How Do Elderly Poor Prognosis Patients Tolerate Palliative Concurrent Chemoradiotherapy for Locally Advanced Non–Small-Cell Lung Cancer Stage III? A Subset Analysis From a Clinical Phase III Trial☆

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Abstract

In a phase III trial of patients with unresectable stage III non–small-cell lung cancer and a poor prognosis, palliative concurrent chemoradiotherapy (CRT) provided a significantly better outcome than chemotherapy alone, except among performance status 2 patients. The results of the present exploratory subgroup analysis indicate that elderly patients with poor prognosis can also experience health-related quality of life and survival benefits from CRT, provided the treatment modalities have been adapted to a palliative setting.

Background: In a phase III trial of patients with unresectable, locally advanced, stage III non–small-cell lung cancer (NSCLC) with a poor prognosis, palliative concurrent chemoradiotherapy (CRT) provided a significantly better outcome than chemotherapy alone, except among performance status (PS) 2 patients. In the present subgroup analysis, we evaluated the effect on patients aged $\geq$ 70 years (42% of all included) compared with patients aged $<$ 70 years enrolled in the trial. **Patients and Methods:** All patients received 4 courses of intravenous carboplatin and oral vinorelbine. The experimental arm also received radiotherapy (42 Gy in 15 fractions). The included patients were required to have large tumors ($>$ 8 cm), weight loss ($>$ 10% within the previous 6 months) and/or PS 2. **Results:** The overall survival was increased among the CRT patients in both age groups, but the difference was significant only in patients aged $<$ 70 years (median survival, 14.8 vs. 9.7 months; $P = .001$; age $\geq$ 70 years, median survival, 10.2 vs. 9.1 months; $P = .09$). Patients aged $\geq$ 70 years experienced better preserved health-related quality of life (QOL) and significantly less hematologic toxicity. The 2- and 3-year survival was significantly increased in both age groups receiving CRT. **Conclusion:** Elderly patients aged $\geq$ 70 years with unresectable, stage III, locally advanced, NSLCL and a poor prognosis can tolerate CRT with the doses adjusted to age and palliative intent. These results indicate that CRT can provide both survival and QOL benefits in elderly patients, except for those with PS 2 or worse. The male predominance in the $\geq$ 70-year-age group and the reduced chemotherapy intensity for the patients aged $>$ 75 years might explain the lack of significant survival improvement among those patients aged $\geq$ 70 years.

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Introduction

Among the approximately 2900 Norwegians annually diagnosed with lung cancer, the median age at diagnosis is 70 years, regardless of stage.[1-3] Advanced age has often been associated with a poor performance status (PS) and comorbidities. Elderly patients with lung cancer have been significantly underrepresented in clinical trials,[4] and advanced age has been a prevalent reason for not administering treatment according to the guidelines.[5,6] Despite the clear survival benefits, most elderly patients with advanced non–small-cell lung cancer (NSCLC) have been undertreated or do not receive chemotherapy.[7,8]

Several explanations can be found. First, elderly patients with locally advanced (LA)-NSCLC will experience more toxicity and side effects from combination chemotherapy and chemo-radiotherapy than will younger patients.[9] Second, physicians might be reluctant to offer treatment known to give troublesome side effects owing to the unwarranted assumption that elderly patients will not benefit from cytotoxic therapy.[10,11] Trials that have included elderly patients, and even more so, elderly patients with a poor prognosis and unresectable, stage III LA-NSCLC, have been lacking. The treatment recommendations for this group have often conflicted. Some investigators have questioned the indications for concomitant chemoradiotherapy (CRT),[12,13] and others have recommend CRT only for patients with a good performance status (PS).[14] Some have simply considered patient age $\geq$ 75 years a contraindication for CRT.[15] An additional problem has been that few of the existing trials concerning this patient group have adhered to the standard treatment of unresectable stage III LA-NSCLC.[11,13] It has been tenaciously argued that clinical trials of treatment in older populations are necessary.[8,16]

It should be possible to adjust the therapies and doses to the patient's age and physical condition and, thus, still offer older patients a meaningful treatment regimen. Palliative radiation doses might alleviate symptoms, with resultant local control, and the generalized cytotoxicity from adjusted chemotherapy doses might delay the development of metastases. In a recently published study, Temel et al[17] concluded that patients receiving early palliative care for NSCLC were in need of less aggressive care at the end of life and had longer survival. Therefore, additional research on palliative treatment using CRT has been recommended, especially including symptoms and validated health-related quality of life (HRQoL) data as outcomes.[18]

We conducted a national phase III trial, comparing palliative concurrent CRT and palliative chemotherapy alone in patients with nonresectable LA-NSCLC and a poor prognosis.[19] Age was not an exclusion criterion, and 42% of the randomized patients were aged $\geq$ 70 years and 22% were aged $\geq$ 75 years. Because limited treatment outcome data have been available for elderly patients with lung cancer, we present the data from a subset analysis that focused on the efficacy, toxicity, and HRQoL in elderly patients included in the phase III trial.

