiency (creatinine clearance: 30–60 ml/min): 13/66 (20%), and psychiatric or neurological disorders: 11/60 (18%, missing data: 6). In nine cases, NSCLC was the second or third malignant lesion (prior tumors: prostatic carcinoma: $n = 3$, ear–nose–throat tumor: $n = 2$, bladder cancer: $n = 2$, malignant melanoma: $n = 1$, germ cell tumor: $n = 1$, renal cell carcinoma: $n = 1$).

The χ^2 test was used to test for differences between > 70-year-olds and ⩽70-year-olds. The groups did not differ in terms of the frequency of kidney disease (7/24 vs. 6/42; $P = 0.144$), pulmonary dysfunction (9/20 vs. 16/31; $P = 0.645$), myocardial dysfunction (5/18 vs. 12/36; $P = 0.679$), diabetes (6/24 vs. 7/40; $P = 0.470$), or history of cancer (4/22 vs. 5/38; $P = 0.599$), psychiatric or neurological disorders (3/22 vs. 8/38; $P = 0.474$), significant pretreatment weight loss (7/24 vs. 15/42; $P = 0.587$), and poor general health (WHO performance status 2/3) (14/24 vs. 25/42; $P = 0.925$).

Table 2 Patient characteristics.

Number of patients	66
Age (years)	
Median; range	68; 39–77
Sex	
Male	56 = 85%
Female	10 = 15%
WHO performance status	
0 and 1	27 = 40%
2 and 3	39 = 60%
Marital status	
Married	49 (74%)
Unmarried	9 (14%)
Not specified	8 (12%)
Nicotine abuse	
Past and present	58 (88%)
Negative	3 (4%)
Not specified	5 (8%)
Alcohol abuse	
Negative	29 (44%)
Past and present	27 (41%)
Not specified	10 (15%)
Tumor stage	
I and II	8 = 12%
IIIa	12 = 18%
IIIb	46 = 70%
Tumor extent	
T1and T2	20 = 30%
T3	16 = 24%
T4	30 = 46%
N0 and N1	19 = 29%
N2	25 = 38%
N3	22 = 33%
Histology	
Squamous cell carcinoma	41 = 62%
Adenocarcinoma	17 = 26%
Other non-small-cell carcinoma	8 = 12%

Age, morbidity and treatment toxicity

The side effects of treatment were moderate and mostly myelotoxic in nature. Grade 3 or 4 thrombocytopenia occurred in 18/66 (27%) patients, and grade 3 or 4 leukocytopenia in 28/66 (42%). Local toxicity was manageable; 5% of patients developed severe and very severe esophagitis (grade 3: 2, grade 4: 1), and two (3%) developed clinically relevant pneumonia (grade 3). One patient died during treatment without an unequivocally determinable cause of death. A post mortem examination was not declined. The 30-day mortality after completion of treatment was 4/66 (6%). Since there were only sporadic reports of late toxicities, this data was not included in the analysis.

All 66 patients received at least one dose of vinorelbine and one cycle of cisplatin or carboplatin. Sixty-two patients received at least 90% of the prescribed radiotherapy dose, and 41 (62%) of the patients received at least one carboplatin or cisplatin cycle (50% dose level) and four vinorelbine doses (60% dose level).

Advanced age (>70) did not impair the feasibility of radiation therapy. All 24 patients over 70 received more than 90% of the prescribed radiotherapy dose compared to 38/42 (90%) of the younger patients ($P = 0.079$). Only 12/24 (50%) of patients over 70 received at least four doses of vinorelbine and one cycle of cisplatin or carboplatin compared to 29/42 (69%) of the younger patients ($P = 0.125$). In addition, there were significantly higher rates of grade 3–4 thrombocytopenia (11/24 vs. 7/42; $P = 0.010$) and grade 3–4 leukocytopenia (14/24 vs. 14/24; $P = 0.048$) in the patients over 70 than in the younger patients.

