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Concurrent palliative chemoradiation leads to survival and quality of life benefits in poor prognosis stage III non-small-cell lung cancer: a randomised trial by the Norwegian Lung Cancer Study Group

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Background: The palliative role of chemoradiation in the treatment of patients with locally advanced, inoperable non-small-cell lung cancer stage III and negative prognostic factors remains unresolved.

Methods: Patients not eligible for curative radiotherapy were randomised to receive either chemoradiation or chemotherapy alone. Four courses of intravenous carboplatin on day 1 and oral vinorelbine on days 1 and 8 were given with 3-week intervals. Patients in the chemoradiation arm also received radiotherapy with fractionation 42 Gy/15, starting at the second chemotherapy course. The primary end point was overall survival; secondary end points were health-related quality of life (HRQOL) and toxicity.

Results: Enrolment was terminated due to slow accrual after 191 patients from 25 Norwegian hospitals were randomised. Median age was 67 years and 21% had PS 2. In the chemotherapy versus the chemoradiation arm, the median overall survival was 9.7 and 12.6 months, respectively ($P < 0.01$). One-year survival was 34.0% and 53.2% ($P < 0.01$). Following a minor decline during treatment, HRQOL remained unchanged in the chemoradiation arm. The patients in the chemotherapy arm reported gradual deterioration during the subsequent months. In the chemoradiation arm, there were more hospital admissions related to side effects ($P < 0.05$).

Conclusion: Chemoradiation was superior to chemotherapy alone with respect to survival and HRQoL at the expense of more hospital admissions due to toxicity.

Approximately 2800 Norwegians are diagnosed with lung cancer every year (Cancer Registry of Norway, 2011). Due to lack of early symptoms, patients are in general diagnosed at advanced stages, where curative treatment is not possible. For non-small-cell lung cancer (NSCLC), the crucial line between curative and palliative treatment is usually drawn at stage III disease, though depending on clinical prognostic factors.

Twenty years ago, palliative radiotherapy was considered the main treatment for locally advanced NSCLC, yielding effective symptom relief for a limited time, regardless of the dose-fractionation regime (Lester *et al*, 2006). Palliative radiation is still frequently used. Based on a previous Norwegian study, Sundstrøm *et al* reported (Sundstrøm *et al*, 2004, 2006) that some of the stage III NSCLC patients in the palliative setting benefited from

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receiving higher-dose thoracic radiotherapy schedules, obtaining long-term survival.

During the last two decades, chemotherapy has been confirmed to prolong survival of advanced NSCLC. Moreover, combinations of chemo- and radiotherapy have been recommended for locally advanced disease (O'Rourke *et al*, 2010). In theory, the chemotherapy will minimise the risk of distant metastasis and the radiotherapy will preserve loco-regional control (Le Chevalier *et al*, 1994). A chemotherapeutic drug may, in addition, act as a radio sensitizer and increase the effect of a radiation treatment (Blackstock and Govindan, 2007). Today, the absence of negative clinical prognostic factors, such as poor performance status (PS) and weight loss is considered a prerequisite for achieving the effect of this combined treatment (Crinò *et al*, 2010). For the patients with negative prognostic factors though, benefit of chemoradiation is presently not documented.

At the time this study was planned, recommended chemotherapy consisted of two-drug platinum-based regimens. The efficacy of carboplatin and vinorelbin is well documented (Helbekkmo *et al*, 2007; Plessen Von *et al*, 2008), and the activity of oral vinorelbin is comparable with the intravenous formulation (Jassem *et al*, 2001; Krzakowski *et al*, 2008).

For this study, concurrent chemoradiation was chosen as the treatment modality due to the documented superiority over the sequential approach in locally advanced NSCLC (Fournel *et al*, 2005). The selected fractionation was 42 Gy/15 fractions, as this is a pragmatic palliative regimen used in Norway. Besides, it is in line with the prolonged survival observed by Sundstrøm *et al*. (2004) after more protracted palliative radiation schedules.

This phase III trial was carried out to compare a palliative chemoradiation regimen to palliative chemotherapy alone, with respect to survival, health-related quality of life (HRQOL) and toxicity in incurable stage III NSCLC patients with negative prognostic factors.

