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Original Article

The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial)

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ABSTRACT

Background and purpose: The PET-boost randomized phase II trial (NCT01024829) investigated dose-escalation to the entire primary tumour or redistributed to regions of high pre-treatment FDG-uptake in inoperable non-small cell lung cancer (NSCLC) patients. We present a toxicity analysis of the 107 patients randomized in the study.

Materials and methods: Patients with stage II–III NSCLC were treated with an isotoxic integrated boost of ≥72 Gy in 24 fractions, with/without chemotherapy and strict dose limits. Toxicity was scored until death according to the CTCAEv3.0.

Results: 77 (72%) patients were treated with concurrent chemoradiotherapy. Acute and late ≥G3 occurred in 41% and 25%. For concurrent (C) and sequential or radiotherapy alone (S), the most common acute ≥G3 toxicities were: dysphagia in 14.3% (C) and 3.3% (S), dyspnoea in 2.6% (C) and 6.7% (S), pneumonitis in 0% (C) and 6.7% (S), cardiac toxicity in 6.5% (C) and 3.3% (S). Seventeen patients died of which in 13 patients a possible relation to treatment could not be excluded. In 10 of these 13 patients progressive disease was scored. Fatal pulmonary haemorrhages and oesophageal fistulae were observed in 9 patients.

Conclusion: Personalized dose-escalation in inoperable NSCLC patients results in higher acute and late toxicity compared to conventional chemoradiotherapy. The toxicity, however, was within the boundaries of the pre-defined stopping rules.

The majority of inoperable non-small cell lung cancer (NSCLC) patients have high loco-regional progression rates of approximately 30% at two years after treatment with concurrent chemo-radiotherapy (cCRT) [1]. Standard chemo-radiotherapy for patients with a good performance status consists of at least 60 Gy in 6 weeks combined with cis- or carboplatin-based chemotherapy delivered concurrently [2]. A reduction of the overall treatment time (OTT) through the delivery of hypofractionated radiotherapy schedules, e.g. 66 Gy in 24 fractions in 5 weeks, improves both locoregional control and overall survival (OS) in locally advanced NSCLC [3–5]. The outcome of fit patients treated with modern radiotherapy regimes in combination with chemotherapy has improved in recent years with 3-year OS rates of 30–40% [6]. It is promising that comparable survival rates have been reported after 5 years [7,8].

Locoregional recurrences are predominantly observed within the primary tumour, and less frequently within the involved mediastinal lymph nodes [9–12]. Therefore, the local control rate may be improved by escalating the radiation dose to the primary tumour [13–16]. ^{18}F-fluoro-2-deoxy-glucose positron emission tomography (FDG-PET)-scans generate a biological target volume that can be used to guide dose-escalation [17–19]. A study demonstrated that regions of FDG-uptake remained stable during the course of radiotherapy and that the high FDG-uptake regions (≥50% maximum standardized uptake value, SUV_{max}) in the pre-treatment-scan geometrically correlated with residual uptake in the 3-months post-treatment-scan [20]. Furthermore, patients with persisting FDG-uptake within the primary tumour post-radiotherapy had a poorer OS compared to patients achieving complete metabolic response [21–23]. Subsequently, we hypothesized that local tumour control can be increased by dose-escalation to

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the areas of high pre-treatment FDG-uptake within the primary tumour (concept of 'dose-painting') as opposed to a homogeneous dose-escalation to the entire tumour volume [24,25].

These considerations led to the design of the international randomized phase II PET-boost trial (NCT01024829), which investigated dose-escalation using an isotoxic hypofractionated schedule either to the entire primary tumour or redistributed to the regions of high pre-treatment FDG-uptake ($SUV_{max} \geq 50\%$) within the primary tumour. Here, we present the acute and late toxicity results of the 107 patients randomized in the study.

Material and methods

Trial protocol and eligibility

Patients in the PET-boost trial (NCT01024829) were accrued in six hospitals in the Netherlands, Belgium, Denmark, Sweden and the United Kingdom. Patients eligible for registration had pathologically proven inoperable stage II–III NSCLC with a primary tumour diameter ≥4 cm (to allow boosting of a subvolume) and a $SUV_{max} \geq 5$ on the pre-treatment FDG-PET-CT-scan. Patients were ineligible if they had prior RT to the chest, tumour invasion in large blood vessels, clinical vena cava superior syndrome or multiple nodules in the same or ipsilateral lobes.

Eligible patients were randomized to receive ≥72 Gy in 24 fractions (≥3 Gy/fraction) in 32 days with an integrated boost to the planning target volume (PTV) of the entire primary tumour or only to the regions with a $SUV_{max} \geq 50\%$ within the PTV of the primary tumour on the pre-treatment FDG-PET-scan. The maximum boost dose was calculated for each individual patient based on OAR constraints (concept of 'isotoxicity') (Table 1). The dose prescription to involved lymph nodes was not escalated (66 Gy in 2.75 Gy per fraction). Elective nodal irradiation was not permitted. If dose-escalation was not possible due to organ at risk (OAR) constraints, the patient was not randomized and the dose delivered was 66 Gy (in 2.75 Gy fractions) or lower. Chemotherapy was delivered concurrently or sequentially, and RT alone was also allowed.

