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Phase II randomised trial

Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab

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ABSTRACT

Background and purpose: Radiation dose escalation using hypofractionation might improve overall survival (OS). We investigated OS in a phase II multicenter study in locally advanced non-small cell lung cancer (LA-NSCLC) patients treated with hypofractionated concurrent chemoradiotherapy.

Materials and methods: A 2-armed phase II, multi-center study (NTR2230) was performed with the aim to assess the effect of cetuximab to concurrent chemoradiotherapy in LA-NSCLC patients (stage II/IIIA/B). Arm A received high dose radiotherapy (24 × 2.75 Gy) and concurrent daily low-dose cisplatin (6 mg/m^2). Arm B received an identical treatment regimen with additional weekly cetuximab. Kaplan–Meier survival curves and 1-, 2- and 5-year OS proportions were calculated.

Results: Between February 2009 and May 2011, 102 patients were randomly allocated in two arms. Median OS was 31.5 months (range 12.8–52.3), not significantly different between arms A and B; 33.0 (range 17.0–57.0) and 30.0 (11.0–52.0) months. 1-, 2- and 5-year OS rates were 74.5%, 59.4% and 37.3%, respectively. In multivariate analyses, worse performance score, V35 of the esophagus and the existence of comorbidities were significantly (P-value < 0.05) associated with a shorter OS.

Discussion: In this phase II trial, the median OS for the entire group was remarkably high; 31.5 months. Furthermore, 5-year OS was still 37.3%. Hypofractionation might contribute to improved OS in LA-NSCLC patients.

Concurrent chemoradiotherapy imposes beneficial effects on overall survival (OS) in patients with locally advanced non-small cell lung cancer (LA-NSCLC), compared to sequential chemoradiotherapy or radiotherapy alone [1–3]. Nonetheless, the optimal radiation scheme still needs to be identified. Dose escalation above 60 Gy up to a maximum of 74 Gy with concurrent chemoradiotherapy initially showed to be promising in terms of improved local control and overall survival (OS) [4–8]. However, the RTOG 0617 trial [9] recently showed that patients receiving a conventional high dose radiation scheme (37 × 2 Gy) had a significant shorter median OS (22.9 months) compared to patients receiving a conventional (30 × 2 Gy) radiation scheme (28.7 months) [9].

Dose escalation with prolonged overall treatment time in LA-NSCLC patients has previously proven disappointing [10]. Furthermore, it is shown that when the duration of RT exceeds six weeks (30 fractions), each additional treatment day is associated with a 1.6% survival loss each day, probably due to accelerated repopulation [11]. In fact, this might be one of the reasons why local control and OS of RTOG 0617 trial were disappointing for the high dose arm.

Dose escalation using hypofractionation, however, seems promising and might contribute to improved OS. Hypofractionation embodies the delivery of an increased dose per fraction (>2 Gy), typically once daily. Initially, hypofractionation imposed concerns about severe side effects on the lung [12]. Nonetheless, a recent review identifying outcomes in concurrent chemoradiotherapy using hypofractionation up to 3 Gy per fraction, showed that it can be delivered safely with concurrent chemotherapy [12].

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To our knowledge, long-term OS (>3 years) in LA-NSCLC patients receiving concurrent hypofractionated chemoradiotherapy has not yet been evaluated. Therefore, we investigated 60-month OS in LA-NSCLC patients treated with concurrent chemoradiotherapy (±cetuximab), using a hypofractionation scheme of 24 fractions of 2.75 Gy.

Materials and methods

Study design

The Raditux trial: A randomized multicenter phase II trial (http://trialregister.nl Trial ID: NTR2230) was performed, of which the short-term effects and methods are described previously [13]. The study was approved by the independent local medical-ethical committee and was designed in accordance with the International Conference on Harmonization and Good Clinical Practice, and the Declaration of Helsinki.

Patient selection

18-Fluorodeoxyglucose-positron emission tomography and computed tomography scans (FDG PET/CT) were used as a staging tool and were performed within six weeks prior to the start of treatment. The planning CT-scan was with IV contrast. In 17 patients a repeat FDG-PET/CT scan was obtained. The mean time between the planning CT scan and start of the irradiation for all patients was 30.6 days (range 3–59 days).

The possibility of brain metastases was excluded using magnetic resonance imaging (MRI). Non-invasive procedures such as endoscopic ultrasound were, whenever possible performed to assess mediastinal nodal involvement. The highest nodal level was cytologically confirmed. The patient was scored as having comorbidities when the following question was positively answered; " Is the patient suffering from, or has he/she suffered from significant medical or surgical conditions (other than protocol cancer or conditions related to protocol cancer)?" [13].