Patients and Methods

The Conrad study was an open, multicenter, phase III trial comparing the efficacy and safety of palliative chemotherapy versus palliative CRT in patients with stage III NSCLC and a poor prognosis.[19] The chemotherapy regimen consisted of 4 courses of oral vinorelbine 60 mg/m^2 on day 1 and 8 and intravenous carboplatin (area under the curve, 5; Calvert's formula) on day 1, administered every 3 weeks. Patients aged > 75 years received 75% of the full dose. The patients in the experimental arm received, in addition, thoracic radiotherapy with 42 Gy in 15 fractions between the second and third chemotherapy course. This regimen has been the standard palliative approach in Norway since the 1980s.[20] The treatment and dosimetry planning were conducted according to the participating institutions' protocols.

Patients with nonresectable stage III LA-NSCLC and negative prognostic factors were eligible, if they were not candidates for radical radiotherapy (> 60 Gy) and had not received previous chemotherapy. The cancer was staged according to the American Joint Committee on Cancer, 7th edition.[21] PS 2, weight loss (> 10% within the previous 6 months), and a large tumor mass ($\geq$ 8 cm) were considered negative prognostic factors. Only thoracic and upper abdominal computed tomography (CT) imaging was mandatory, and verified malignant pleural effusion was an exclusion criterion. Positron emission tomography (PET)-CT was not widely available in Norway during the enrollment period.

The Regional Ethics Committee of North Norway approved the Conrad study, and all patients provided written informed consent before study participation. The details of the original study have been previously published.[19]

Response Assessment

The primary endpoint of the Conrad study was overall survival. The secondary endpoints were the interval to progression, HRQoL, and treatment toxicity. Questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC) regarding HRQoL were distributed to the patients at randomization, at every chemotherapy course, and every 8 weeks after treatment completion.[22] Before each chemotherapy course, blood samples and information about esophagitis were obtained. A summary of the chemotherapy and radiation administered was provided for each patient by all the participating centers. The PS and disease status were recorded at all follow-up visits (weeks 12, 20, 28, 36, 44, and 52). Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

Definition of the Elderly Subgroup and Study Aims

In accordance with common practice, we defined the elderly as patients aged $\geq$ 70 years.[4,13,23-25] Age was a stratification factor specified in the original protocol. The aims of the present analysis were to (1) explore the efficacy and safety of palliative CRT in elderly patients (aged $\geq$ 70 years) with nonresectable LA-NSCLC and a poor prognosis enrolled in a phase III study setting and (2) compare the results with those of younger patients. Age was treated as a binary variable in all analyses.

Statistical Analysis

Overall survival and the interval to progression were compared using the Kaplan-Meier method and the log-rank test, using the intention to treat. The date of death was chosen as the date of progression if no other information on progression was available. On multivariate analysis, the estimation and 95% confidence interval (CI) of the hazard ratio (HR) were calculated using a Cox

proportional hazard model that included age, gender, weight loss, tumor size, PS, and cancer stage. Not to lose information, age and tumor size were not dichotomized in the present analysis.

The chi-square test and the Fisher exact test, in the Statistical Package for Social Sciences, were used to compare the patient characteristics and evaluate the treatment-related differences between the patient groups. P values $< .05$ were considered statistically significant. The PS was compared using analysis of variance (ANOVA) and the nonparametric Mann-Whitney U test.

The responses to the EORTC questionnaires were analyzed according to the EORTC scoring manuals.[26] The changes in the mean score relative to time were calculated by subtracting the baseline score, and a difference of ≥ 10 points was considered clinically relevant. Repeated ANOVA measures were used to analyze the HRQoL changes over time. The nonparametric Mann-Whitney U test was used to compare the scores. A higher score for the symptom domains indicated more pronounced symptoms, but a higher score for the functional domains indicated better function.