Patients with cardiac/pulmonary dysfunction (LVEF < 50%, FEV_1 < 60% or VC < 60% or DLCO < 60%) received 90% of the prescribed radiotherapy dose just as frequently (33/36 vs. 13/14; $P = 0.889$) and received 60% of the vinorelbine dose+50% of the carboplatin or cisplatin dose (21/36 vs. 8/14; $P = 0.939$) just as frequently as patients without cardiac/pulmonary dysfunction. The stage of the disease (stage 1–2 vs. stage 3) also did not affect the frequency of receiving an adequate dose intensity of radiotherapy (8/8 vs. 53/58; $P = 0.388$) or chemotherapy (5/8 vs. 36/58; $P = 0.388$).

A history of alcohol did not affect the feasibility of radiotherapy (26/27 vs. 25/29 patients received an adequate dose; $P = 0.186$), but did decrease the patient's chances of receiving an adequate chemotherapy dose (abstinent: 22/29 vs. positive history of alcohol: 12/27; $P = 0.016$). Patients with a past or present history of alcohol consumption showed a tendency to develop leukocytopenia more often (15/27 vs.10/29; $P = 0.113$), and they developed grade 3–4 thrombocytopenia significantly more often (13/27 vs. 3/29; $P = 0.002$).

Survival

Sixty-one (92%) of the 66 patients had died by the data cut-off date (1 October 2006). The cause of death was determined in 49 cases: intrathoracic tumor with or without pneumonia or heart failure (cardiac dysfunction): 32/61 (53%), death due to metastases to the brain (6/61 = 10%) or liver (2/61 = 3%); in 3/61 (5%) of these patients, death was attributed to both the metastatic and thoracic tumor situation. Six of the 61 patients (10%) died of causes unrelated to cancer. Four of them (7%) died of heart failure and one of cerebral ischemia; the sixth patient committed suicide.

Cumulative median survival for the overall population was 13.0 months (95% CI: 10.6 months; 15.4 months). The 1, 2, 3 and 5-year survival rates were 53% (S.D. ±6.1%), 21.2% (±5.0%), 11.9% (±4.0%) and 6.8% (±3.2%), respectively.

Univariate and multivariate analyses were performed to determine the effect of various tumor and patient-related variables on survival. The univariate analysis showed a significant impact of pretreatment cardiac dysfunction, which was defined as a decreased left ventricular ejection fraction, on survival ($P = 0.02$ by log-rank test; HR = 1.97, 95% CI of HR: 1.07–3.63).

Gender, age, marital status, WHO performance status, pretreatment weight loss, tumor stage and histological classification, and other concomitant diseases did not exhibit any significant correlation. Table 3 shows the data for median survival (with 95% confidence interval), 1-year survival, 2-year survival (±standard deviation) and the corresponding *P*-values, as calculated using the log-rank test.

The multivariate analysis was used to assess data that the univariate analysis identified as showing statistical trends ($P < 0.20$). Because of the low number of patients in the individual groups, cardiac dysfunction and pulmonary dysfunction were combined as a single group, as were the UICC tumor stages. In this analysis, the presence of cardiac/pulmonary dysfunction vs. the absence of cardiac/

Table 3 Univariate analysis of potential prognostic factors for survival following concurrent chemoradiation for treatment of inoperable bronchial carcinomas.