The primary endpoint of the study is freedom from local failure (FFLF) at 1 year according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1). We hypothesized that dose-escalation and redistribution to regions of high FDG-uptake could improve the 1-year FFLF from 70% to 85%. It was calculated ($\alpha = 5\%$; $\beta = 80\%$, reported 1-year survival in large volume tumours is around 60% [26]) that 82 patients per arm were needed to test this hypothesis. Secondary endpoints included acute and late toxicity, overall survival (OS), distant metastases, out-of-field recurrences and quality of life (EORTC-QoL). The study closed for recruitment on the 31st of October 2017.

FDG-PET-scans, radiotherapy planning and treatment

Eligible patients underwent a 4D-CT-scan and a pre-treatment 3D FDG-PET-scan within 4 weeks of the RT according to the NEDPAS protocol or EANM guidelines [27]. The subvolume of high FDG-uptake for boosting was the fraction of the volume within the primary tumour with a $SUV_{max} \geq 50\%$.

The delineation of the target volumes and the treatment planning procedure were previously reported by Van Elmpt et al. [28]. The OARs were delineated according to the Amsterdam-Maastricht normal tissue atlas (Supplementary material). In addition to the standard thoracic OARs, the mediastinal envelope was delineated to encompass the large blood vessels, the proximal bronchi, the heart and the oesophagus. A planning organ-at-risk volume (PRV) margin of 5 mm was added to the mediastinal envelope.

During treatment planning, an isotoxic radiation treatment plan was optimized for each arm with an equal mean lung dose (MLD). In case of overlap between the primary tumour and the PRV, the PTV was underdosed (maximum 15% of the volume) to meet the dose constraints of the mediastinal envelope (Fig. 1). A maximum dose of 94 Gy (equivalent dose in 2 Gy fractions, EQD_2) in 0.1% of the volume was allowed in the mediastinal envelope. Setup corrections were performed according to local policy. Replanning was advised in case of significant changes of the anatomy.

Toxicity assessment and dose limiting toxicities (DLT)

Patients were evaluated weekly during RT to assess toxicity. Toxicity was scored at each visit and defined according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0) for acute and late toxicity: acute toxicity occurring within 90 days from start of RT and late toxicity ≥90 days after the start of RT. Follow-up consisted of appointments 1 and 3 weeks after RT and subsequently every three months until 18 months. Thereafter, patients were followed-up every 6 months until death.

The pre-defined stopping rules were: ≥20% of patients developing a pre-specified ≥grade 3–4 (G3 or G4) acute and/or late toxicity while the lower bound of the one-tailed 95% CI exceeds 10%. The pre-specified stopping rules were defined for oesophageal, pulmonary, skin and haematologic toxicity (Supplementary material). Dysphagia was a combination of 3 adverse events: oesophagitis, mucositis and dysphagia. For patients with progressive disease, it is challenging to distinguish symptoms related to progressive disease to those related to toxicity. Therefore, the late toxicity rates until progression and until death are reported separately. G4 and G5 toxicities were centrally reviewed by the principal investigators and reported to the Independent Data Monitoring Committee (IDMC).

Statistical analysis

The incidence of toxicity was calculated as a proportion of patients experiencing a specific toxicity calculated for all randomized patients ($N = 107$). Confidence intervals for those proportions were calculated using the exact method. The Mann–Whitney *U*-test was performed to test differences of the prescribed doses to the OARs between the two treatment arms (Table 1). No significant differences were revealed between the 2 arms, except for the brachial plexus, which was only delineated when the tumour was in the upper lobe. The toxicity analyses were performed for both treatment arms combined, however they were presented for concurrent chemotherapy versus sequential chemotherapy/RT alone. Fisher exact test was used to compare toxicity between concurrent chemotherapy versus sequential chemotherapy/RT alone. Analyses were performed for early toxicity versus late. Late toxicity was reported both throughout the entire follow-up period and also until disease progression. Additionally, we calculated the maximum grade of acute and late toxicity per patient. All statistical analyses were done using R (version 3.3.1).

