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Radiotherapy and Oncology 181 (2023) 109492

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

^{18}F-FDG-PET guided vs whole tumour radiotherapy dose escalation in patients with locally advanced non-small cell lung cancer (PET-Boost): Results from a randomised clinical trial

Saskia A. Cooke [a,*], Dirk de Ruysscher [b], Bart Reymen [b], Maarten Lambrecht [c,d], Gitte Fredberg Persson [e,f,g], Corinne Faivre-Finn [h], Edith M.T. Dieleman [i], Rolf Lewensohn [j,k], Judi N.A. van Diessen [a], Karolina Sikorska [l], Ferry Lalezari [m], Wouter Vogel [a,n], Wouter van Elmpt [b], Eugène M.F. Damen [a], Jan-Jakob Sonke [a], José S.A. Belderbos [a,*]

[a] Department of Radiation Oncology, Netherlands Cancer Institute (NKI-AVL), Amsterdam, the Netherlands; [b] Department of Radiation Oncology (MAASTRO Clinic), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands; [c] Department of Oncology, Experimental Radiation Oncology, KU Leuven – University of Leuven, Leuven, Belgium; [d] Department of Radiotherapy-Oncology, University Hospitals Leuven, Gasthuisberg, Belgium; [e] Department of Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [f] Department of Oncology, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark; [g] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [h] Department of Clinical Oncology, University of Manchester, The Christie NHS Foundation Trust, Manchester, UK; [i] Department of Radiation Oncology, location AMC, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands; [j] Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden; [k] Theme Cancer, Section of Head, Neck, Lung and Skin Tumours, Karolinska University Hospital, Stockholm, Sweden; [l] Department of Biometrics, Netherlands Cancer Institute (NKI-AVL), Amsterdam, the Netherlands; [m] Department of Radiology, Netherlands Cancer Institute (NKI-AVL), Amsterdam, the Netherlands; [n] Department of Nuclear Medicine, Netherlands Cancer Institute (NKI-AVL), Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 9 September 2022
Received in revised form 20 December 2022
Accepted 17 January 2023
Available online 24 January 2023

Keywords:
Locally advanced non-small cell lung cancer
Radiotherapy
Dose escalation
18F-FDG-PET
Hypofractionation

ABSTRACT

Background and purpose: We aimed to assess if radiation dose escalation to either the whole primary tumour, or to an ^{18}F-FDG-PET defined subvolume within the primary tumour known to be at high risk of local relapse, could improve local control in patients with locally advanced non-small-cell lung cancer.
Materials and methods: Patients with inoperable, stage II-III NSCLC were randomised (1:1) to receive dose-escalated radiotherapy to the whole primary tumour or a PET-defined subvolume, in 24 fractions.
The primary endpoint was freedom from local failure (FFLF), assessed by central review of CT-imaging. A phase II 'pick-the-winner' design (alpha = 0.05; beta = 0.80) was applied to detect a 15 % increase in FFLF at 1-year. ClinicalTrials.gov:NCT01024829.
Results: 150 patients were enrolled. 54 patients were randomised to the whole tumour group and 53 to the PET-subvolume group. The trial was closed early due to slow accrual. Median dose/fraction to the boosted volume was 3.30 Gy in the whole tumour group, and 3.50 Gy in the PET-subvolume group. The 1-year FFLF rate was 97 % (95 %CI 91–100) in whole tumour group, and 91 % (95 %CI 82–100) in the PET-subvolume group. Acute grade $\geq$ 3 adverse events occurred in 23 (43 %) and 20 (38 %) patients, and late grade $\geq$ 3 in 12 (22 %) and 17 (32 %), respectively. Grade 5 events occurred in 19 (18 %) patients in total, of which before disease progression in 4 (7 %) in the whole tumour group, and 5 (9 %) in the PET-subvolume group.
Conclusion: Both strategies met the primary objective to improve local control with 1-year rates. However, both strategies led to unexpected high rates of grade 5 toxicity. Dose differentiation, improved patient selection and better sparing of central structures are proposed to improve dose-escalation strategies.
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Until recently, for fit patients with unresectable, locally advanced non-small cell lung cancer (LA-NSCLC), the standard of care consisted of concurrent radiotherapy and platinum-based chemotherapy. Despite the curative intent of this treatment, survival rates are poor, with 5-year survival rates of only 25–33 %. [1–3] High rates of local relapses occurring as first event in about one third of the patients and cumulatively in > 50 % are recognised to have a negative impact on overall survival.[1,4].