PATIENTS AND METHODS

This study was an open, multicenter phase III trial, with a balanced (1:1) randomisation, where patients in both arms received chemotherapy with carboplatin and vinorelbin. The patients in the experimental arm also received radiotherapy between chemotherapy course two and three.

Eligible participants were adults of all ages with locally advanced, unresectable NSCLC stage III with one or more negative prognostic factors (tumour size ≥ 8 cm, PS ≥ 2 , or weight loss of $>10\%$ over the last six months). Patients were ineligible if they (1) were candidates for radical radiotherapy, (2) had received previous chemotherapy or (3) had pleural effusion. Patients with WHO performance status of 0–2 were eligible, provided they had adequate haematological, liver and kidney function, and no other active malignant disease (World Health Organization, 1979).

Patients were to stop treatment if the chemotherapy dose was reduced or postponed three times, postponed more than three weeks, or if there were signs of progression during treatment.

The patients were stratified by performance status, age and sex. Written consent and preserved cognitive functions were also mandatory. All patients underwent CT-staging of the thorax and upper abdomen. The Regional Ethical Committee, the Norwegian Social Data Services, and the Norwegian Medicines Agency approved the study. It is registered in ISRCTN (ISRCTN63778716 – Concomitant chemotherapy for treatment of non-small-cell lung cancer – The Conrad study).

Randomisation was performed by phone or fax to the randomisation centre (Clinical Cancer Research Office, University Hospital of North Norway). As the inclusion progressed in a slower

rate than expected, the Regional Ethical Committee accepted an extension of the inclusion period. The protocol was amended accordingly.

Therapy. All participants were to receive four courses of chemotherapy in 3-week intervals: Vinorelbin capsules 60 mg m^{-2} orally on days 1 and 8 and intravenous carboplatin (area under the curve = 5 (Calvert's formula)) (Calvert *et al*, 1989) administered for 1 h on day 1. Patients >75 years of age received 75% of the estimated full dose. To prevent chemotherapy-induced nausea and vomiting, all patients received premedication with intravenous 5-HT₃ antagonists and dexamethasone on day 1 and orally the following two days. On day 8 they received oral 5-HT₃ antagonists only.

Before each chemotherapy course, the absolute neutrophil count had to be $>1.0 \times 10^9 \text{ l}^{-1}$ and platelet $>75 \times 10^9 \text{ l}^{-1}$. The doses were reduced by 25% if absolute neutrophil count was $1.0\text{--}1.49 \times 10^9 \text{ l}^{-1}$, platelets were $75\text{--}99 \times 10^9 \text{ l}^{-1}$, or preceding nadir absolute neutrophil count was $<0.5 \times 10^9 \text{ l}^{-1}$. Doses were reduced by 50% if the nadir platelet count was $<50 \times 10^9 \text{ l}^{-1}$, and continued throughout the treatment period. If a treatment course was delayed by more than 21 days, chemotherapy was to be discontinued. If grade 3–4 toxicity or neutropenic infections occurred, chemotherapy was to be postponed until the patients recovered fully, clinically and/or haematologically. Subsequent doses were reduced by 25%. Study treatment was discontinued in cases of disease progression, unacceptable toxicity, or at patient request.

In the chemoradiation arm, radiotherapy was administered as 42 Gy/15 fractions. This slightly hypofractionated radiation regimen has been used safely in Norway since the 1980s (Kaasa *et al*, 1988). A decade ago, advanced NSCLC patients randomised to 42 Gy/15 fractions had median survival data at least comparable to the normofractionated regimen (50 Gy/25 fractions) (Sundstrøm *et al*, 2004). Biologically, 42 Gy/15 fractions compares to about 50 Gy in 2 Gy daily fractions. As the risk of spinal cord myelopathy at 54 Gy, given 2 daily fractions, is only $<1\%$, this fractionation regimen is considered safe (Kirkpatrick *et al*, 2010). As this regimen was already established, the protocol allowed the treatment planning and dosimetry to be conducted according to the participating institution's standard routines. The radiotherapy was to start simultaneously or shortly after initiation of the second chemotherapy course.