Radiotherapy

Treatment planning was performed using 3D conformal radiotherapy or intensity-modulated radiotherapy (IMRT) using a treatment planning CT-scan. An IMRT-treatment plan was made with seven equally spaced, 10 or 6 MV photon beams through the homo-lateral lung. The treatment-plan was optimized with a direct aperture-optimalization-technique of the Pinnacle radiotherapy planning system (version 9.0). The prescription-dose was specified at a representative point in the PTV. The dose inhomogeneity within the PTV was >90% and <115%.

The involved radiation fields encompassed the primary tumor and pathological lymph nodes on the FDG-PET/CT scan. The Gross Tumor Volume (GTV) and normal structures were delineated according to a formalized Radiotherapy protocol. The GTV was expanded to a planning target volume (PTV) using a 12 mm margin +1/4 of the tumor peak-to-peak amplitude. For the lymph nodes an isotropic PTV margin of 12 mm was used for all patients.

The following normal organ dose constraints were taken into account: Spinal cord dose $\leqslant$50 Gy (EQD2); Esophagus: V35 <65%; Heart $\leqslant$40 Gy and $\leqslant$50 Gy to 2/3 and $\leqslant$66 Gy to 1/3; Mean Lung Dose <20 Gy. We considered the old heart dose constraints. The mean heart dose $\leqslant$40 Gy, 2/3 heart $\leqslant$50 Gy, and 1/3 heart $\leqslant$66 Gy (α/β = 3 Gy). For the esophagus a V_{35} < 65% (α/β = 10 Gy) was used when optimizing the IMRT-plan. Radiation was delivered using cone beam CT guidance. All patients were treated with photon beams of 10 MV. The dose was specified according to the ICRU 50 guidelines, using advanced tissue inhomogeneity corrections [13].

Follow-up measurements

The tumor and lymph nodes were assessed at onset of therapy and response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [14]. Regular follow up consisted of a 3-monthly visit and included physical examination and radiologic evaluation. PET-CT was performed on week 10, a CT-thorax was performed on week 12, week 31–32 and week 57–59 and a x-ray of the thorax was made on week 12, week 20–21, week 40–41 and week 57–58. All-cause mortality information was received from the patients' medical record or general practitioners in case patients died at home or in a hospice. Mortality follow-up was completed from February 2009 until January 2015.

Statistical analysis

Variables are presented as percentage, mean (±SD) or median (+interquartile range) in case of a skewed distribution. Normality was tested and in case of a skewed distribution, log-transformation was performed. Differences in baseline characteristics between Arm A and Arm B were tested using Student's *t*-tests (continuous variables) and chi-square tests (categorical variables).

The follow-up duration was calculated as the time between randomization and date of death, loss to follow-up or January 2015. Cumulative incidence-, 6-month-, 1-, 2-, and 5-year mortality rates were investigated. Kaplan–Meier survival curves were plotted for OS. Statistical significance between the two arms was calculated with Log-Rank tests. To investigate factors influencing OS, cox proportional hazard analyses were performed. First, univariate analyses were constructed and second, a multivariate model was constructed using a backward selection procedure, including only statistically significant variables. Proportional hazard assumptions for every model were tested by interpretation of the survival plots.

Sensitivity analyses were performed to assess the potential confounding effect of NSCLC staging on overall survival, by including only patients with stage IIIA/B and excluding stage IIA/B patients.

Data are presented as Hazard Ratios (HR) with 95% confidence intervals (CI), which can be interpreted as relative risks. *P*-values less than 0.05 were considered statistically significant. All analyses were performed with SPSS 22.0.

Results

Between February 2009 and May 2011, 102 patients from four centers were randomly allocated in two arms; 51 patients (50%) in arm A and 51 patients (50%) in arm B. Follow-up information on all-cause mortality was completed for 102 patients (100%). Median follow-up duration for the study population while censoring mortality, was 60 months (range 59–60 months).

Table 1 shows baseline characteristics for the total study population and stratified for the two arms. Mean age was 61.6 years and most patients (68.6%) were male. Most patients (92%) presented with stage III NSCLC. IMRT was applied in more than three-quarters of the patients (76.1%). Comorbidities were significantly more present in arm B (95.7% versus 77.6%). No other significant differences in patient characteristics between the two arms were observed. Furthermore, comparable GTVs (107 cm^3 versus 120 cm^3), PTVs (547 cm^3 versus 451 cm^3) and mean lung doses (16 Gy versus 16 Gy [Table 1]) across study arms A and B were observed.