Tumour control probability models suggest intensified radiation doses are required to achieve higher rates of local control. [5–7] Based on the premise that areas within a tumour are heterogeneously sensitive to treatment, some areas may need higher doses of radiation. Previous studies have shown areas with high

* Corresponding authors at: Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam 1066 CX, the Netherlands.
E-mail addresses: s.cooke@nki.nl (S.A. Cooke), J.belderbos@nki.nl (José S.A. Belderbos).

https://doi.org/10.1016/j.radonc.2023.109492
0167-8140/

uptake of ^{18}F-fluordeoxyglucose (^{18}F-FDG) on pre-treatment positron emission tomography (PET) scan correspond with residual metabolic-active areas after chemoradiotherapy, and these areas correspond to preferential sites of local relapse.[8,9] As these areas also have been demonstrated to remain stable within the primary tumour during a course of radiotherapy, these areas present an attractive target for dose escalation.[10].

The question we addressed in the ARTFORCE PET-boost trial was whether dose redistribution within the tumour, targeting the most ^{18}F-FDG-avid area, or homogenously escalated to the whole primary tumour, is beneficial in improving local control rates.[11].

Materials and methods

This phase 2, open-label, randomised, investigator-initiated clinical trial was part of the European ARTFORCE consortium, and conducted at seven sites in five countries. The trial protocol, with all in- and exclusion criteria, is provided in Appendix A.

In summary, inclusion criteria were age $\geq$ 18 years, inoperable stage II-III pathologically confirmed NSCLC, a primary tumour $\geq$ 4 cm in diameter with no satellite lesions and a SUVmax $\geq$ 5 on the pre-treatment 18F-FDG-PET scan (to allow targeting of sub-volumes), Eastern Cooperative Oncology Group performance score of $\leq$ 2 and adequate pulmonary, hepatic, renal and haematological function. Exclusion criteria included prior chest radiotherapy, and atelectasis or infiltration that could not be distinguished from tumour on ^{18}F-FDG-PET/CT scan.

Pre-defined stopping rules entailed $\geq$ 20 % of patients developing grade $\geq$ 3 or $\geq$ 4 of pre-specified oesophageal, pulmonary, skin or haematologic toxicities. An independent data monitoring committee performed an interim analysis after enrolment of 90 patients to assess adverse events. This led to an amendment (Feb 02, 2016) of the eligibility criteria to exclude patients with > 50 % encasement of large blood vessels, or tumour growth into large blood vessels, and reduction in the maximum dose to the mediastinum.

Baseline investigations included medical history and physical examination, chest radiography, pathologic confirmation of NSCLC, ^{18}F-FDG-PET/CT scan, blood tests, and pulmonary function tests. Staging was performed according to American Joint Committee on Cancer TNM 7th edition, and Union for International Cancer Control version 7.

All patients provided written informed consent before enrolment. The study was performed with ethics committee approval from each participating site, and in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The trial was registered at ClinicalTrials.gov:NCT01024829.

Treatment

Patients were randomised to receive an integrated, escalated radiation dose delivered either to the primary tumour as a whole, or redirected towards a PET-defined subvolume within the primary tumour. This PET-subvolume was defined as the area within the primary tumour that held a SUV $\geq$ 50 % SUV$_{max}$ on the pre-treatment ^{18}F-FDG-PET scan.

The aim of the treatment strategy was to increase the probability of primary tumour control for each patient in both treatment arms, hypothesising further escalated doses are needed for areas with highest FDG uptake, isotoxically within healthy tissue dose limits.

Two dose plans, one for each treatment arm, were made and approved before randomisation to ensure pulmonary isotoxicity (Fig. 1). Predefined organs at risk (OAR) constraints were prioritised higher than dose escalation. If the fraction dose could not be escalated to $\geq$ 3 Gy due to OAR constraints, the patient was not randomised, but registered and planned to receive conventional treatment ($\leq$ 24 x 2.75 Gy).