In addition, patients received best supportive care according to individual needs. If patients allocated to the chemotherapy-alone arm were in need of palliative radiotherapy in thorax, a hypofractionated regimen of 17 Gy/2 fractions (one week apart) was recommended. If skeletal metastases developed, one 8 Gy fraction was recommended.

Study end points. The main end point was overall survival. Further end points were time to progression, HRQOL, and treatment toxicity.

HRQOL was assessed using the EORTC QLQ-C30 questionnaire version 3.0 and the supplementary questionnaire module LC13, designed specifically for lung cancer and used by the Norwegian Lung Cancer Study Group for more than 10 years (Hjermstad *et al*, 1998). Toxicity was graded using the Common Terminology Criteria of Adverse Events version 3.0.

Patient follow-up. Blood samples and information about esophagitis were obtained before each chemotherapy course (weeks 0, 3, 6, and 9). The HRQOL questionnaires were distributed to the participants at randomisation and at the time of every chemotherapy course, as well as every 8th week after the end of the treatment period, until one year after randomisation. Reminders were mailed if questionnaires were not returned within 14 days. Every study site provided a summary of the radiation and the chemotherapy given

for each patient, including registered haematological toxicity and esophagitis as well as reasons for any discontinuation of the treatment. During follow-up visits (weeks 12, 20, 28, 36, 44, and 52) PS and possible progression were registered.

Statistical considerations. We aimed to obtain a 15% change in 1-year survival, selected HRQOL items, as well as toxicity. On the basis of existing documentation, provided a significance level of 5% and a statistical power of 80%, 350 patients needed to be included in the study.

Overall survival and time to progression were compared using the Kaplan–Meier method and the Log-rank test, based on intention to treat. The date of death was chosen as the date of progression if no other information was available.

The HRQOL questionnaires were analysed according to the EORTC scoring manuals (Fayers *et al*, 2001, 2002). Mean scores were calculated from the reported scores. The mean changes were calculated by subtracting the baseline score from the score at each designated time point during and after the treatment for each study arm. The non-parametric Mann–Whitney *U*-test was used for comparing scores. A mean change of ≥ 10 points was considered clinically relevant and significant (Osoba *et al*, 2005; Brundage *et al*, 2007).

RESULTS

Patients. From November 2006 to November 2011, 191 patients from 25 Norwegian hospitals were randomised. Based on our earlier experiences involving monomodality trials, we expected to include the planned 350 patients in three years, that is, 13 patients per month (Plessen Von *et al*, 2006). Due to slow and declining patient accrual, the Norwegian Lung Cancer Study Group decided to end patient inclusion at five years (November 2011). The planned study size was dimensioned according to an expected 15% difference in 1-year survival at a significance level of 0.05 and a statistical power of 80%. Given the survival differences between treatment arms, presented below, calculated power estimates for the included 191 patients are 75% and 97%, respectively for the 1-year and 2-year survival.

Three patients had to be excluded (Figure 1, Consort diagram (Moher *et al*, 2010)). Forty patients (42.6%) in the chemotherapy arm and thirty-nine patients (41.5%) in the chemoradiation arm were 70 years or older. Further baseline demographic and clinical characteristics for each treatment arm are summarised in Table 1.

Study therapy. In the treatment arms, 75.5% (chemotherapy alone) and 77.7% (chemoradiation) completed all four chemotherapy courses (Figure 1). Eighty-nine percent of patients in the chemoradiation arm completed the radiotherapy. The median start times for the second, third, and fourth chemotherapy course were day 22, day 44, and day 68. In the chemoradiation arm, the median radiation start and termination times were day 24 and day 44, respectively. Five patients did not receive any radiotherapy.

Reasons for discontinuing therapy differed clearly between the treatment arms (Figure 1). In the chemotherapy-alone arm, 14 of the 23 patients stopped chemotherapy prematurely due to disease progression, whereas in the chemoradiation arm 10 of the 23 stopped treatment because of toxicity.

Overall survival and time to progression. Data are presented in Figure 2. The median overall survival was significantly longer in the chemoradiation arm than in the chemotherapy-alone arm with 12.6 and 9.7 months, respectively (Figures 2B, $P < 0.001$). Furthermore, the 1- and 2-year survival rates were 53.2% vs 34.0% ($P < 0.01$) and 27.7% vs 7.4% ($P < 0.01$), respectively.