Results

Patients and Study Treatment

From November 2006 to November 2011, 191 patients were included from 25 hospitals in Norway. The characteristics of the 188 eligible patients are presented in Table 1. Of the 191 patients, 3 were excluded; 1 had stage IV disease, 1 had synchronous lung and uterine cancer, and 1 had a neuroendocrine tumor. Significantly more men than women were included among the patients aged ≥ 70 years receiving CRT compared with the corresponding group who was < 70 years old. Stage IIIB was predominant in the youngest patient group, regardless of treatment, and stage IIIA was predominant among the oldest. The difference with respect to stage was statistically significant for patients receiving CRT. Apart from these findings, no statistically significant differences were found in the clinical features between the two age groups.

Survival

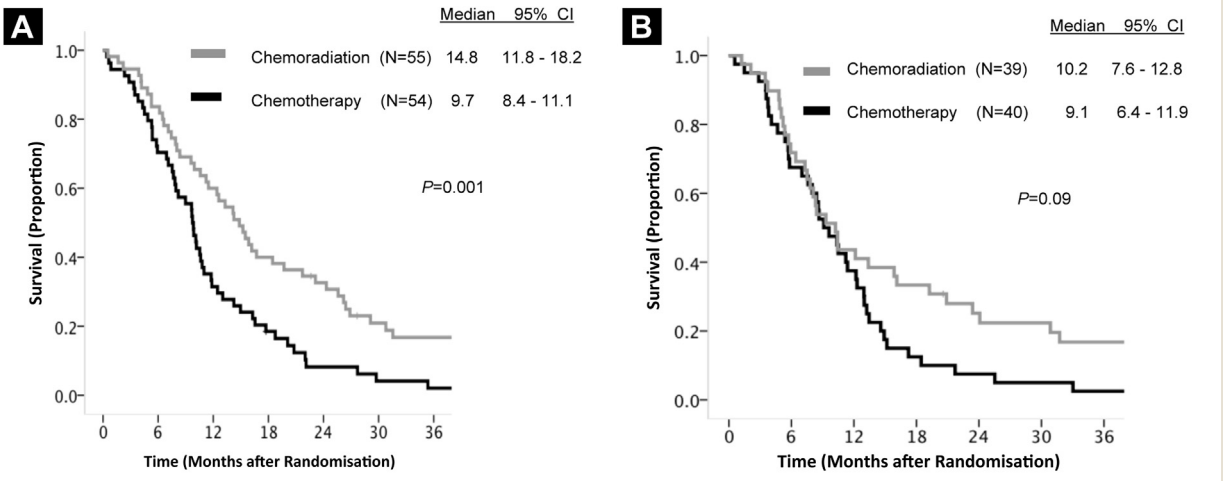
The overall survival increased for both age groups among patients receiving CRT, but the improvement was statistically significant only for the patients aged < 70 years (Figure 1A,B). The 2- and 3-year survival was significantly increased in both age groups receiving CRT (Figure 1C). Among the elderly with PS 2, no difference was seen in survival between the two treatment arms (n = 19; chemotherapy, 7.9 months; CRT, 7.8 months; $P = .64$). On multivariate analysis of age, gender, weight loss, tumor size, PS, and stage, PS was the only clinical factor with a significant effect

Table 1 Patient Characteristics Stratified by Age and Treatment

Characteristic	Age < 70 Years (n = 109)			Age ≥ 70 Years (n = 79)			
	Chemotherapy	CRT	*2P* Value[a]	Chemotherapy	CRT	*2P* Value[a]	*2P* Value[b]
Age (years)							
Median	62	63		75	76		
Range	48-69	53-69		70-88	70-85		
Gender			NS			NS	.03
Male	34 (63)	30 (55)		25 (63)	30 (77)		
Female	20 (37)	25 (46)		15 (37)	9 (23)		
Performance status			NS			NS	NS
0-1	44 (82)	44 (80)		31 (78)	29 (75)		
2	10 (18)	11 (20)		9 (22)	10 (24)		
Tumor size (cm)			NS			NS	NS
<8	30 (56)	22 (40)		19 (47)	16 (41)		
≥8	24 (44)	33 (60)		21 (53)	23 (59)		
Weight loss (%)			NS			NS	NS
<10	36 (67)	34 (62)		27 (68)	21 (54)		
≥10	18 (33)	21 (38)		13 (32)	18 (46)		
Stage			NS			NS	.03
IIIA	24 (44)	18 (33)		22 (55)	22 (56)		
IIIB	30 (56)	37 (67)		18 (45)	17 (44)		
Histologic type			NS			NS	NS
Squamous cell carcinoma	17 (31)	26 (47)		19 (47)	20 (51)		
Adenocarcinoma	22 (41)	17 (31)		9 (23)	14 (36)		
Large cell carcinoma	3 (5.6)	1 (1.8)		1 (2.5)	0		
Other	12 (22)	11 (20)		11 (27)	5 (13)		

Data presented n (%).
Abbreviations: CRT = chemoradiotherapy; NS = nonsignificant.
[a]Fisher's 2-sided P value for testing the null hypothesis of no difference between patients receiving chemotherapy or CRT.
[b]Fisher's 2-sided P value for testing the null hypothesis of no difference between the 2 age groups receiving CRT.