The fraction dose in both arms was escalated as high as possible, within the range of 3.0 to 5.4 Gy, and was determined by OAR constraints. To achieve pulmonary isotoxicity, the two treatment plans were required to have an equal mean lung dose (MLD). [11] As the PET-subvolume is generally smaller than the whole tumour, the dose in this arm could be escalated higher before reaching the same MLD (max. 20 Gy EQD2$_{\alpha/\beta=3Gy}$). In both arms, the dose was prescribed integrated in 24 fractions (daily 5 days/week, overall treatment time 32–39 days).

In our trial, lymph nodes did not receive an escalated dose, as isolated lymph node recurrences are known to occur less commonly than local recurrences,[12] and to limit exceeding doses to lung and critical mediastinal structures, including to the oesophagus and heart. Instead, involved lymph nodes were planned to receive 66 Gy (24 x 2.75 Gy). Elective nodal irradiation was also not allowed.

Appendix Table B.3 details amendments of OAR constraints during the course of the study. In the most recent protocol, constraints included: mediastinum max. dose < 84 Gy (EQD2$_{\alpha/\beta=3Gy}$), oesophagus V$_{35Gy}$ < 65 % (EQD2$_{\alpha/\beta=10Gy}$), oesophagus + 5 mm margin max. dose < 70 Gy (EQD2$_{\alpha/\beta=10Gy}$), heart max. dose < 84 Gy (EQD2$_{\alpha/\beta=3Gy}$).

For radiotherapy planning, a 4D-^{18}F-FDG-PET/CT-scan, or an ^{18}F-FDG-PET with a matched 4D-planning CT-scan, was acquired maximum four weeks before start of radiotherapy and followed NEDPAS protocol,[13] or EANM PET-imaging guidelines. Details

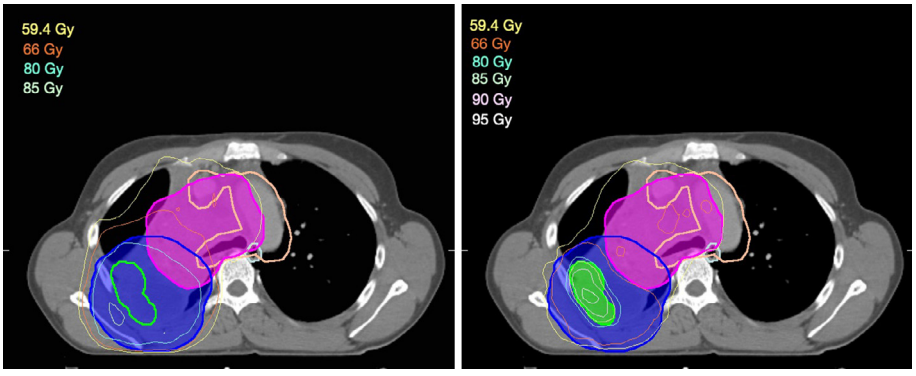

Fig. 1. Panel A shows a dose distribution for escalation to the primary tumour as a whole (PTV$_{prim}$ in blue). Panel B shows a dose distribution escalation to the PET-subvolume (PTV$_{PET}$ in green, $\geq$50% SUV$_{max}$ on patients' pre-treatment ^{18}F-FDG-PET/CT) within the primary tumour for the same patient. The two plans were required to have an equal mean lung dose, delivering 24 fractions in the range of 3.0-5.4 Gy, determined by predefined organ at risk constraints. As the PET-subvolume is generally smaller than the whole tumour, the fraction dose in this plan could generally be escalated higher before reaching the same mean lung dose. Lymph nodes (PTV$_{ln}$ in pink) did not receive a dose escalation, but were planned to receive 66 Gy in the same 24 fractions. Organ at risk constraints were prioritised over fraction dose escalation. The mediastinal envelope plus a 5 mm margin, used as planning risk volume, is represented by the salmon line. PTV=planning target volume.

on planning-CT reconstruction procedures, planning target volumes (PTV), required dose homogeneity, study centre onboarding procedures, and methods to calculate an equivalent dose in 2 Gy per fraction (EQD2) and biological effective doses (BED) are described in Appendix Methods B.1.