Parameter	Median survival	One-year survival	Two-year survival	*P*-value
Sex				
Male: $N = 56$	13 mos (11;15)	53.6%±06.7%	19.6%±05.3%	0.559
Female: $N = 10$	07 mos (00;30)	50.0%±15.8%	30.0%±14.5%	
Age				
$\leqslant$70 years: $N = 42$	15 mos (10;20)	57.1%±07.6%	23.8%±06.6%	0.424
>70 years: $N = 24$	12 mos (08;16)	45.8%±10.2%	16.7%±07.6%	
Marital status				
Married: $N = 49$	14 mos (11;17)	55.1%±07.1%	22.4%±06.0%	0.821
Unmarried: $N = 9$	23 mos (4;42)	55.6%±16.6%	22.2%±13.9%	
WHO performance status				
0/1: $N = 27$	15 mos (12;18)	59.3%±09.5%	11.1%±06.0%	0.687
2/3: N = 39	12 mos (09;15)	48.7%±08.0%	38.5%±07.8%	
Pretreatment weight loss				
Positive: $N = 22$	13 mos (07;19)	54.5%±10.6%	36.4%±10.3%	0.218
Negative: $N = 44$	13 mos (10;16)	52.3%±07.5%	13.6%±05.2%	
Histology				
Squamous cell carcinoma: $N = 41$	14 mos (11;17)	56.1%±07.8%	24.4%±06.7%	0.570
Adenocarcinoma: $N = 17$	12 mos (09;15)	41.2%±11.9%	11.8%±07.8%	
Nicotine abuse				
Negative: $N = 3$	Not applicable			
Past and present: $N = 58$	13 mos (11;15)	53.4%±06.5%	19.0%±05.1%	
Alcohol abuse				
Negative: $N = 29$	15 mos (12;18)	58.6%±09.1%	31.0%±08.6%	0.050
Past and present: $N = 27$	12 mos (05;19)	48.1%±09.6%	14.8%±06.8%	

Table 3 (*continued*)

Parameter	Median survival	One-year survival	Two-year survival	*P*-value
Tumor stage				
I and II: $N = 8$	19 mos (00;40)	75.0%±15.3%	50.0%±17.7%	0.112
III: $N = 58$	12 mos (09;15)	50.0%±06.6%	17.2%±05.0%	
IIIa: $N = 12$	13 mos (03;22)	58.3%±14.2%	0%	0.648
IIIb: $N = 46$	12 mos (10;15)	47.8%±07.4%	21.7%±06.1%	
T1, T2: $N = 20$	19 mos (06;32)	75.0%±09.7%	25.0%±09.7%	0.239
T3, T4: $N = 46$	12 mos (09;14)	43.5%±07.3%	19.6%±05.8%	
N0, N1, N2: $N = 44$	14 mos (09;19)	56.8%±07.5%	25.0%±06.5%	0.072
N3: $N = 22$	12 mos (09;15)	45.4%±10.6%	13.6%±07.3%	
Chemotherapy				
Carboplatin/vinorelbine: $N = 59$	14 mos (10;16)	59.3%±06.4%	23.7%±05.5%	0.386
Cisplatin/vinorelbine: $N = 7$	17 mos (04;30)	57.1%±18.7%	28.6%±17.1%	
Pulmonary dysfunction ($FEV_1 < 60\%$ or $VC < 60\%$ or $DLCO < 60\%$)				
Positive: $N = 25$	9 mos (06;12)	28.0%±09.0%	16.0%±07.3%	0.121
Negative: $N = 26$	15 mos (12;18)	69.2%±09.1%	15.4%±07.1%	
Cardiac dysfunction ($LVEF < 50\%$)				
Positive: $N = 17$	12 mos (08;16)	35.3.6%±11.6%	05.9%±05.7%	0.022
Negative: $N = 37$	15 mos (09;20)	59.5%±08.1%	24.3%±07.1%	
Cardiac or pulmonary dysfunction ($LVEF < 50\%$ or $FEV_1 < 60\%$ or $VC < 60\%$ or $DLCO < 60\%$)				
Positive: $N = 36$	11 mos (08;14)	36.1%±8.0%	11.1%±05.2%	0.074
Negative: $N = 14$	21 mos (15;26)	71.4%±12.1%	21.4%±11.0%	
Renal dysfunction				
Positive: $N = 13$	16 mos (01;31)	53.8%±13.8%	30.8%±12.8%	0.863
Negative: $N = 53$	13 mos (11;15)	52.8%±06.9%	18.9%±05.4%	
Diabetes				
Positive: $N = 13$	16 mos (09;16)	69.2%±12.8%	15.4%±10.0%	0.943
Negative: $N = 51$	12 mos (12;20)	49.0%±07.0%	21.6%±05.8%	
Prior malignant disease				
Negative: $N = 9$	13 mos (10;16)	51.0%±07.0%	19.6%±05.6%	0.452
Positive: $N = 51$	23 mos (0;46)	77.8%±13.9%	33.3%±15.7%	
Psychiatric or neurological disorders				
Negative: $N = 49$	14 mos (11;17)	51.0%±07.1%	22.4%±06.0%	0.900
Positive: $N = 11$	13 mos (11;15)	63.6%±14.5%	18.2%±11.6%	