Figure 1 Overall Survival for (A) Patients Aged < 70 Years and (B) Patients Aged ≥ 70 Years. (C) Survival at 1, 2 and 3 Years According to Age and Treatment. (D) Performance Status According to Age Group, Registered Through the First Year

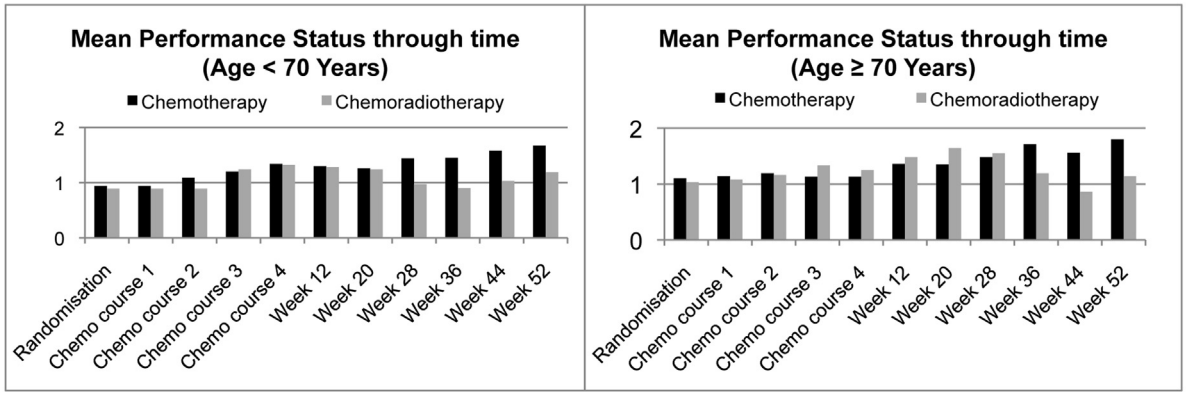


C

	Patients < 70 years			Patients ≥ 70 years		
	Chemo	CRT	*P*	Chemo	CRT	*P*
	N=55	N=54		N=39	N=40	
1-year survival (%)	31.5	60.0	0.003	37.5	43.6	NS
2-years survival (%)	7.4	32.7	0.001	7.5	25.6	0.04
3-years survival (%)	1.9	16.4	0.016	2.5	17.9	0.03

P: Fisher's two-sided P value for testing the null hypothesis of no difference between patients receiving chemotherapy or CRT. NS = Non Significant.

D



Abbreviations: Chemo = chemotherapy; CI = confidence interval; CRT = chemoradiotherapy.

on survival (HR, 1.86 for PS 0-1 vs. PS 2; 95% CI, 1.26-2.72; $P = .002$).

Treatment Discontinuation and Toxicities

The mean number of completed chemotherapy cycles ranged from 3.5 to 3.6 in all 4 groups (Table 2). Chemotherapy discontinuation because of disease progression was more prevalent among the younger patients receiving chemotherapy only. A similar discontinuation rate was not observed among patients aged ≥ 70 years. In the CRT group aged < 70 years, the mean number of radiation fractions received was 14.6. For patients aged ≥ 70 years, it was 12.3.

No overall differences were seen in hematologic toxicities between the two treatment modalities (Table 3), except for a greater incidence of thrombocytopenia among the younger patients receiving CRT. Comparing the two age groups receiving CRT, we found significantly fewer hematologic toxicities and fewer infections related to neutropenia among the elderly. Esophagitis was less prominent among the elderly receiving CRT than among the younger patients, but the difference was not significant.

HRQoL and PS

Of the 188 patients, 186 (99%) completed the HRQoL questionnaire at randomization. The median percentage of completed questionnaires in the first 6 months after randomization ranged from 84% to 86% in all groups, declining to a range of 67% to 75% during the final 6 months of the observation period.