During delineation, a distinction was made between the gross tumour volume of the primary tumour (GTV_{prim}), the PET-defined area within the primary tumour (GTV_{PET}) and the involved lymph nodes (GTV_{ln}). The escalated fraction dose was prescribed to the PTV_{prim} or PTV_{PET}, in accordance with randomisation. In the PET-subvolume dose-escalation plan, the annular region formed by the PTV_{prim} minus PTV_{PET} was prescribed at least 90 % of 66 Gy in the same 24 fractions. If overlap existed between PTV_{prim} or PTV_{PET} and an OAR, 15 % of the PTV could be underdosed (Appendix Fig.B.1). The final PTV dose to the entire tumour depended on the fraction dose to which could be escalated before reaching an OAR limit, and therefor depended on individual patient factors, such as tumour size and location, ratio of PET-subvolume to whole primary tumour volume, and whether an edit was made to the PTV in case of overlap with an OAR. The PTV doses were not kept consistent as a pre-specified goal during planning for both arms, only the MLD was kept consistent.

Treatment was delivered using intensity modulated radiotherapy, or volumetric modulated arc therapy. Image guidance with daily cone-beam CT was mandatory. In case of significant changes during treatment, re-planning was advised.

Patients were treated with concurrent or sequential chemotherapy, or radiotherapy alone. Choice of chemotherapy depended on local policy, and consisted of concurrent daily low-dose Cisplatin (6 mg/m^2), or concurrent or sequential Cisplatin (75 mg/m^2 d1) with Etoposide (100 mg/m^2 d1-3, Q31-days) or 3-weekly Cisplatin (75 mg/m^2 d1) with Vinorelbine (60 mg/m^2, d2 + 8, Q21-days). Chemotherapy was limited to three cycles. Consolidation chemotherapy was not allowed.

Endpoints

The primary endpoint was freedom from local failure (FFLF) at 1-year. Local failure was defined as $\geq$ 20 % (and minimum $\geq$ 5 mm) growth of the primary tumour from nadir, as assessed by independent central review of CT-imaging. Secondary endpoints were overall survival, local and regional failures outside PTV, distant metastases, toxicity, and quality of life. Additionally, for comparison purposes, progression free survival was assessed. Appendix Methods B.2 provides definitions of local, regional and distant recurrences.

Clinical assessment took place weekly during treatment, after treatment at 1 and 3 weeks, at 3, 6, 12 and 18 months, and thereafter yearly until death. Local investigators scored adverse events using the Common Terminology Criteria (version 3.0), and were categorised as acute or late ($\leq$ 90 days or > 90 days from start radiotherapy).

Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumours (v1.1), with the use of CT-imaging or ^{18}F-FDG-PET/CT planned at 3, 6, 12 and 18-months. An independent central review of response on thoracic CT-scans was done by a dedicated thoracic radiologist, unaware of the treatment assignments. A biopsy was not required to confirm disease progression.

Statistical methods

The study was setup as a 'pick-the-winner' trial, using an A'Hern's single stage phase-II design.[14] The primary objective was to improve the 1-year FFLF rate by + 15 %, comparing each arm with a historical rate of 70 % achieved with standard dose (66 Gy).[15] Fixing one-sided type I error to 0.05, power to 80 %, and assuming 60 % 1-year survival, the trial required 82 patients in each arm. In the pick-the-winner design, each arm is evaluated separately, hence no formal statistical tests were performed for differences between the two groups.

The protocol was amended (May 6, 2015) changing the primary endpoint from 1-year local progression-free survival (LPFS), primarily to focus the analysis on local effect of treatment, precluding death as an event. We reasoned LPFS would be partly determined by the number of deaths, not revealing the ratio between local failures vs deaths, nor the cause of death. The sample size calculation was adjusted accordingly.

Randomisation was performed 1:1, computer-generated through minimisation, and stratified by treatment centre and chemotherapy schedule (concurrent vs sequential/none). After randomisation, clinicians and participants were aware of the treatment assignment.