Table 2 shows OS rates and Fig. 1 shows the Kaplan-Meier survival curve for the two study arms. During a median follow-up of 60 months, 65 (63.7%) patients died, which was not significantly different across study arms. Median OS was 31.5 months, not significantly different between the two arms; 33 and 30 months

Table 1
Baseline characteristics of the total study population and the two study arms.

	Total study population	Arm A	Arm B	*P*-value
Total	102 (100%)	51 (50%)	51 (50%)	–
Age (years)	61.6 (10.0)	60.6 (9.8)	62.7 (10.3)	0.955
Gender (% male)	70 (68.6%)	36 (70.6%)	34 (66.7%)	0.670
Ethnic origin (% non-Asian)	99 (97.1)	50 (98.0%)	49 (96.1%)	0.558
Staging				
IIA/B	8 (8.0%)	2 (4.0%)	6 (11.7%)	0.538
IIIA	52 (52.0%)	27 (55.1%)	25 (49.0%)	
IIIB	40 (40.0%)	20 (40.8%)	20 (39.2%)	
WHO performance score				
0	39 (39.4%)	20 (41.7%)	19 (37.7%)	0.507
1	59 (59.6%)	27 (56.3%)	32 (62.7%)	
2	1 (1.0%)	1 (2.1%)	0 (0.0%)	
Comorbidities				
Yes (%)	82 (86.3%)	38 (77.6%)	44 (95.7%)	0.015
Histology				
Adeno	31 (31.6%)	15 (30.6%)	16 (32.7%)	0.995
Squamous	40 (40.8)	20 (40.8%)	20 (40.8%)	
Large cell	25 (25.5%)	13 (26.5%)	12 (24.5%)	
Other	2 (2.0%)	1 (2.0%)	1 (2.0%)	
Radiation technique				
Three-dimensional conformal	21 (23.9%)	10 (23.8%)	11 (23.9%)	0.992
IMRT	67 (76.1%)	32 (76.2%)	35 (76.1%)	0.991
Pulmonary function				
FEV1 (%)	81.1 (21.1)	82.9 (22.2)	79.0 (19.9)	0.571
Treatment planning				
GTV (cm^3)	119 (62.0–211.0)	107 (25.0–907.0)	120 (5–460)	0.137
PTV (cm^3)	500 (59–1810)	547 (66–1766)	451 (49–1855)	0.104
Mean lung dose (Gy)	16 (4.1–22.7)	16 (4.1–22.7)	16 (7.0–20.0)	0.381
Heart dose 66 Gy $\leqslant$ 33% (% yes)	84% (96.6%)	95.1%	97.8%	0.490

Abbreviations: WHO; World Health Organization, IMRT; intensity modulated radiotherapy, FEV; forced expiratory volume, GTV; gross target volume, PTV; planning target volume, Gy; gray.
P-values $\leqslant$0.05 were considered statistically significant.

Table 2
Overall survival rates.

	Total study population	Arm A	Arm B	*P*-value
Total	102 (100%)	51 (50%)	51 (50%)	–
Mortality	65 (63.7%)	32 (62.7%)	33 (65.7%)	0.837
6-month (%)	94 (92.2%)	48 (94.1%)	46 (90.2%)	0.461
1-year (%)	76 (74.5%)	41 (80.4%)	35 (68.6%)	0.173
2-year (%)	61 (59.8%)	31 (60.8%)	30 (58.8%)	0.840
5-year (%)	38 (37.3%)	19 (37.3%)	19 (37.3%)	1.000
Median (months)	31.5 (12.8–52.3)	33.0 (17.0–57.0)	30.0 (11.0–52.0)	0.722

P-values $\leqslant$0.05 were considered statistically significant.

(*P*-value 0.722). Six-month, 1-, 2- and 5-year OS rates for the total study population were 92.2%, 74.5%, 59.4% and 37.3%, respectively.

In univariate analyses, none of the included characteristics were significantly associated with a shorter OS (Table 3). The existence of comorbidities at baseline was borderline significantly (*P*-value 0.051) associated with a shorter OS (HR 2.76 96% CI 1.00–7.62). In multivariate analyses, worse performance score (HR 2.30 96% CI 1.27–4.16), V35 of the esophagus (HR 1.02 96% CI 1.01–1.04) and the existence of comorbidities (HR 3.29 96% CI 1.01–10.68) were significantly associated with a shorter OS. Additionally, squamous cell carcinoma compared to adenocarcinoma (reference group) was associated with a significantly longer OS (HR 0.50 95% CI 0.28–0.89) within multivariate analyses (Table 3).