To provide an adequate and clinically useful HRQoL assessment of the two different treatment regimens, we chose to report three functional (global QoL, physical function, and social function) and four symptom (dysphagia, fatigue, pain, and dyspnea) domains (Figure 2).[27] The null hypothesis was that the variations in QoL over time would be similar in the two age groups, depending on the treatment. No significant difference was found in the mean score between the age groups at baseline.

Among the patients receiving CRT, the variations in the functional scores for patients aged ≥ 70 years were less pronounced

Table 2 Administered Therapy and Reasons for Discontinuation

Variable	Age < 70 Years			Age ≥ 70 Years			
	Chemotherapy (n = 54)	CRT (n = 55)	*2P* Value[a]	Chemotherapy (n = 40)	CRT (n = 39)	*2P* Value[a]	*2P* Value[b]
Chemotherapy							
Cycles (n)							
0	0	1 (1.8)		0	0		
1	3 (5.6)	1 (1.8)		1 (1.8)	1 (1.8)		
2	4 (7.4)	3 (5.5)		4 (10)	8 (21)		
3	7 (13)	6 (11)		4 (10)	1 (2.6)		
4	40 (74)	44 (80)		31 (78)	29 (74)		
Discontinued							
Disease progression	11	2	.008	3	2	NS	
Unacceptable toxicity	1	7	NS	3	3	NS	
Intercurrent disease	3	2	NS	2	1	NS	
Patient request	1	3	NS	2	2	NS	
Other	2	5	NS	2	2	NS	
Radiotherapy							
Fractions (n)							NS
0		1 (1.8)			3 (7.7)		
1-6		0			2 (5.2)		
10-14		3 (5.4)			1 (2.6)		
15		51 (93)			33 (83)		
Mean		14.6			12.3		
Discontinued							
Disease progression		4			2		NS
Unacceptable toxicity		1			1		NS
Intercurrent disease		0			0		NS
Patient request		0			0		NS
Other		3			4		NS

Data presented as n (%).
Abbreviations: CRT = chemoradiotherapy; NS = nonsignificant.
[a]Fisher's 2-sided *P* value for testing the null hypothesis of no difference between patients receiving chemotherapy only or CRT.
[b]Fisher's 2-sided *P* value for testing the null hypothesis of no difference between the 2 age groups receiving CRT.

Table 3 Toxicity According to Age and Treatment

Toxicity	Age < 70 Years			Age ≥ 70 Years			*P* Value[b]
	Chemotherapy	CRT	*2P* Value[a]	Chemotherapy	CRT	*2P* Value[a]	
Anemia (183 valid cases)			NS			NS	
Grade 3	5 (9.8)	4 (7.4)		0	1 (2.6)		
Grade 4	0	0		0	0		
Neutropenia (183 valid cases)			NS			NS	<.05
Grade 3	14 (28)	14 (26)		7 (18)	4 (11)		
Grade 4	7 (14)	17 (32)		7 (18)	6 (16)		
Thrombocytopenia (183 valid cases)			<.05			NS	<.05
Grade 3	3 (5.9)	6 (11)		0	0		
Grade 4	1 (2.0)	3 (5.6)		0	0		
Infections in relation to leukopenia (170 valid cases)			NS			NS	<.05
1	11 (23)	16 (35)		5 (13)	7 (18)		
2	1 (2.1)	4 (98)		0	0		
3	0	0		1 (2.6)	0		
Hospital admissions in relation to side effects (170 valid cases)			NS			<.01	NS
1	14 (30)	20 (43)		4 (10)	13 (35)		
2	3 (6.4)	5 (11)		1 (2.6)	4 (11)		
3	0	3 (6.4)		1 (2.6)	0		
Esophagitis in relation to RT (157 valid cases)			<.01			<.01	NS
Grade 1	3 (7.9)	8 (15)		1 (3.4)	8 (21)		
Grade 2	1 (2.6)	19 (37)		3 (10)	16 (42)		
Grade 3	1 (2.6)	20 (39)		0	7 (18)		
Grade 4	0	0 (0)		0	0 (0)		

Data presented as n (%).
Abbreviations: CRT = chemoradiotherapy; NS = nonsignificant; RT = radiotherapy.
[a]Fisher's 2-sided *P* value for testing null hypothesis of no difference in parameter distribution between patients receiving chemotherapy or CRT.
[b]Fisher's 2-sided *P* value for testing null hypothesis of no difference in parameter distribution between the two age groups receiving CRT.

than were the variations among the younger patients. Regardless of age, the scores indicated that the functional domains were best preserved among the patients receiving CRT. The patients receiving only chemotherapy experienced a gradual decline in all functions during the whole observation period, which were most pronounced and clinically relevant among the elderly.