All time-to-event endpoints were measured from date of randomisation. FFLF, OS and PFS were estimated using the Kaplan-Meier method (with two-sided 95 % confidence interval, 95 % CI). In the Kaplan Meier estimate of FFLF, local failure was taken as event, and patients who did not experienced a local failure at last follow-up, or died without a known local failure, were censored.

Additionally, we estimated the cumulative incidence of local, regional and distant recurrences, applying competing-risks method.[16] Using this method, the first recurrence was taken as event, in competing risk with death. Descriptive statistics summarise baseline patient, tumour and treatment parameters, and adverse events. In a post-hoc analysis, we assessed an association between dose to normal tissue and the occurrence of grade $\geq$ 3 adverse events using Wilcoxon-rank-sum tests.

All analysis were done in the intention-to-treat population, i.e., all randomised patients. A statistical analysis plan was approved by investigators before analysis commenced. Analyses of quality-of-life data will be reported separately. Statistical analyses were performed with SAS (v9.4) and R (v4.0.2).

Results

Hundred-fifty patients were enrolled between April 23, 2010 and September 15, 2017 from five European institutions (Fig. 2, Appendix Table B.2). As a result of slower accrual than anticipated, the trial management group decided to close the trial early. Of 150 patients included, 107 were eligible for dose escalation and were subsequently randomised: 54 to receive escalated-dose to the whole tumour, and 53 to the PET-subvolume. Here we publish analysis of data reported as of April 29, 2021. The median follow-up was 73.3 months (IQR 61.4–77.6).

The most common reason for ineligibility (n = 43) was dose to normal tissue precluding dose escalation (49 %). Patients who were not randomised generally had larger tumour volumes compared to randomised patients ($GTV_{prim+nodes}$ 244 vs 133 cm^3, p = 0.005). No analysis of outcome was performed for this group.

Table 1. provides baseline characteristics. Median GTV_{prim} was 99 cm^3 (IQR 65–176) in the whole tumour group, and 115 cm^3 (IQR 64–180) in the PET-subvolume group. The median GTV_{PET} was 29 cm^3 (IQR 14–52) in the PET-subvolume group. Overall, 72 % of patients received concurrent and 9 % sequential chemoradiotherapy, while 19 % were treated with radiotherapy alone. Details on chemotherapy regimens, compliance and adverse events per regime were published previously.[17].

The median escalated fraction dose was 3.30 Gy (IQR 3.20–3.40) to the PTV_{prim} in the whole tumour group, and 3.50 Gy (IQR 3.40–3.78) to the PTV_{PET} in the PET-subvolume group. In the PTV_{prim} group, the maximum fraction dose planned was 4.1 Gy, while in