Median time to progression (Figure 2A) was 7.0 months in the chemoradiation vs 4.2 months in the chemotherapy arm ($P < 0.001$).

The significant survival benefit of the chemoradiation arm was retained for patients with weight loss $\geq 10\%$ and tumour size > 7 cm at randomisation. For PS 2 patients, however, overall survival was similar in both treatment arms: 7.5 months in the chemotherapy arm and 7.8 months in the chemoradiation arm ($P = 0.24$). One-year survival was 10.5% and 28.6%, respectively.

Grade 5 toxicity was similar in the treatment arms. Six patients in the chemotherapy arm died during the treatment period, two following progression during treatment. Four patients in the chemoradiation arm died. Altogether, four patients died from causes not related to their lung cancer (ruptured aortic aneurysm, myocardial infarction, and two from complications following fracture of the femoral neck).

Health-related quality of life. Proportions of completed questionnaires are presented in Figure 3. Of the 188 eligible patients, 186 (99%) completed the HRQOL questionnaire at randomisation. The median percentages of completed questionnaires the first six months after randomisation were 84.0 in the chemotherapy arm and 85.5 in the chemoradiation arm. The percentage of responders declined in the last six months of the observation period (medians 67.0% vs 75.0%).

The QLQ-C30/LC13 covers several domains. In order to provide an adequate and sufficient HRQOL assessment of the two different treatment regimens in our trial, we have chosen to report global HRQOL, social function, physical functions and dysphagia (Claassens *et al*, 2011).

Mean scores over time and mean changes from baseline to week 52 are presented in Figure 4, relative to treatment arm. During the treatment period, the patients in the chemoradiation arm recorded a significant temporary worsening in physical and social functioning, as well as dysphagia. However, the values returned to a level near baseline. The patients receiving chemotherapy alone experienced a significant and clinically relevant decline in physical and social function, as well as global HRQOL following the end of the treatment period (Figure 4).

Toxicity. Data on toxicity and side effects are presented in Table 2. During the treatment period, there were significantly more episodes of esophagitis and hospital admissions in the chemoradiation arm (both $P < 0.01$). More than 85% of the patients receiving chemoradiation reported various degrees of esophagitis, but none reported grade 4. The few episodes of esophagitis in the chemotherapy arm were probably related to post study radiation. Neutropenia was somewhat more pronounced ($P = 0.258$) and the number infections was somewhat higher ($P = 0.172$) in the chemoradiation arm. Slightly more patients in the chemoradiation arm required blood transfusion ($P = 0.85$), but there were no differences with respect to bleeding, thrombocytopenia, or number of platelet transfusions given.

Post study treatment. Our data reveal that more patients in the chemotherapy alone than in the chemoradiation arm received supplemental radiation, 58.0% vs 31.2%, respectively ($P < 0.05$). Correspondingly, 43.7% in the chemotherapy arm and 24.7% in the chemoradiation arm received supplemental chemotherapy ($P < 0.05$). Thirteen patients were still alive by 15 January 2013.

DISCUSSION

In patients with locally advanced NSCLC stage III and negative prognostic factors, our randomised study demonstrates that concurrent chemoradiation is superior to chemotherapy alone with respect to both survival and HRQOL. The benefit is