Compared with the patients receiving chemotherapy alone, dysphagia was significantly increased among the CRT patients during the treatment period, regardless of age. However, this symptom was most pronounced among the younger patients. Regarding fatigue and dyspnea, the scores indicated no difference between the groups, before the latter part of the observational period. In the latter study period, the patients aged ≥ 70 years receiving only chemotherapy reported more clinically relevant symptoms than did the CRT patients.

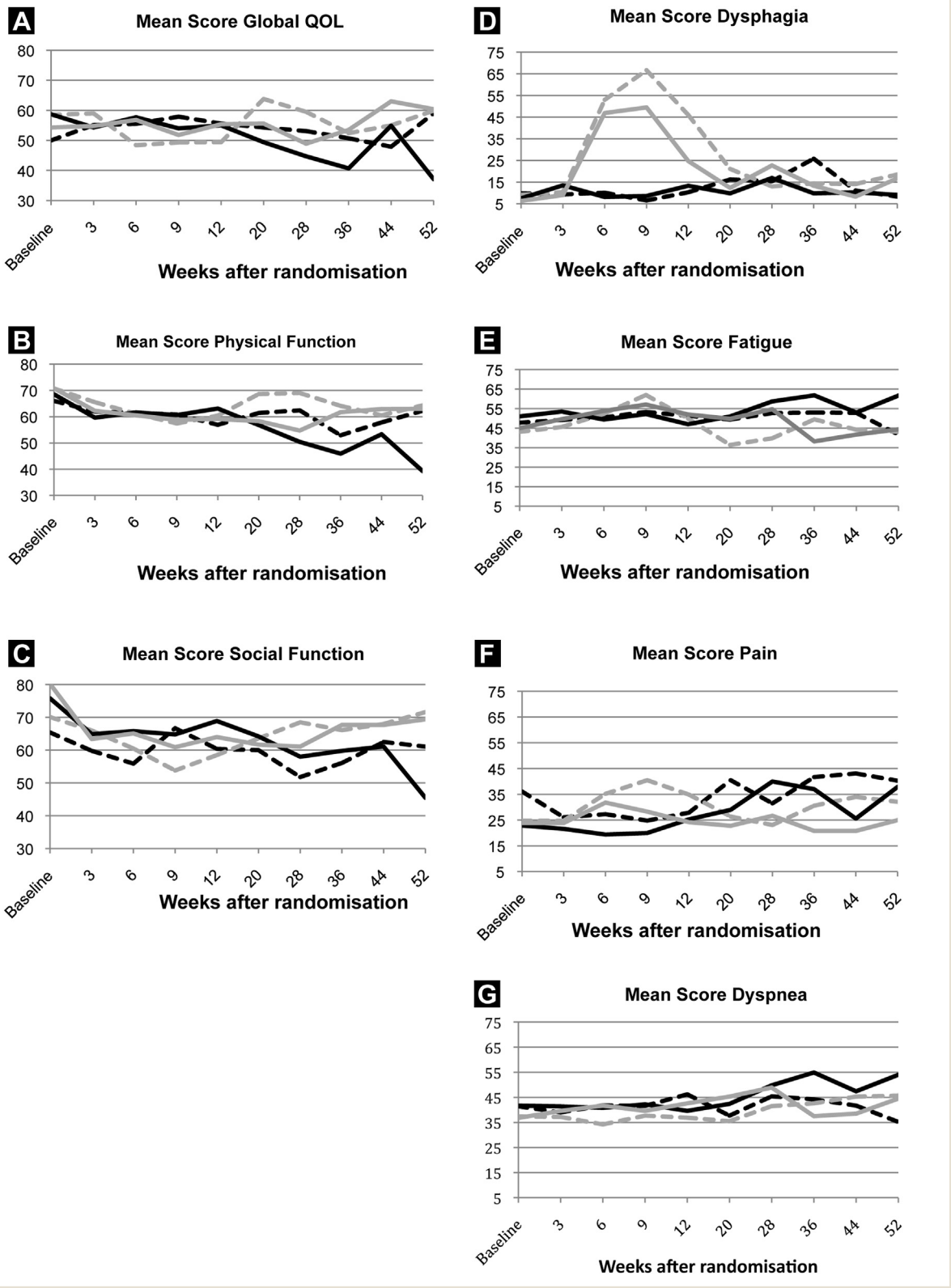
The reported PS scores (Figure 1D) indicated a decreased PS for patients treated with chemotherapy alone, regardless of age. Among the patients administered CRT, only a transient decline was found in the PS after treatment. This was normalized for both age groups during the observational period.