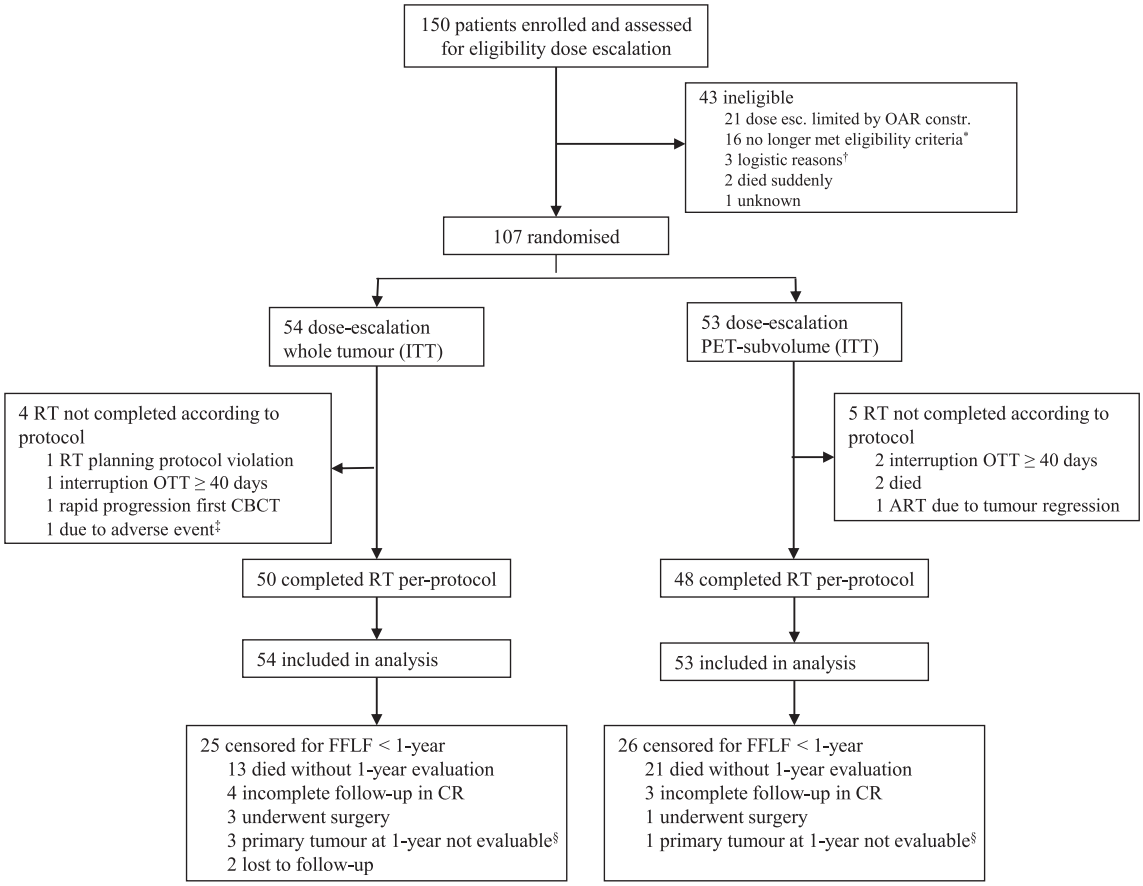

Fig. 2. *Consists of renal failure (n=3), no longer measurable primary tumour (n=3), rapidly progressive disease (n=7), adverse events (n=2), and atelectasis (n=1). † Consists of treatment planning system switch (n=2) and availability of PET-scanner (n=1). ‡ In the whole tumour group, adverse event was reason not to complete radiotherapy for one patient, which consisted of febrile neutropenia followed by a cardiac event. Two patients in the PET-subvolume group died suddenly during treatment, one from pulmonary embolism, and one from progressive disease. § Total of 4 patients had radiographic changes (including fibrosis, atelectasis) hampering response assessment of primary tumour. Abbreviations: OAR = organ at risk. ITT = intention to treat. OTT = overall treatment time. RT = radiotherapy. CBCT = cone beam chest-CT imaging. ART = adaptation of radiotherapy plan, in this case early termination due to tumour regression, which would have resulted in excess dose to healthy tissue. FFLF = freedom from local failure, primary endpoint of the study. CR = central review of CT-scans for assessment of primary endpoint.

the PET-subvolume group five patients were planned to receive the maximum allowed 5.4 Gy per fraction to the PET-defined target. The median PTV_{prim} mean dose was 77.5 Gy in the whole tumour, and 74.2 Gy in the PET-subvolume group. Further treatment details are provided in Table 2.

Protocol compliance is summarised in Appendix Table B.3. Of 107 patients randomised, one major protocol deviation was noted (fractionation schedule). Further, four patients underwent surgical resection of the primary tumour after study treatment. These patients were selected during tumour board meetings after response evaluation. None of these patients had documented local progression by central review, and this therefore represented a deviation from protocol.

CT-images were assessed by central review for 49 (92 %) and 48 (91 %) patients, respectively, with a median follow-up of 12.6 months (IQR 5.2–24.6). At 1-year, 29 and 27 patients were evaluable for assessment of local control, respectively. The primary tumour was non-evaluable at 1-year due to equivocal post-radiotherapy changes on CT-scans, in three and in one patients, respectively. Patients who underwent non-protocol surgery were considered in the analysis up to the date of last centrally reviewed CT-scan prior to surgery.