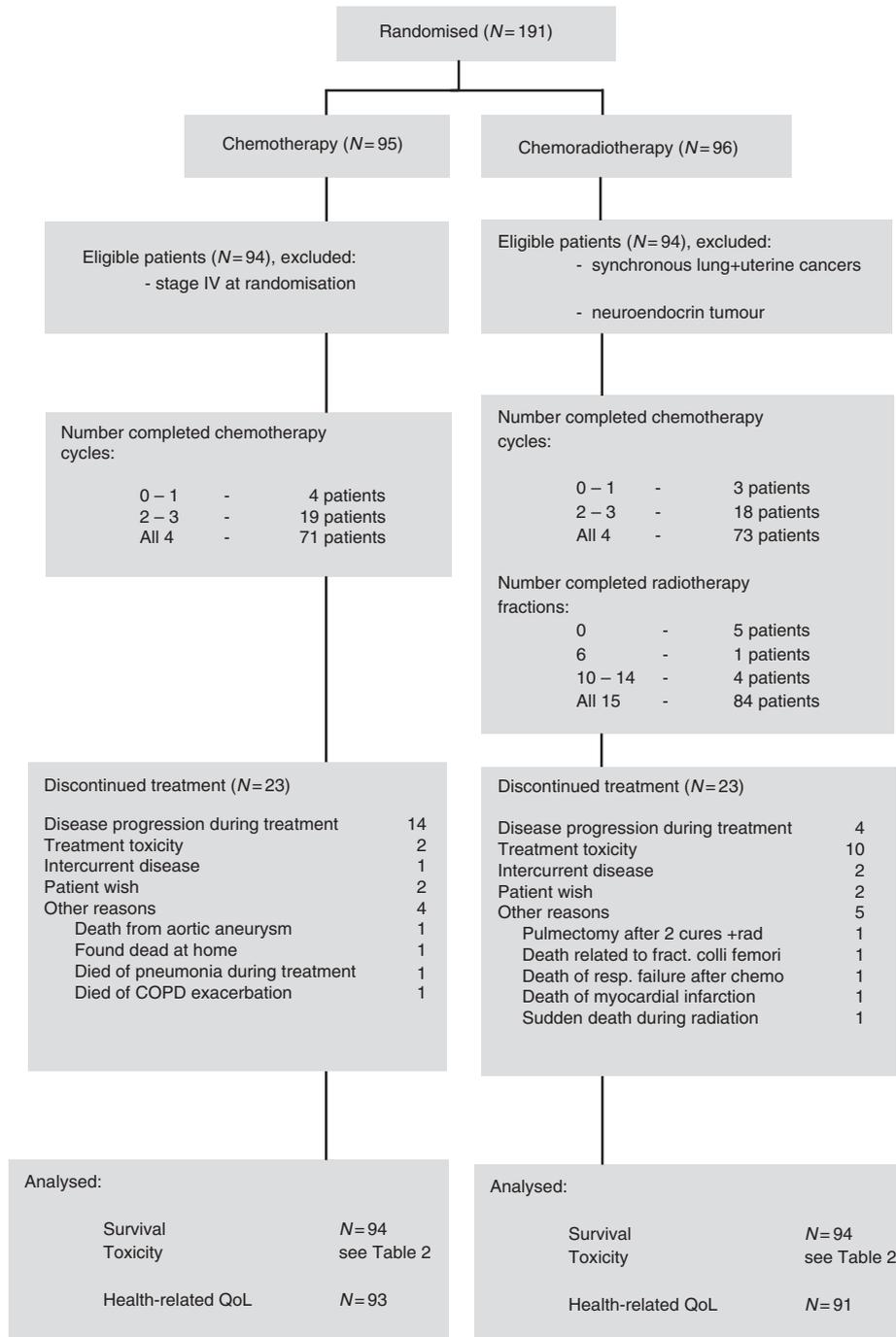


Figure 1. CONSORT flow diagram for the Conrad study.

countered, however, by more hospital admissions due to toxicity.

The role of chemoradiation in palliation of poor-risk patients with incurable stage III NSCLC is not yet settled (Wagner, 2008; Rodrigues *et al*, 2012). Some investigators have called for more use of radiotherapy in the palliative setting (Barbera and Bezjak, 2013), whereas randomised radiotherapy trials are infrequently including HRQOL end points (Claassens *et al*, 2011). A major strength of this study is the inclusion of both survival and HRQOL end points. The inability to include the planned number of patients is a weakness. Nevertheless, previous investigators have encountered accrual difficulties, especially with respect to multimodal clinical trials (Baggstrom *et al*, 2011; Lally *et al*, 2011). Doctors hesitate to

enrol patients with poor PS and patients cite geographical barriers among reasons for their nonparticipation (Lara *et al*, 2001). A multimodal treatment trial is an additional challenge in a sparsely populated country like Norway.

To our knowledge, this is the first prospective randomised phase III trial specifically addressing palliative chemoradiation for patients with stage III NSCLC and negative prognostic factors. Our data reveal a significant benefit from palliative chemoradiation compared with chemotherapy alone.