FEV_1: forced expiratory volume in 1 s; mos: months; DLCO: lung transfer factor; VC: vital capacity.

pulmonary dysfunction was the only independent prognostic parameter for survival (Table 4). Patients with cardiac/pulmonary dysfunction had significantly poorer survival rates than those without cardiac/pulmonary dysfunction (adjusted HR = 2.185, $P = 0.039$, 95% CI for HR: 1.039–4.594) (Figure 2).

Discussion

This analysis suggests that in this population cardiac or pulmonary dysfunction may have an impact on the prognosis of patients with inoperable NSCLC. Until today, objective cardiac/pulmonary dysfunction has rarely been regarded in clinical trials or in treatment guidelines. Patients with cardiac/pulmonary dysfunction are generally excluded from clinical trials in order to ensure proper interpretation of results or to protect patients with such organ dysfunctions from potentially hazardous side effects.

In routine clinical practice, patients are most often excluded from concurrent CRT for three reasons: advanced age, poor health status and comorbidities, which are weighted differently by different clinicians mainly based on individual experience. Our present work might aid in the assessment of these frequent yet critical patients. Elderly individuals and those with concomitant diseases are

Table 4 Multivariate Cox regression analysis of potential prognostic factors following concurrent chemoradiation for treatment of inoperable bronchial carcinomas.

Parameter	*P*-value	Adjusted hazard ratio	95% Confidence interval
Alcohol consumption			
Past/present vs. abstinent*	0.068	1.812	0.957–3.431
Tumor stage			
UICC III vs. UICC I and II*	0.148	2.219	0.755–6.525
Cardiac/pulmonary dysfunction			
$FEV_1 < 60\%$ or $VC < 60\%$ or $DLCO < 60\%$ or $LVEF < 50\%$ vs. $FEV_1 \geqslant 60\%$ and $VC \geqslant 60\%$ and $LVEF \geqslant 50\%$*	0.039	2.185	1.039–4.594

FEV_1: forced expiratory volume in 1 s; mos: months; DLCO: lung transfer factor; UICC: International Union Against Cancer; VC: vital capacity.
*Reference.

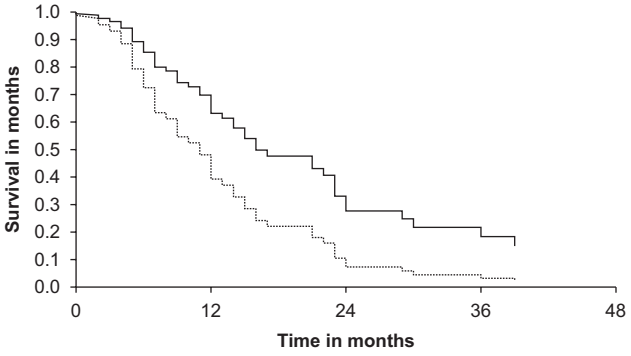

Figure 2 Overall survival curves (%) according to cardiac/pulmonary dysfunction. Solid line: $FEV_1 \geqslant 60\%$ and $VC \geqslant 60\%$ and $DLCO \geqslant 60\%$ and $LVEF \geqslant 50\%$. Dotted line: $FEV_1 < 60\%$ or $VC < 60\%$ or $DLCO < 60\%$ or $LVEF < 50\%$.

generally classified as those with a poor performance. The percentage of >70-year-olds in our study population was 36% and the median age was 68 years. So compared to other clinical trials investigating the efficacy of concurrent CRT for optimization of treatment for patients with inoperable NSCLC[1,3] it was 14 to 4 years higher. The French NPC 95-01 trial[3] excluded all patients over 70 years. In addition, the patients in previous trials tended to be in a good to very good state of general health. Although the Japanese[1] and Czech studies[4] did include some patients with WHO performance status 2, the percentage of these patients was marginal (5–10%). Firat et al.[12] found in their systematic analysis that many investigators assume that old age alone implies an inability to tolerate chemoradiation and that, consequently, these patients received concurrent CRT less often than other cancer patients, even through age is not an independent factor for survival.