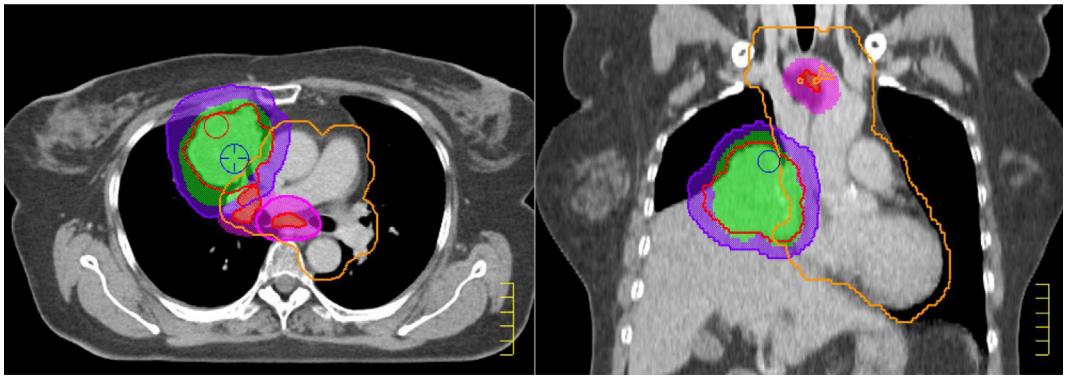
Results

Between April 2010 and June 2015, 150 patients were registered of which 107 patients were randomized. Forty-three patients were not randomized due to OAR constraints, the inability to obtain a CT-thorax with intravenous contrast, logistical problems or regression of primary tumour diameter after chemotherapy to <4 cm. The majority of the 107 randomized patients had stage III NSCLC (87%) and WHO performance status of 0–1 (91%). The patient and tumour characteristics are shown in Table 2. cCRT was given to 77 (72%) patients, RT alone to 20 (19%) and sCRT to 10 (9%). Concurrent chemotherapy regimens consisted of daily Cisplatin (6 mg/m^2) in 34 patients, 3-weekly Cisplatin (75 mg/m^2 d1)-Etoposide

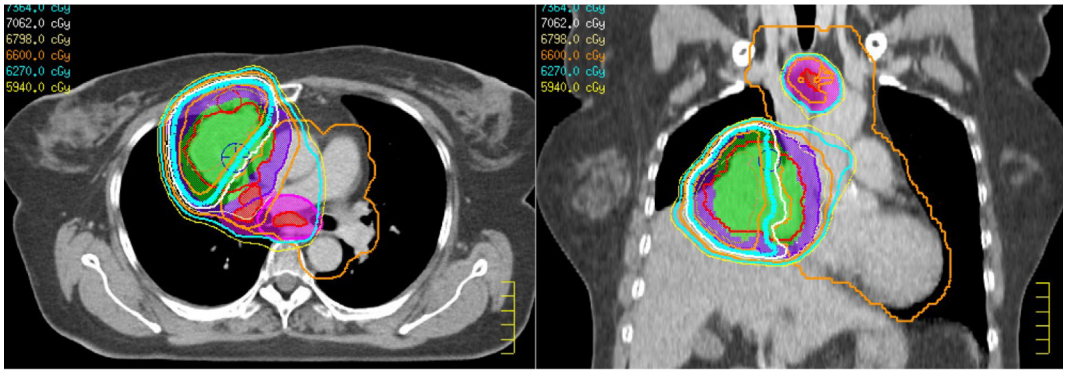
Table 1
Dose constraints to the organs at risk as well as the median dose and interquartile range (IQR) of the organs at risk and tumour volume compared between the 2 treatment arms. Data was not available in all 107 patients; the available cases are shown. All doses are normalized total dose (EQD2) for spinal cord and plexus $\alpha/\beta = 2$ Gy; for lungs, heart and mediastinal envelope $\alpha/\beta = 3$ Gy and for the oesophagus $\alpha/\beta = 10$ Gy.

Organ at risk	Maximum allowed dose	Homogeneous boost (Median, IQR)	Inhomogeneous boost (Median, IQR)	*P*-value	Available cases
Brachial plexus ($EQD2_2$)	D0.1% <79 Gy	64.2 (52.2–65.5)	52.4 (14.8–62.1)	0.03	53
Oesophagus ($EQD2_{10}$)	D0.1% <70 Gy	65.7 (63.9–70.3)	65.4 (62.5–70.6)	0.46	102
Oesophagus mean dose ($EQD2_{10}$)		23.2 (18.4–30.5)	21.7 (15.0–30.9)	0.48	102
Oesophagus ($EQD2_{10}$)	V_{35} < 80%	34.7 (25.2–46.7)	34.0 (16.7–47.3)	0.36	101
Heart ($EQD2_3$)	D0.1% <94 Gy	67.2 (52.5–75.2)	68 (35.5–72.6)	0.56	74
Heart mean dose		8.1 (3.1–17.8)	10.9 (2.2–16.7)	0.96	102
Lung MLD ($EQD2_3$)	<20 Gy	17.2 (14.5–19.2)	16.5 (13.0–18.7)	0.25	102
Lung V20		24.1 (18.3–28.6)	23.8 (17.6–31.3)	0.91	102
Lung V5		73.2 (60.0–86.0)	67.3 (50.9–93.2)	0.63	102
Mediastinal envelope ($EQD2_3$)	D0.1% <94 Gy	90.4 (83.7–92.2)	90.8 (86.4–92.4)	0.47	102
Spinal cord ($EQD2_2$)	D0.1% <53 Gy	46.8 (41.8–49.1)	48.5 (38.0–50.4)	0.40	102
Volume (cc)	GTV tumour	99 (66.5–175)	115 (63.5–175.2)	0.98	99
	GTV LNs	17 (11–47)	19 (9–49)	0.86	78

D0.1% = maximum allowed dose to 0.1% of the volume of the organ at risk.
V_{35} = the volume of the oesophagus receiving 35 Gy.
GTV = Gross tumour volume.
LNs = Involved lymph nodes.