There are few previous chemoradiation studies in poor-risk advanced NSCLC patients. Two phase II studies (Lau *et al*, 1998; Davies *et al*, 2006) examined the tolerability and effect of chemoradiation, total radiation dose of 61 Gy concurrent with

Table 1. Patients characteristics at baseline

	Chemotherapy (N = 94)		Chemoradiotherapy (N = 94)		P-value
Age (years)					
Median	66.5		67		
Range	48–88		48–85		
Sex					1.0
Female	35		34		
Male	59		60		
	No. patients	%	No. patients	%	
Performance status					0.859
0–1	75	79.8	73	77.7	
2	19	20.2	21	22.3	
Stage of disease					0.464
IIIA	46	49	40	43	
IIIB	48	51	54	57	
Histology					
Squamous cell carcinoma	36	38.3	46	48.9	
Adenocarcinoma	31	33.0	31	33.0	
Large cell carcinoma	4	4.3	1	1.1	
Other	23	24.5	16	17.0	

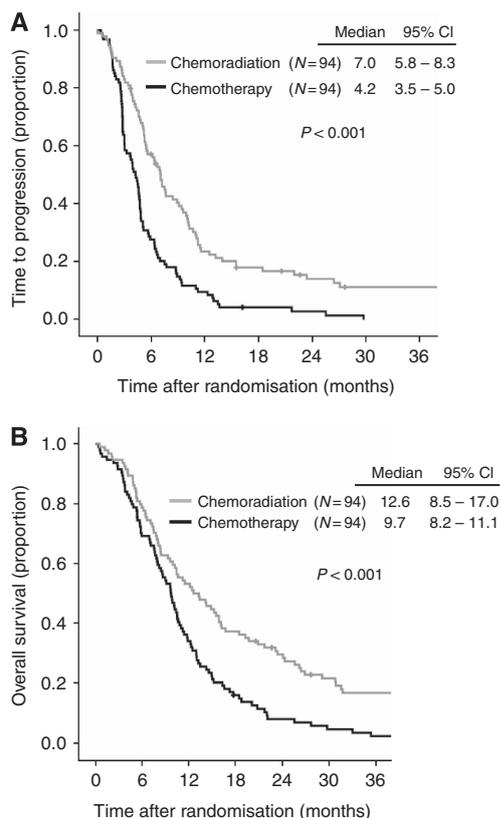


Figure 2. Kaplan–Meier plots for (A) time to progression and (B) overall survival.

carboplatin and etoposid. This regimen was well tolerated and yielded a median survival comparable to that of patients with better prognosis who received cisplatin-based chemoradiotherapy. In a

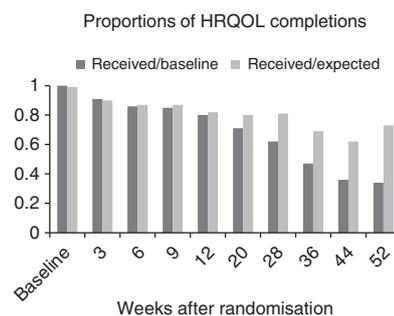


Figure 3. Proportions of health-related quality of life (HRQOL) questionnaires completed at baseline and during the study. The median received/expected proportions were 87.5% in the first 6 months of the study and 72.3% for the last 6 months.

recent randomised phase II study, Nawrocki *et al* (2010) concluded that upfront chemotherapy combined with palliative radiotherapy (30 Gy/10 fractions) resulted in superior response rates and survival when compared with radiotherapy alone in patients with stage III locally advanced NSCLC and poor prognostic factors (tumours >8 cm and/or poor pulmonary reserve, performance status 0–2, tumour-related chest symptoms).