Age is indisputably the most comparable parameter in all studies. Our retrospective analysis shows no indication that the >70-year-olds in the population had a poorer survival because of advanced age alone. These results differ from those of the "recursive partitioning analysis" performed by the Radiation Therapy Oncology Group (RTOG) in 1999, a retrospective analysis of data from clinical trials performed from 1983 to 1994. Radiation therapy was the predominant form of treatment in these patients with locally advanced NSCLC.[13] Most of the >70-years-olds in the RTOG analysis had a poorer prognosis than the younger patients. Other unfavorable factors were: large-cell tissue components, malignant pleural effusion, and a low Karnofsky performance status (<90%).[13] At the same time, we infer that the recruited patients were in good general condition. In a later retrospective analysis in which the RTOG excluded some of its earlier treatment escalation studies (RTOG 88-4, RTOG 83-21), age over 70 did not appear as a negative factor.[14] Movsas et al.[14] also analyzed the effect of old age on survival of NSCLC patients who received intensified treatment. Their analysis shows that 71-year-old patients also reached the longest survival time after concurrent CRT as well as after standard radiotherapy (14.1 vs. 13.1 months). However, only a very small number of patients received concurrent CRT in this study. Considering the questionable information value of these studies, more recent phase II trials and case studies provide more valid data on this patient subgroup. In the RTOG 94-10 study, for example, a subgroup analysis showed that "fit elderly patients" had even better survival rates than younger patients.[15] Schild et al.[16] showed that patients of 70 years and older achieve comparable median survival rates after concurrent radiation and chemotherapy with etoposide and cisplatin vs. hyperfractionated radiation therapy. This is in agreement with Atagi et al.[17] who found that concurrent radiation and daily low-dose carboplatin can be successfully applied in >75-year-olds, with the predominant dose-limiting toxicity being hematotoxicity. Although the >70-year-olds in our study population were not healthier than the patients under 70, our results still support this change in mindset towards age. When treating elderly patients, one must consider that there are more limitations on dose adjustment of cytostatic drugs in these patients, and that they have higher rates of thrombo- and leukocytopenia which, in most cases, did not result in a decreased dose of chemotherapy for the selected drug combinations and doses. However, this also implies that there are limitations and hazards during and immediately after concurrent CRT.

Tumor-associated parameters and other factors, especially those involving organ function or functional deficits due to habitual intoxication, had a greater impact on survival than age.

In previous studies, comorbidities have been mainly analyzed using comorbidity scores. The advantage of scoring systems is that they can paint an overall picture of the patient's health status by rating target parameters items using graduated scales. Investigators using the Cumulative Illness Rating Scale for Geriatrics (CIRSG) determined that concurrent CRT correlated with poorer survival more than radiotherapy alone in patients with high CIRSG scores.[12] Other scoring systems, such as the Charlson Index, did not show any reproducible correlation.[18] These findings are ambivalent, especially since the scoring systems cannot be tested prospectively using stratification instruments. The use of an overall score is problematic when the side effects of treatment are less global in nature, but are more organ-related.

A number of parameters commonly used for scoring of concomitant diseases did not exhibit any effect on survival in our retrospective analysis. We did not find any evidence that diabetes, controlled prior malignant diseases or kidney failure had a negative effect on survival provided that potential complications were considered when selecting carboplatin or cisplatin for chemotherapy.