A – Red=gross tumor volume; orange=PRV (mediastinal envelope + 5 mm margin); pink=planning target volume (PTV) of involved lymph nodes; green=PTV of FDG-avid regions (>50% SUV_{max}); purple=PTV of primary tumor.



B – Typical dose distribution of a patient treated with a high radiation dose to the whole primary tumor (homogeneous boost). The thick blue line represents the 95% isodose of the boost dose to the primary tumor; the thin blue line depicts the 95% isodose of 66 Gy to the involved lymph nodes. This example shows that a part of the PTV of the primary tumor overlaps with the mediastinal envelope. This part of the PTV is not escalated and receives the conventional dose of the mediastinal envelope.

Fig. 1. Example of treatment planning taking into account the mediastinal envelope.

Table 2
Baseline patient and tumour characteristics of the 107 randomized patients treated in the PET-boost trial.

Characteristic	Concurrent chemotherapy $N = 77$ (72%)	Sequential chemotherapy $N = 10$ (9%) or RT alone N = 20 (19%)	Total $N = 107$
Median age	64	76	66
Gender			
Male	47 (61%)	21 (70%)	68 (64%)
Female	30 (39%)	9 (30%)	39 (36%)
Performance status			
WHO 0	35 (45%)	5 (17%)	40 (37%)
WHO 1	37 (48%)	22 (73%)	59 (55%)
WHO 2	4 (5%)	3 (10%)	7 (7%)
NA	1 (1%)	0	1 (1%)
T-stage			
T1	1 (1%)	0	1 (1%)
T2	29 (38%)	8 (27%)	37 (35%)
T3	20 (26%)	14 (47%)	34 (32%)
T4	27 (35%)	8 (27%)	35 (33%)
N-stage			
N0	9 (12%)	11 (37%)	20 (19%)
N1	5 (6%)	4 (13%)	9 (8%)
N2	52 (68%)	11 (37%)	63 (59%)
N3	11 (14%)	3 (10%)	14 (13%)
Nx	0	1 (3%)	1 (1%)
TNM-stage (%)			
II	3 (4%)	10 (33%)	13 (12%)
IIIA	50 (65%)	13 (43%)	63 (59%)
IIIB	24 (31%)	7 (23%)	31 (29%)
Histology (%)			
Squamous cell	27 (35%)	14 (47%)	41 (38%)
Adenocarcinoma	24 (31%)	9 (30%)	33 (31%)
Large cell carcinoma	12 (16%)	4 (13%)	16 (15%)
Not otherwise specified	14 (18%)	3 (10%)	17 (16%)

(100 mg/m^2 d1-3) in 27 patients and 3-weekly Cisplatin (75 mg/m^2 d1)–Vinorelbine (60 mg/m^2 d2,8) in 16 patients. Sequential chemotherapy consisted of Cisplatin-Gemcitabine in 10 patients.

Ninety-six of the 107 patients (90%) completed the chemotherapy and radiotherapy according to the study protocol. cCRT was terminated in 1 patient after the first fraction due to a transient ischaemic attack (TIA) secondary to hypotension and pneumonia. One patient died secondary to a pulmonary embolism after 2 fractions. In 2 patients, RT was stopped after 23 fractions because in 1 patient the dose constraint to the PRV in 1 patient had been exceeded (due to tumour regression) and the other patient died due to progressive disease. In 3 patients, the concurrent chemotherapy was discontinued due to an allergic reaction, a TIA secondary to hypotension, and thrombocytopenia. Furthermore, in 3 patients the overall treatment time of 32 days was exceeded (Supplementary material). All patients were treated using a daily Cone-Beam CT-scan (CBCT) based set-up procedure.

The median FU was 38 months and 63 out of 107 patients had died. The acute and late toxicity are shown in Table 3. Table 3B and 3C shows the late toxicity until progression and until death separately. The rate of any G3-5 acute adverse event (maximum grade) per patient was 47% of the patients in the cCRT-group versus 23% in the sCRT/RT group, which was statistically significant ($p = 0.03$). G3-5 late toxicity until progression and until death respectively, was observed in 27% and 43% in the cCRT-group versus 23% and 40% in the sCRT/RT-group, which were not significantly different ($p = 0.81$ and $p = 0.83$; Table 3D).

The rate of $\geq$G3 acute dysphagia was 14.3% in patients treated with cCRT compared to 3.3% in patients treated with sCRT or RT alone ($p = 0.17$) (Table 4). Out of the 107 randomized patients, late dysphagia $\geq$G3 was reported in 15.6% treated with cCRT and in 3.3% of the patients treated with sCRT/RT ($p = 0.11$). Two patients developed dysphagia, which started as an acute toxicity and continued as late, but eventually resolved after 6 and 10 months respectively.