In advanced-stage NSCLC, age has a significant impact on treatment choice and elderly patients are less frequently treated according to guidelines (De Rijke *et al*, 2004; Blanco *et al*, 2008). In our study, 42% of patients were above 70 years and 22% ≥75 years. Nevertheless, higher age was not a poor prognostic factor for survival. This is in agreement with previous studies (Schild *et al*, 2003; Atagi *et al*, 2012) on even more aggressive chemoradiation where elderly patients were found eligible as long as they were fit. In our data, only PS was found to be a significant negative prognostic factor for survival. When compared with chemotherapy alone, we conclude that concomitant chemoradiation offers a significant survival benefit to PS 0–1 patients with locally advanced

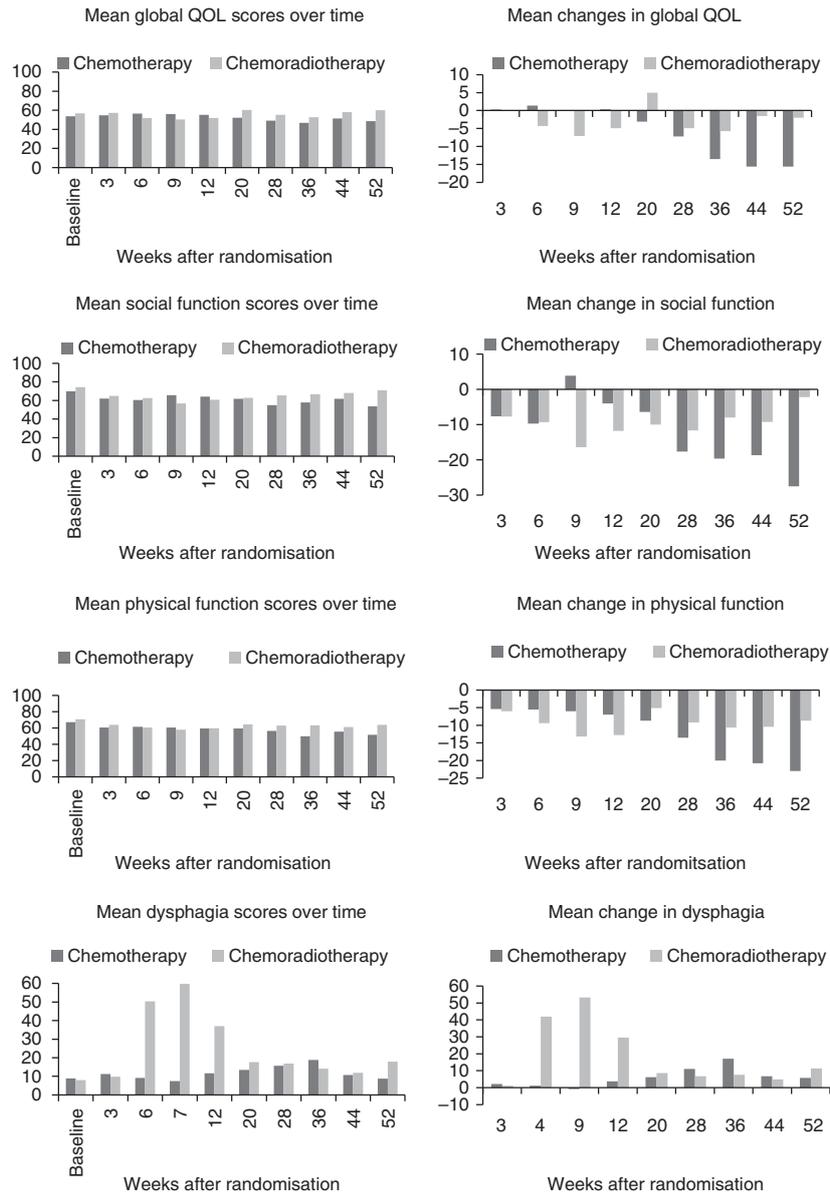


Figure 4. Mean scores and mean change in the selected domains. A higher score for dysphagia indicate more pronounced symptoms, whereas higher score for the three other domains indicate better function.

NSCLC and negative prognostic factors. For PS 2 patients, overall survival was similar in both treatment arms.

During the latter part of the observation period, the compliance with respect to completing questionnaires decreased in parallel with the reported declining quality of life, which is a familiar phenomenon (Fayers *et al*, 2001). Palliative care patients may find the HRQOL questionnaires too lengthy and some of the items less relevant (Kaasa *et al*, 1998). At baseline, patients in the chemoradiation arm had a 3.1–4.4 points higher score for the domains reported than those in the chemotherapy-alone arm. First, this difference is considered nonsignificant, and second the interpretation of HRQOL data was based on mean change values (Osoba *et al*, 1998).