On the other hand, pretreatment cardiac and pulmonary dysfunction had an independent significant effect. Nevertheless one must be aware of the fact, that the small number of patients and the retrospective character of the analysis are limitations of our study. Therefore, the results of our study should be considered as an advice to investigate these parameters in further prospective trials. The main objective of our study was to investigate easily available, objective and reproducible pathophysiological parameters, describing the broad spectrum of comorbidies. In contrast to previous results[12] patients with weight loss and low performance status or stage III showed only a tendency to have a reduced survival rate but the missing significance may also be an effect of the small patient number.

The reason why patients with pulmonary or cardiac risk factors have a poorer prognosis remains an open question. Three hypotheses have been proposed:

- Patients with myocardial dysfunction have, a priori, a poor prognosis. Mortality rates of 16% within a 6-month period in patients with a decreased ejection fraction have been reported.[19] The same is true for COPD, although mortality rates may be lower.[20]
- Myocardial dysfunction and pulmonary dysfunction impair the feasibility of CRT in that they necessitate a reduction of dose intensity. Our data do not support this hypothesis.
- In the long term, intensified treatment (concurrent radiochemotherapy) could lead to disproportionate exacerbations of existing myocardial and pulmonary disorders causing patients to die sooner than from the natural course of the disease. A definitive answer to these questions requires further analysis.

An association between radiotherapy and myocardial fibrosis, valvular lesions and pericarditis has been reported.[21,22] Little data is available concerning their temporal relationship. Results of epidemiological long-term toxicity studies of cardiac mortality following radiation therapy have been published for Hodgkin's disease,[23] breast cancer,[24] and childhood cancer[25]; evidence of significant cardiac mortality and mortality following radiotherapy for breast cancer was found. However, this situation is not comparable to our present study where most of the NSCLC patients had normal cardiac function at the beginning of treatment, the irradiated ventricular volume was small, and the total radiation doses were lower. In patients with breast cancer, on the other hand, anthracyclines are frequently used. Patients with esophageal cancer have a comparable prognosis and a similar cardiac status. Ishikura et al.[26] observed lethal myocardial infarction in 3% of their esophageal cancer patients, 2% of whom had clinically manifest pneumonia or heart failure, respectively, and 8% of whom had symptomatic pericarditis. Short- and medium-term cardiac side effects can be characterized according to the CTC and LENT classifications, which attract little interest up to now considering that most of the patients have tumor recurrences.

Apart from cardiac toxicity, little is known about pulmonary compensation potentials following radiotherapy, e.g., secondary increase in right ventricular afterload due to impairment of the pulmonary flow bed, tumor-related necrosis, interstitial fibrosis, or hypoxygenation due to extension of the diffusion pathway in conjunction with frequency stress. This information is speculative. Still, the expectation of long-term survival in the patients is associated with a risk of cardiopulmonary morbidity and impaired quality of life. Consequently, further research on this subject must be performed.

The next question is, ''What are the consequences for treatment?'' In NSCLC patients with myocardial or pulmonary dysfunction, median survival following concurrent CRT is at least as good as that achieved with radiotherapy alone (see review by Fietkau[11]). One can therefore assume that concurrent CRT does, at least, not cause additional harm to patients. There is still the question of whether concurrent CRT could be improved by reducing the irradiation volume or by changing the irradiation technique (to protect the irradiated heart volume). Furthermore, age-adjusted selection and administration of the chemotherapy drugs is essential. Inversely, we observed that patients with good cardiopulmonary function had a prognosis that was virtually the same as that of patients with surgically treated stage III NSCLC.

Conclusions

Elderly patients and patients with multiple comorbidities tolerate concurrent CRT, and age was not associated with increased treatment-related morbidity or a poorer prognosis. However, the incidence of significant hematotoxicity has higher in these patients.

Cardiac/pulmonary dysfunction may be an independent prognostic parameter in patients with concomitant diseases. Considering the frequency of occurrence of these impairments, further investigation in epidemiological and morphological cross-sectional and longitudinal studies is required.

Conflict of interest

The authors hereby declare that they have no financial or personal interests or relations with the manufacturers of the drugs and medical devices used in this study.

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