Using the Kaplan Meier method (Fig. 3), the 1-year FFLF rate was 97 % (95 %CI 91–100) and 91 % (95 %CI 82–100), respectively. At 18-months, the FFLF rate was 89 % (95 %CI 78–100) and 82 % (95 %CI 68–99), respectively.

In the whole tumour group, when accounting for competing risk of events (Fig. 3, Appendix Table B.4), the 1-year estimate of site of first recurrence was local in 1.9 %(95 %CI 0.0–5.6 %), regional in 1.9 %(95 %CI 0.0–5.6), distant in 37.4 %(95 %CI 24.4–50.4), and simultaneous local/regional and distant in 3.7 %(95 %CI 0.0–8.7), while death as first event occurred in 7.5 %(95 %CI 0.4–14.5). In the PET-subvolume, the 1-year estimate of first recurrence was local in 1.9 %(95 %CI 0.0–5.5 %), regional in 5.7 %(95 %CI 0.0–11.9), distant in 35.8 % (95 %CI 22.9–48.8), simultaneous local/regional and distant in 1.9 %(95 %CI 0.0–5.5). Death as first event occurred in 9.4 %(95 %CI 1.6–17.3). Regional recurrences differentiated to be in-field or out-of-field, are reported in Appendix Fig.B.2.

For overall survival (Fig. 3), two patients were lost to follow-up. Median OS was 18 months (95 %CI 15–50) and 18 months (95 %CI 12–30), and 1-year OS 76 %(95 %CI 65–88) and 62 %(95 %CI 50–77), respectively. PFS at 1-year was 46 %(95 %CI 34–61) and 43 %(95 %CI 32–59), respectively (Appendix Fig.B.3).

Adverse events, recorded up to progression, are comprehensively provided in Appendix B. Acute ≥ grade 3 (≥G3) AEs in the whole tumour group occurred in 23 patients (43 %), consisting mainly of leukocytopenia (13 %), dysphagia/oesophagitis (11 %), dyspnoea (7 %), and radiation pneumonitis (4 %). Acute ≥ G3 AEs in the PET-subvolume group, occurred in 20 patients (38 %), consisting mainly of dysphagia/oesophagitis (11 %), leukocytopenia (9 %), cough (4 %), nausea/vomiting (4 %), and pain (4 %), but no radiation pneumonitis.

Table 1
Baseline characteristics and chemotherapy data.

	Dose escalation to whole primary tumour (n = 54)	Dose escalation to PET-subvolume (n = 53)
Age, years (median, range)	65.5 (40–83)	69.0 (60–74)
Sex		
Male	37 (69 %)	31 (58 %)
Female	17 (31 %)	22 (42 %)
T-stage		
T1	0 (0 %)	1 (2 %)
T2	18 (33 %)	19 (36 %)
T3	17 (31 %)	18 (34 %)
T4	19 (35 %)	15 (28 %)
N-Stage		
N0	8 (15 %)	12 (23 %)
N1	3 (6 %)	6 (11 %)
N2	36 (67 %)	27 (51 %)
N3	7 (13 %)	7 (13 %)
Nx	0 (0 %)	1 (2 %)
Stage (UICC 7th edition)		
Stage II	5 (9 %)	8 (15 %)
Stage IIIA	30 (56 %)	33 (62 %)
Stage IIIB	19 (35 %)	12 (23 %)
Histology		
Squamous cell carcinoma	17 (31 %)	24 (45 %)
Adeno carcinoma	17 (31 %)	16 (30 %)
Large cell carcinoma	10 (19 %)	7 (13 %)
Other NSCLC	10 (19 %)	6 (11 %)
ECOG performance status		
0 – 1	49 (91 %)	51 (96 %)
2	5 (9 %)	2 (4 %)
Pulmonary function FEV1 (L/s)	2.27 (1.71 – 2.77)	2.20 (1.44 – 2.70)
Smoking history		
Previous	32 (59 %)	31 (58 %)
Current	22 (41 %)	20 (38 %)
Never	0 (0 %)	2 (4 %)
Chemotherapy		
Concurrent	41 (76 %)	36 (68 %)
Sequential	4 (7 %)	6 (11 %)
None	9 (17 %)	11 (21 %)

Data are median (IQR) or number (%), unless otherwise indicated. UICC = Union for International Cancer Control. ECOG = Eastern Cooperative Oncology Group. FEV1 = forced expiratory volume in 1 second.