Discussion

Our data have demonstrated that patients aged ≥ 70 years with negative prognostic factors and nonresected, stage III LA-NSLCL can tolerate CRT with the doses adjusted to age and a palliative intent. After CRT, patients aged ≥ 70 years experienced significantly increased two- and three-year survival, less pain, and better preserved HRQoL than did patients in same age group who received only chemotherapy. However, PS 2 patients did not experience a survival benefit from palliative CRT compared with chemotherapy alone, regardless of age.

For patients with a good PS and nonresectable LA-NSCLC, CRT has been considered the standard therapy.[14] For elderly patients, however, the best treatment approach has not been determined.[12,28] In two recent Japanese studies of elderly patients with unresectable LA-NSCLC receiving CRT, the reported median survival was > 22 months. Both trials consisted almost entirely of patients with PS 0 to 1, and the treatment was given with curative intent (radiation 60 Gy).[25,29] In a subanalysis of a phase III trial, Jalal et al[30] found a median survival period of 17.1 months for patients aged ≥ 70 years who had received cisplatin and etoposide and concurrent chest radiation (59.4 Gy). They concluded

Figure 2 Health-Related Quality of Life (QOL) Scores Until One Year From Randomization. (A-C) Functional Scores (High Scores Represent Good QOL). (D-G) Symptom Scores (High Scores Represent More Symptoms). Black Dotted Line Indicates Chemotherapy Alone, Patient Age < 70 Years; Gray Dotted Line, Chemoradiotherapy (CRT) and Patient Age < 70 Years; Black Solid Line, Chemotherapy Alone and Patient Age ≥ 70 Years; Gray Solid Line, CRT and Patient Age ≥ 70 Years



that fit older adults experienced greater rates of hospitalization and toxicity. In a recent retrospective Brazilian study, Domingues et al[28] found an overall survival of 15.5 months among patients aged ≥ 65 years with LA-NSCLC treated with CRT (radiation dose ≥ 40 Gy).

These treatment regimens should be considered radical or "curative." Most patients with NSCLC have been diagnosed with advanced disease and the elderly will have more comorbidities than younger patients.[9,31] Thus, only a few will be able to endure radical treatment. However, the significant increase in two- and three-year survival in our study indicates that CRT, with the doses adjusted to a palliative intent, might be a practical and relevant treatment alternative for elderly patients with negative prognostic factors and comorbidities.

Several factors in our study reduced or prevented the treatment effect in the experimental arm among the group aged ≥ 70 years. A male predominance was present in our data (77% male in the older vs. 55% in the younger CRT group). Women with lung cancer are known to have a better prognosis than men, older women even more than younger women.[2,32] It can, in part, be explained by the late diagnosis and more advanced disease in the men. Because we recruited patients with poor prognostic factors from the original phase III study, a male predominance could be expected.[2,33]

Another important factor was patient age. About 50% of our older treatment group (age ≥ 70 years) was > 75 years old. In line with the palliative intent and advanced age, these patients were administered 25% reduced chemotherapy doses. These reductions are expected to have influenced the survival rate negatively but corresponded to the favorable hematologic profile among patients aged ≥ 70 years, regardless of the treatment. The CRT patients aged < 70 years experienced significantly more hematologic toxicity. The relatively low overall survival in our data set might imply that the chemotherapy dose for patients aged > 75 years was reduced too liberally.

The hospital admissions related to side effects and esophagitis were significantly increased among the elderly CRT patients. The difference in hospital admissions related to side effects was most prominent among the patients aged ≥ 70 years, possibly owing to the dose-reduced chemotherapy in this age group. Nevertheless, the rate of esophagitis and hematologic toxicity among the elderly were in accordance with the findings from Kang et al.[34] They reported an incidence of treatment-related toxicity in the elderly that was noticeably lower than previously reported.[34] We should expect that more modern planning techniques and radiologic equipment will help to reduce the radiologic effects on the esophagus and bone marrow in the future.

Today, most centers consider CT alone to be insufficient in the diagnostic workup of patients with lung cancer. Magnetic resonance imaging is considered more sensitive in detecting brain metastases and PET-CT more sensitive in detecting other organ metastases. Accordingly, using CT alone in the investigation might have resulted in patients with more advanced disease being included in our study. However, if this were so, this would only strengthen the argument for the beneficial effects of CRT for subjects with a poor prognosis.