Seventeen patients died secondary to a G5 event, of which 5 (4.7%) patients died within 3 months after completion of the treatment (Table 5). Most common cause of death was pulmonary haemorrhage (5 patients) and an oesophageal fistula (4 patients). Most fatal events developed between 10 and 19 months after treatment, although one patient died after 6 weeks only and another patient after almost 6 years. Patients with fatal pulmonary haemorrhages all had centrally located tumours with encasement of large vessels on the pre-treatment CT-scan. Four patients with a fatal pulmonary haemorrhage had local tumour progression at the time of death and the histology was SCC. The patients that developed G5 fatal pulmonary haemorrhages and fistulae are described in detail in the Supplementary Material.

Discussion

This analysis presents detailed toxicity data of 107 inoperable NSCLC patients randomized in the PET-boost trial between radiation dose-escalation to the primary tumour or to regions with high FDG-uptake within the primary tumour. The dose to the mediastinal envelope and lymph nodes was not escalated. For each patient individually, the RT dose was escalated to a pre-determined maximum dose to OARs with a fixed overall treatment time. This isotoxic strategy as well as the selection of patients with large primary tumour volumes (>4 cm) resulted in higher OAR doses. Therefore, a higher toxicity profile was anticipated compared to patients treated with conventionally fractionated schedules. Furthermore, in this study we continued scoring toxicity even after disease progression, which is not commonly performed.

Table 3
Acute (3A) and late (3B and 3C) toxicity (CTCAEv3.0) in absolute and relative numbers of the 107 randomized patients treated in the PET-boost trial. The late toxicity is reported excluding the patients with progressive disease (PD) (3B) and including the patients with progressive disease (3C). Table 3D shows the maximum grade of toxicity per patient.

A	G1	G2	G3	G4	G5	≥G3 (%) (95% CI)
Cough	52 (48.6%)	17 (15.9%)	3 (2.8%)	0	0	2.8 (0.6–8.0)
Dysphagia	25 (23.4%)	42 (39.3%)	12 (11.2%)	0	0	11.2 (5.9–18.8)
Dyspnoea	39 (36.4%)	12 (11.2%)	4 (3.7%)	0	0	3.7 (1.0–9.3)
Fatigue	39 (36.4%)	20 (18.7%)	2 (1.9%)	1 (0.9%)	0	2.8 (0.6–8.0)
Haematological	11 (10.3%)	9 (8.4%)	9 (8.4%)	4 (3.7%)	0	12.1 (6.6–19.9)
Nausea/vomiting	17 (15.9%)	17 (15.9%)	4 (3.7%)	0	0	3.7 (1.0–9.3)
Weight loss	26 (24.3%)	17 (15.9%)	5 (4.7%)	0	0	4.7 (1.5–10.6)
Pneumonitis	0	5 (4.7%)	2 (1.9%)	0	0	1.9 (0.2–6.6)
Pulmonary haemorrhage	13 (12.1%)	0	0	0	2 (1.9%)	1.9 (0.2–6.6)
Cardiac	3 (2.8%)	1 (0.9%)	3 (2.8%)	1 (0.9%)	2 (1.9%)	5.6 (2.1–11.8)
Other	29 (27.1%)	35 (32.7%)	16 (15.0%)	3 (2.8%)	1 (0.9%)	18.7 (11.8–27.4)

B	G1	G2	G3	G4	G5	≥G3 (%) (95% CI)
Cough	45 (42.1%)	16 (15.0%)	2 (1.9%)	0	0	1.9 (0.2–6.6)
Dysphagia	15 (14.0%)	12 (11.2%)	8 (7.5%)	0	0	7.5 (3.3–14.2)
Dyspnoea	27 (25.2%)	12 (11.2%)	7 (6.5%)	2 (1.9%)	1 (0.9%)	9.3 (4.6–16.5)
Fatigue	29 (27.1%)	13 (12.1%)	2 (1.9%)	0	0	1.9 (0.2–6.6)
Haematological	6 (5.6%)	1 (0.9%)	0	1 (0.9%)	0	1.9 (0.2–6.6)
Nausea/vomiting	7 (6.5%)	2 (1.9%)	2 (1.9%)	0	0	1.9 (0.2–6.6)
Weight loss	14 (13.1%)	7 (6.5%)	2 (1.9%)	0	0	1.9 (0.2–6.6)
Pneumonitis	6 (5.6%)	12 (11.2%)	5 (4.7%)	0	1 (0.9%)	5.6 (2.1–11.8)
Pulmonary haemorrhage	7 (6.5%)	0	1 (0.9%)	0	0	0.9 (0.0–5.1)
Cardiac	4 (3.7%)	4 (3.7%)	1 (0.9%)	1 (0.9%)	0	1.9 (0.2–6.6)