In a longitudinal study of NSCLC patients undergoing concurrent chemoradiation therapy, Wang *et al* (2006) observed a temporal pattern of treatment effects affecting the patients' symptoms and daily function during and after treatment. Consistently, we found a temporary, reversible decline in HRQOL regarding both symptom and functional domains

during therapy, in agreement with others (Pijls-Johannesma *et al*, 2009).

Despite a transient decrease in global HRQOL due to side effects during the radiation period, the HRQOL decline during this period was limited and clinically insignificant. After the first three months though, a reasonable global HRQOL was maintained in the chemoradiation arm, whereas it declined significantly in the chemotherapy-alone arm. Thus, chemoradiation offers a longer lasting palliation relevant to HRQOL in contrast to chemotherapy alone.

In our study, we used a slightly hypofractionated radiation schedule (42 Gy/15 fractions), and 30% of the patients in the chemoradiation arm experienced esophagitis grade 3, but not grade 4. Esophagitis is common in chemoradiation, but the reported incidence rates are conflicting. In patients with locally advanced NSCLC and PS 0–1 given concurrent chemoradiation, Werner-Wasik and co-workers (RTOG) (Werner-Wasik *et al*, 2011) reported 75% esophagitis grade 3–4 and 34% grade 4 following standard (63 Gy) or hyperfractionated radiation therapy

Table 2. Toxicity and side effects according to treatment arm

	Carboplatin/ vinorelbine		Carboplatin/vinorelbine + concurrent radiation		P-value
	No. patients	%	No. Patients	%	
Haematologic toxicity (183 valid cases)	(N = 91)		(N = 92)		
Anaemia					0.514
Grade 3	5	5.5	5	5.4	
Grade 4	0	0	0	0	
Neutropenia					0.258
Grade 3	21	23.1	18	19.6	
Grade 4	14	15.4	23	25.0	
Thrombocytopenia					0.094
Grade 3	3	3.3	6	6.5	
Grade 4	1	1.1	3	3.3	
No. infections in relation to leukopenia (170 valid cases)	(N = 86)		(N = 84)		0.172
1	16	18.6	23	27.4	
2	1	1.2	4	4.8	
3	1	1.2	0	0	
No. hospital admissions in relation to side effects (170 valid cases)	(N = 86)		(N = 84)		<0.01
1	18	20.9	33	39.7	
2	4	4.7	9	10.7	
3	1	1.2	3	3.6	
Esophagitis in relation to radiation (156 valid cases)	(N = 67)		(N = 90)		<0.01
Grade 0	58	86.6	12	13.3	
Grade 1	4	6.0	16	17.8	
Grade 2	4	6.0	35	38.9	
Grade 3	1	1.5	27	30.0	
Grade 4	0	0	0	0	

(69.6 Gy). In two Japanese studies (Takigawa *et al*, 2011; Atagi *et al*, 2012) on elderly patients with good PS, given concurrent curative chemoradiation (60 Gy), only 1–6% were reported to have grade 3–4 esophagitis. A high percentage of our poor-risk patient population completed the planned courses of chemotherapy and radiotherapy, but a relatively large proportion of patients in the chemoradiation arm suffered from esophagitis and infections related to leucopenia.

The haematological toxicities were comparable to other studies (Helbekkmo *et al*, 2007; Gronberg *et al*, 2009; Takigawa *et al*, 2011), but the number of hospital admissions in relation to side effects was relatively large (45 in the chemoradiation vs 23 in the chemotherapy arm). One patient in the chemoradiation arm died during radiation (after 11 fractions). The cause of death was arrhythmia.

In conclusion, we found that concurrent chemoradiation is superior to chemotherapy alone in poor prognosis patients with locally advanced stage III with respect to both survival and HRQOL. Higher age and large tumour size were not negative prognostic factors. PS 2 patients had no survival benefit and should receive chemotherapy alone. Future trials to establish the best concurrent chemoradiotherapy regimen (radiation dose/fractionation, volume, planning, and new systemic therapies) are required to provide further information regarding the optimal treatment for this challenging patient population. Herein, HRQOL should be a study end point in addition to survival.

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