Few previous studies have addressed HRQoL > 3 months after radiotherapy in patients with LA-NSCLC. However, Wang et al[35] and Pijls-Johannesma et al[36] have described some general tendencies that occur after CRT. Most functioning scores usually decline over time. Symptoms such as hemoptysis, pain, and cough tend to show improvement initially but usually increase later during the disease course. Dysphagia is related to esophagitis secondary to CRT and usually improves after radiotherapy completion.

The social and physical function reported by patients aged ≥ 70 years in our study followed this pattern to a certain extent. The global QoL score illustrates the most prominent functional benefit of CRT for the elderly, because these patients did not experience any clinical relevant QoL reduction during treatment or observation.

In accordance with earlier studies,[36,37] the initial CRT-related symptoms, such as dysphagia and pain in our study, were transient and less prominent among the elderly. From HRQoL investigations in two prospective CRT-based trials of patients with stage III NSCLC, Hallqvist et al[37] reported a gradual worsening of dyspnea and fatigue during the observation period, regardless of age. Among the patients aged ≥ 70 years in our study, the CRT patients reported less dyspnea during the latter part of the observation period compared with those administered chemotherapy only. The increase in the incidence of fatigue was clinically relevant during treatment in the CRT groups; however, it declined subsequently during the observation period to levels slightly lower than those in the non-CRT patients. In contrast, patients aged ≥ 70 years who received chemotherapy only had a slight reduction in the incidence of fatigue during the treatment period but experienced a clinically relevant increase during the observation period.

In a HRQoL study of patients with NSCLC from 2001, Langendijk et al[38,39] found that neither palliative nor radical radiotherapy gave satisfactory palliation of respiratory symptoms in patients followed up for 12 months. These data are in conflict with our findings. Major problems were present in the cited HRQoL study. The main problem was the poor HRQoL compliance rates, because the response rates were as low as 28% to 68% for all scales, except hemoptysis (83%). Because the response rate for several of the function and symptom scores was < 38%, one might question the validity of the HRQoL data from that study. In addition, during the 17-year period since these patients were treated (1994-1996), the ability to spare healthy tissue in the proximity of tumors from radiation has developed with advances in modern radiotherapy techniques.[16]

It could be argued that the apparent CRT-related beneficial HRQoL effects we observed late in the observation period could be explained by patient selection (ie, that after 10 months only those with the best response remained). This objection would be applicable to any study of malignancies with a short patient life expectancy. The 1- and 2-year survival of 44% and 23%, respectively, after CRT for patients aged ≥ 70 years, such as was seen in our study, should be a strong argument for both the use of CRT and the relevance of HRQoL recordings for 12 months after treatment initiation.

Another objection to the relevance of HRQoL and PS registration late in the disease course is the declining compliance in questionnaire completion as the disease progresses.[40] However, the

decline in compliance was moderate and would be expected to affect the study groups without introducing any biases.[19]

Conclusion

We have concluded that even in patients aged ≥ 70 years with a poor prognosis, tailored CRT does not reduce HRQoL to any clinical relevant degree. We found that PS and HRQoL can be preserved, even late in the observation period after CRT. Although CRT has routinely been reserved for younger fit patients, the results of the present exploratory analysis have indicated that CRT can result in both survival and HRQoL benefits to elderly patients with a poor prognosis and nonresectable LA NSCLC, except for PS 2 patients, provided the treatment modalities have been adapted to a palliative setting. Given the low frequency of hematologic toxicity, especially among patients aged > 75 years, one might speculate that the chemotherapy dose was reduced too low in our study.

Clinical Practice Points

- The treatment recommendations for elderly patients with advanced NSCLC are often conflicting. Thus, many elderly patients with advanced NSCLC will be undertreated or will not receive chemotherapy. It has been tenaciously argued that clinical trials of treatment in older populations are necessary.
- We found that, even in patients with a poor prognosis aged ≥ 70 years, tailored CRT does not reduce HRQoL to any clinical relevant degree. We also found that, except for PS 2 patients, the PS and HRQoL were preserved even late in the observation period after CRT. Given the low frequency of hematologic toxicity, especially among patients aged > 75 years, one might speculate that the chemotherapy dose was reduced too low in our study.
- CRT might give both survival and HRQoL benefits to elderly patients with poor prognosis and nonresectable LA-NSCLC, except for PS 2 patients, provided the treatment modalities are adapted to a palliative setting.

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Disclosure

The authors have stated that they have no conflict of interest.

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