C	G1	G2	G3	G4	G5	≥G3 (%) (95% CI)
Cough	48 (44.9%)	21 (19.6%)	3 (2.8%)	0	0	2.8 (0.6–8.0)
Dysphagia	19 (17.8%)	17 (15.9%)	11 (10.3%)	2 (1.9%)	0	12.1 (6.6–19.9)
Dyspnoea	29 (27.1%)	18 (16.8%)	8 (7.5%)	4 (3.7%)	3 (2.8%)	14 (8.1–22.1)
Fatigue	35 (32.7%)	21 (19.6%)	3 (2.8%)	1 (0.9%)	0	3.7 (1.0–9.3)
Haematological	10 (9.3%)	2 (1.9%)	3 (2.8%)	1 (0.9%)	0	3.7 (1.0–9.3)
Nausea/vomiting	9 (8.4%)	4 (3.7%)	4 (3.7%)	0	0	3.7 (1.0–9.3)
Weight loss	20 (18.7%)	11 (10.3%)	3 (2.8%)	1 (0.9%)	0	3.7 (1.0–9.3)
Pneumonitis	6 (5.6%)	12 (11.2%)	6 (5.6%)	0	1 (0.9%)	6.5 (2.7–13.0)
Pulmonary haemorrhage	13 (12.1%)	0	1 (0.9%)	0	4 (3.7%)	4.7 (1.5–10.6)
Cardiac	5 (4.7%)	5 (4.7%)	2 (1.9%)	2 (1.9%)	2 (1.9%)	5.6 (2.1–11.8)
Fistula	0	1 (0.9%)	0	0	4 (3.7%)	3.7 (1.0–9.3)
Other	22 (20.6%)	29 (27.1%)	29(27.1%)	4 (3.7%)	1 (0.9%)	31.8 (23.1–41.5)

D	G0	G1 (%)	G2 (%)	G3 (%)	G4 (%)	G5 (%)	Total
Maximum grade of acute toxicity	6 (6%)	14 (13%)	44 (41%)	32 (30%)	6 (6%)	5 (5%)	107
Maximum grade of late toxicity until PD	28 (26%)	21 (20%)	30 (28%)	23 (21%)	2 (2%)	3 (3%)	107
Maximum grade of late toxicity	13 (12%)	13 (12%)	36 (34%)	29 (27%)	4 (4%)	12 (11%)	107

The rates of ≥G3 acute dysphagia of 14.3% in patients treated with cCRT and 3.3% in patients treated with sCRT or RT alone are comparable to those reported in the Auperin meta-analysis [2]. The use of a PRV around the mediastinal envelope and strict dose constraints (accepting that 15% of the volume of the PTV could be underdosed in order to meet the mediastinal envelope dose constraints) contributed to this outcome. Also, 96% of the patients treated with cCRT had stage III (versus 66% in the sCRT/RT-group) and only 12% had no involved lymph nodes (versus 37% in the sCRT/RT-group). Nevertheless, the ≥G3 acute dysphagia rates in the cCRT-group were higher than in the 60 Gy-arm of the RTOG 0617-trial, which reported a rate of 7% versus 21% in the 74 Gy-arm [8]. In the EORTC 08972-22973 phase III trial the same hypofractionated schedule of 66 Gy in 24 fractions as in the PET-boost trial was delivered [5]. Radiation was delivered to the primary tumour and involved lymph nodes, with either concurrent or sequential chemotherapy. The late oesophageal toxicity of this hypofractionated schedule was analysed by Chen et al., who reported that 11 (6%) of 171 patients treated with cCRT developed severe toxicity: 8 patients developed a G3 stenosis and 3 patients a G4 fistula [29]. The volume of the oesophagus receiving >76.6 Gy ($EQD2_{10}$) was significantly correlated with G4 dysphagia, as well as the maximum grade of acute dysphagia and the recovery rate. In the PET-boost trial, 2 patients had prolonged dysphagia that resolved completely. Nevertheless, 4 patients developed an oesophageal fistula that very likely caused their death.

Cannon et al. reported the late G4-5 toxicity results of a prospective phase I-trial of 79 locally advanced NSCLC-patients treated with dose-escalated RT according to Normal Tissue Complication Probability (NTCP)-modelling to predict ≥G2 pneumonitis [30]. Most of the patients received neoadjuvant or adjuvant chemotherapy, but 25 patients were treated with RT only. The total dose to the primary tumour as well as involved lymph nodes varied between 57 and 85.5 Gy in 25 fractions. Six patients (7.6%) developed a late G4-5 toxicity, of which 3 (3.9%) died due to a G5 pulmonary haemorrhage. Univariate analysis showed that the dose to a small volume (3 cc) of the proximal bronchial tree was significant. The authors estimated a 5% complication rate after 2 years if the D(3 cc) was 75 Gy or higher.

Recently, Ren et al. and Jeter et al. published the preliminary toxicity results of small phase I trials using hypofractionated dose-escalated RT to the tumour and the lymph nodes in stage III NSCLC-patients [31,32]. Both trials used increasing dose levels, starting at 66 Gy and gradually increased with 3 Gy. Different

Table 4
Acute and late dysphagia (4A), dyspnoea (4B), pneumonitis (4C) and cardiac toxicity (4D) (CTCAEv3.0) according to treatment modality. Late toxicity is reported until progressive disease (PD) as well as including progression.