Of the 92 included patients with stage IIIA/B NSCLC, 61 (66.3%) died. Median OS was 30 months, not significantly different across the two arms (30 months and 33 months, respectively). Six-month-, 1-, 2- and 5-year OS rates were 91.3%, 72.8%, 58.7% and 34.8%, respectively. OS rates were not significantly different from the total study population, including stage II NSCLC patients. Median OS was longer, but not significantly, in stage IIIA patients compared to stage IIIB patients (38.5 months versus 28.5 months, respectively).

Discussion

In this 60-month follow-up of a randomized phase II study, no beneficial effect of cetuximab on OS was observed in LA-NSCLC patients. Nonetheless, the median OS for the total study population of 31.5 months was exceptionally long. Further, 37.3% of the total study population was still alive at 5 years.

Our trial did not show a survival benefit for the addition of cetuximab, identical results were reported for the RTOG 0617 [9]. A limitation was that patients were not selected based on EGFR expression. However, EGFR was determined in a subsample of 52 patients and showed that the effect of cetuximab was not significantly associated with EGFR expression [13].

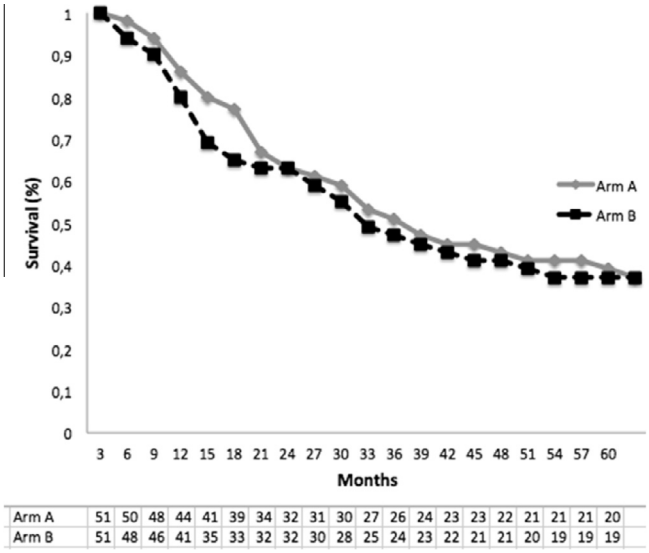

Fig. 1. Kaplan–Meier survival curves for overall survival during 60 months of follow-up. The table represents patients alive during follow-up.

Table 3
Univariate (model 1) and multivariate (model 2) analyses of characteristics associated with overall survival.

	Model 1 (HR)	Model 2 (HR)
Arm (ref; A)	1.09 (0.67–1.77)	
Female (ref; male)	1.08 (0.63–1.82)	
Age (years)	1.01 (0.99–1.04)	
Squamous cell (ref; adenocarcinoma)	0.62 (0.38–1.02)	0.49 (0.28–0.89)*
Comorbidities (ref; no)	2.76 (1.00–7.62)	3.29 (1.01–10.68)*
WHO performance score 1–2 (ref; 0)	1.33 (0.81–2.19)	2.30 (1.27–4.16)*
IMRT (ref; three-dimensional)	0.87 (0.48–1.57)	
Heart dose 66Gy ⩽ 33% (% yes)	1.03 (0.25–4.23)	
Mean lung dose (Gy)	1.00 (0.96–1.04)	
GTV total (cm^3)	1.00 (1.00–1.03)	
PTV (cm^3)	0.98 (0.93–1.04)	
Esophagus V35 (%)	1.01 (1.00–1.03)	1.02 (1.01–1.04)*

Abbreviations: WHO; World Health Organization, IMRT; intensity modulated radiotherapy, GTV; gross target volume, PTV; planning target volume, Gy; gray.
* Statistically significant (*P*-value ⩽ 0.05).