Acute dysphagia	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	≥G3
cCRT	18	34	11	0	0	11 (14.3%)
sCRT/RT	7	8	1	0	0	1 (3.3%)
Late dysphagia until PD						
cCRT	11	10	7	0	0	7 (9.1%)
sCRT/RT	4	2	1	0	0	1 (3.3%)
Late dysphagia						
cCRT	14	14	10	2	0	12 (15.6%)
sCRT/RT	5	3	1	0	0	1 (3.3%)
Acute dyspnoea	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	≥G3
cCRT	27	8	2	0	0	2 (2.6%)
sCRT/RT	11	4	2	0	0	2 (6.7%)
Late dyspnoea until PD						
cCRT	22	5	6	1	1	8 (10.4%)
sCRT/RT	5	7	1	1	0	2 (6.7%)
Late dyspnoea						
cCRT	22	11	7	2	2	11 (14.3%)
sCRT/RT	7	7	1	2	1	4 (13.3%)
Acute pneumonitis	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	≥G3
cCRT	0	4	0	0	0	0
sCRT/RT	0	1	2	0	0	2 (6.7%)
Late pneumonitis until PD						
cCRT	6	10	4	0	1	5 (6.5%)
sCRT/RT	0	2	1	0	0	1 (1.3%)
Late pneumonitis						
cCRT	6	10	5	0	1	6 (7.8%)
sCRT/RT	0	2	1	0	0	1 (3.3%)
Acute cardiac toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	≥G3
cCRT	1	1	2	1	2	5 (6.5%)
sCRT/RT	2	0	1	0	0	1 (3.3%)
Late cardiac toxicity until PD						
cCRT	2	3	1	0	0	1 (1.3%)
sCRT/RT	2	1	0	1	0	1 (3.3%)
Late cardiac toxicity						
cCRT	3	4	2	1	1	4 (5.2%)
sCRT/RT	2	1	0	1	1	2 (6.7%)

N = 77 were treated with cCRT = concurrent chemo-radiotherapy.
N = 30 were treated with sCRT = sequential chemo-radiotherapy.

radiation techniques were applied: 3D-RT (Ren) and IMRT/IMPT (Jeter). The latter excluded T4-tumours showing direct invasion of the OARs. Ren reported that out of 12 patients included in the study 5 (41.7%) developed G3 dysphagia and 3 (25%) patients developed G3 pneumonitis. In the study by Jeter et al., out of 9 patients treated to 72 Gy, 1 (11.1%) developed G3 dysphagia and out of 6 patients treated to 78 Gy, 2 developed (33.3%) ≥G3 pneumonitis. The respective conclusion of the trials is that the maximum tolerated dose is 69 Gy in 3 Gy/fraction and 72 Gy in 2.4 Gy/fraction, which correspond for both trials to 74 Gy $EQD2_{10}$. However, the authors differed in their interpretation: Ren found the results not acceptable and closed the trial, while the fractionation schedule of Jeter is currently under evaluation in a phase 2 trial (NCT01629498). Major differences with our trial were that we did not escalate the dose to the lymph nodes, consolidation chemotherapy was not allowed and the maximum dose to the oesophagus was restricted to 70 Gy ($EQD_{2,10}$). Furthermore, in the PET-boost trial an isotoxic dose-escalation regimen was applied using IMRT or VMAT in all patients, based on 4D-CT-scan planning and strict constraints to the mediastinal envelope and imaging (matched planning-CT and FDG-PET-CT-scan as well as volumetric image-guidance during treatment).

An incidence of up to 10% of fatal haemorrhages was estimated when we designed the trial due to the inclusion of large (≥4 cm) and generally centrally located tumour volumes [33,34]. A total of 5 patients (4.7%) died of a pulmonary haemorrhage (Table 5). Langendijk et al. described an average fatal bleeding risk of 11.3% in 938 inoperable stage I-III NSCLC patients, treated with RT and/or brachytherapy (BT) [34]. The majority of patients were treated with RT alone (*N* = 840), using a heterogeneous RT-schedule with 46 Gy in 23 fractions or 45 Gy in 20 fractions followed by a boost up to a cumulative dose of 60–70 Gy in fractions of 2.0–2.5 Gy. Doses varied between 61.6 and 72 Gy (EQD_2). Almost half of the 840 patients had centrally located tumours with proven endobronchial tumour in the proximal airways, based on bronchoscopy. In this group, the incidence of a fatal bleeding was significantly higher compared to the patients without endobronchial tumour: 13.1% versus 4.3% ($P < 0.001$). The multivariate analysis revealed that localization of the tumour in the upper lobe and hemoptysis prior to RT were significant risk factors for fatal pulmonary haemorrhages. In the PET-boost trial, patients with large and often centrally located tumours were included and were therefore at a higher risk of G5 pulmonary haemorrhage as described above. In our study, all patients with a G5 pulmonary haemorrhage had centrally located tumours as well as encasement of the large vessels. Kong et al. described recently the results of a phase II-trial in which 42 stage II-III patients were treated with RT and weekly Carboplatin-Paclitaxel followed by consolidation chemotherapy

Table 5
Characteristics of grade 5 acute and late adverse events scored until death of all 107 patients randomized in the PET-boost trial.

Pt	AE[1]	Treatment related	Interval (mths)	Site[2]	TNM	PA[3]	Localization	Fraction dose (Gy)	sCRT/ cCRT[4]	PD[5]	Locoregional/ Distant PD
1	Pulmonary embolism	Not related	During treatment (Died after 2 fractions)	RLL	T3N2	LCC	Central	3.2	cCRT, CE	NAS[6]	NAS
2	Cardiac disorder	Not likely	During treatment (Died after 23 fractions)	LUL	T4N1	AC	Central	3.2	cCRT, CE	NAS	NAS
3	Gastro-intestinal bleeding	Not likely	1.5	LUL	T2N2	AC	Peripheral	3.3	No	NAS	NAS
4	Pulmonary haemorrhage	Possible	1.5	RUL	T4N2	SCC	Central	3.2	cCRT, PE	Yes	Locoregional
5	Pneumosepsis	Certain	3	LUL	T4N2	AC	Central	3.4	cCRT, CE	No	No
6	Respiratory insufficiency due to interstitial lung disease	Not related	3	RUL	T3N2	SCC	Peripheral	3.4	cCRT, CE	No, RT terminated after first fraction	No
7	Pulmonary haemorrhage	Possible	7	RLL	T3N2	SCC	Central	3.2	cCRT, CDDP	Yes	Both
8	Empyema due to fistula in bronchus	Certain	8	RLL	T2N2	LCC	Peripheral	3.3	cCRT, CE	Yes	Distant
9	Fistula trachea-oesophagus	Probable	9	RUL	T3N2	AC	Central	3.7	cCRT, CDDP	Yes	Distant
10	Cardiac failure	Possible	10	LUL	T3N2	SCC	Peripheral	3.5	cCRT, CE	Yes	Both
11	Pulmonary haemorrhage	Possible	10	LLL	T4N0	SCC	Central	3.2	cCRT, CDDP	Yes	Distant
12	Fistula trachea-oesophagus	Probable	65	RLL	T2N2	NOS	Peripheral	3.3	cCRT, PE	No	No
13	Fistula trachea-oesophagus	Certain	18	RUL	T4N2	LCC	Central	3.4	cCRT, CE	Yes	Distant
14	Pulmonary haemorrhage	Possible	12	RUL	T4N2	NOS	Central	3.2	cCRT, PE	Yes	Locoregional
15	Respiratory insufficiency	Possible	18	RUL	T2N0	AC	Peripheral	5.4	cCRT, PV	No	No
16	Pulmonary haemorrhage	Possible	19	LLL	T3N1	SCC	Central	3.0	cCRT, CDDP	Yes	Distant
17	Congestive heart failure	Possible	24	LLL	T4N2	SCC	Central	3.5	cCRT, PE	Yes	Locoregional

[1] AE = Adverse Event.
[2] Site = Location of the tumour in the lung; RLL = right lower lobe; RUL = right upper lobe; LUL = left upper lobe; LLL = left lower lobe.
[3] PA = Pathology; LC = large cell carcinoma; AC = adenocarcinoma; SCC = squamous cell carcinoma; NOS = not otherwise specified.
[4] cCRT = concurrent chemo-radiotherapy; CDDP = low dose Cisplatin; CE = Cisplatinum-Etoposide; PV = Carboplatin-Vinorelbin; PE = Carboplatin-Etoposide.
[5] PD = Progressive Disease.
[6] NAS = Not Assessed.

[35]. Replanning was performed after 40–50 Gy and the FDG-avid regions of the tumour ($SUV_{max} \geq 50\%$) as well as the LNs were boosted to a maximum dose of 86 Gy in 30 fractions based on a midtreatment FDG-PET-CT-scan. Four G5 pulmonary haemorrhages were observed; these patients all had T4-tumours with some degree of invasion of the great vessels. Nevertheless, the local control was promising with 82% after 2 years. Urbanic et al. described 2 G5 pulmonary haemorrhages in 21 stage III NSCLC-patients after treatment in several cohorts using an increasing fraction dose concurrently with chemotherapy followed by consolidation chemotherapy [36]. The authors concluded that the MTD was 60 Gy in 24 fractions of 2.4 Gy. These recent papers show that dose-escalation using integrated boost is feasible, although the suggested schedules differ widely, but may cause severe toxicity at the same time. There is currently no agreement regarding the dose constraints of the airways and blood vessels.

The IDMC recommended a protocol amendment after an interim analysis when 90 patients were included. This included the reassessment of the performance status after chemotherapy, central review of the tumour delineation before randomization and the exclusion of patients with >50% encasement of the large vessels by the primary tumour due to the risk of large vessel invasion [37]. The maximum dose to the PRV of the mediastinal envelope of 115% was adapted from a relative volume percentage of 0.1% to an absolute volume of 1 cc.

In conclusion, the toxicity results of the PET-boost trial revealed that hypofractionated dose-escalation to the primary tumour, but not the lymph nodes, is associated with higher acute and late toxicities compared to conventional chemoradiotherapy. Caution may be warranted for centrally located tumours as well as tumours causing >50% encasement of the large vessels. However, the acute and late toxicity rates were within the boundaries of the predefined stopping rules.

Conflict of interest

None.

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Appendix A. Supplementary data

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