To our knowledge, no other study investigating hypofractionation in combination with concurrent chemotherapy has reported such impressive OS rates. Other studies using hypofractionation schemes used a number of fractions ranging from 15 to 30 with doses per fraction ranging from 2.40 Gy to 3.50 Gy [15–18]. Median OS ranged from 8 months to 29.5 months, compared to 31.5 months in our study. However, most studies were phase I trials including only few patients, which might have influenced the results. Two-year OS rates in our study (59%) are slightly higher than those of total population of the Netherlands Cancer Institute (51%) [19] and the phase II SOCCAR trial [20] (50%) in which a hypofractionation scheme of 20 × 2.75 Gy was given concurrently with cisplatinum and vinoralbine. Moreover, the median OS in the SOCCAR trial was slightly lower (27.4 months versus 31.5 months, respectively). The median OS in our study was also longer than the median OS reported for the RTOG 0617 trial [9]. Patients included in our study were comparable to those included within RTOG 0617 with respect to age, performance score, histology, GTV, PTV and dose constraints. The RTOG 0617 included only stage IIIA/B NSCLC patients, while we included inoperable stage IIA/B NSCLC patients as well. Nonetheless, sensitivity analyses showed that the median OS was still 30 months in stage IIIA/B NSCLC patients. Recently, treatment in a low-volume facility (<4 LA-NSCLC patients treated per year, as defined by the RTOG 0617) within RTOG 0617 showed to be associated with a significantly shorter OS [21]. All of our patients were treated in high-volume (⩾4 LA-NSCLC patients treated per year) centers, while in the RTOG 0617 two-thirds of patients were treated within low-volume facilities [21]. With respect to treatment modality techniques, our dose per fraction was higher with a shorter overall treatment time and the use of IMRT was applied in more than 75% of patients, while in the RTOG 0617 less than half of the patients received IMRT [9]. Lastly, patients within RTOG 0617 received consolidation chemotherapy of paclitaxel and carboplatin.

Taxanes given after radiotherapy are generally not prescribed in Europe for the treatment of NSCLC, due to increased risk of pulmonary toxicity [22–24]. All of these factors might have, at least partly, contributed to our favorable results. Compared to conventional radiation schemes, hypofractionation schemes in LA-NSCLC patients have already showed to be beneficial on OS [25]. Nonetheless, future clinical trials comparing concurrent chemoradiotherapy using hypofractionation schemes with the conventional 30 × 2 Gy scheme might be warranted to truly assess the beneficial effect of hypofractionation on OS.

The use of daily low-dose cisplatinum is not a standard treatment regimen given concurrently with radiotherapy. Although earlier proven effective [26], it seems counterintuitive to treat patients without high dose platinum doublets. Considering the apprehensions of hypofractionation on increased toxicity in combination with concurrent chemotherapy, we showed that low-dose cisplatinum is an acceptable and potent treatment regimen without, perhaps unnecessarily, increasing toxicity risk.

Patients with comorbidities at baseline had a significantly shorter OS than patients without comorbidities. Unfortunately, we did not register specific comorbidities so we cannot elucidate which comorbidities at baseline had a significantly shorter OS. LA-NSCLC patients frequently have additional comorbidities, including COPD, which may increase the risk of radiation-induced pneumonitis [27]. Pulmonary toxicity was also seen more frequently in Arm B, although not statistically significant [13]. Moreover, the treatment arms did not remain present in the multivariate model, implying that comorbidities did not significantly alter the association between treatment and OS. Nonetheless, more research might be warranted to assess the applicability of concurrent chemoradiotherapy in patients with (severe) comorbidities.

There are some limitations of our study. We had no information on cause-specific mortality. Therefore, we cannot elucidate on whether mortality was NSCLC specific. Furthermore, although we had information on progression-free survival [13] until 30 months of follow-up, we did not have information on long-term progression free survival. Another limitation is that we did not register specific comorbidities and (long-term) quality of life of the included patients. Lastly, although our results are promising, the sample size was quite small and strict selection criteria were handled. Therefore, our results, as with all clinical trials, might not be generalizable to clinically treated LA-NSCLC patients who are generally older, have a worse performance score and more comorbidities, including COPD, which may limit applicability of aggressive therapies. Nonetheless, inclusion of patients was completed within a short time interval [13].

To conclude, we showed that a hypofractionated radiotherapy scheme of 24 × 2.75 Gy given concurrently with chemotherapy might be beneficial on OS when compared to conventional radiation schemes. More research is needed to compare concurrent chemoradiotherapy using hypofractionation schemes with conventional radiation schemes in LA-NSCLC patients. Next to that, assessing the effectiveness and applicability of hypofractionation in patients treated within routine clinical practice might be warranted.

Conflict of interest statement

There are no conflicts of interests for any of the authors.

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