Late $\geq$ G3 AEs occurred in 12 patients (22 %) in the whole tumour group, consisting mainly of dyspnoea (17 %), dysphagia/oesophagitis (9 %), pain (9 %), and radiation pneumonitis (2 %). In the PET-subvolume group, late $\geq$ G3 AEs occurred in 17 (32 %), consisting of dyspnoea (13 %), pain (15 %), dysphagia/oesophagitis (11 %), infections (13 %), and radiation pneumonitis (11 %).

Grade five events (Appendix Table B.5) occurred in 19 patients in total, of which 15 were scored as (possibly) related to (chemo) radiotherapy. Ten of these 19 had documented progressive disease. In the whole tumour group, grade 5 events (with any relation) consisted of haemorrhage (n = 4), oesophageal fistula (n = 2), respiratory insufficiency (n = 1) and cardiac event (n = 1). In the PET-subvolume group, grade 5 events consisted of haemorrhage (n = 3), cardiac events (n = 3), oesophagus fistula (n = 1), broncho-pleural fistula (n = 1), respiratory insufficiency (n = 1), pneumonitis (n = 1) and pulmonary embolism (n = 1).

A protocol amendment (June 6, 2013), introduced an oesophagus +5 mm maximum dose constraint, after which a substantial reduction was seen in occurrence of grade 4 – 5 oesophageal toxicity (n = 5/54 vs n = 0/53). Additionally, when taking events up to death (after progression) into account, higher oesophagus doses were significantly associated with $\geq$ G3 oesophageal events.

Table 2
Radiotherapy details.

	Dose escalation to whole primary tumour (n = 54)	Dose escalation to PET-subvolume (n = 53)
Gross tumour volume		
primary tumour (cm^3)	99.0 (65.0–176)	115 (62.5–178)
PET-subvolume (cm^3)	n.a.	29.0 (14.3–52.0)
primary tumour + lymph nodes (cm^3)	134 (96.0–230)	131 (85.3–202)
PTV		
primary tumour (cm^3)	334 (260–508)	377 (250–474)
PET-subvolume (cm^3)	n.a.	120 (63.0–168)
primary tumour + lymph nodes (cm^3)	499 (397–647)	487 (344–659)
Prescribed dose to dose escalation target		
Physical fraction dose (Gy)	3.3 (3.2 – 3.4)	3.5 (3.4 – 3.8)
Physical total dose (Gy)	79 (77 – 82)	84 (82 – 91)
Overall treatment time (days)		
Median + IQR	33.5 (32 – 34.8)	34.0 (32.0 – 35.0)
< 32 days (stopped early)	4 (7 %)	1 (2 %)
32 – 39 days (per protocol)	48 (89 %)	50 (94 %)
$\geq$ 40 days (treatment interrupted)	2 (4 %)	2 (4 %)
Fractions received		
24	52 (94 %)	50 (94 %)
< 24 (stopped early)	2 (4 %)	3 (6 %)
> 24 (protocol violation)	1 (2 %)	0
Technique		
IMRT	33 (61 %)	32 (60 %)
VMAT	21 (39 %)	21 (40 %)
Megavoltage beams		
6 MV	10 (19 %)	8 (15 %)
10 MV	44 (81 %)	44 (83 %)
Unknown	0	1 (2 %)
Prescribed dose		
Mean dose to PTV_{prim} (Gy)	77.0 (74.2–80.6)	74.2 (72.3–77.8)
Mean dose to PTV_{PET} (Gy)	n.a.	83.3 (78.0–90.1)
PTV_{prim} V90% (%)	99.1 (86.1–99.7)	99.6 (97.0–99.9)
PTV_{PET} V90% (%)	n.a.	99.0 (85.7–99.2)
OAR – lung		
Mean dose (physical) (Gy)	18.1 (15.0–20.0)	17.7 (14.1 – 20.0)
Mean dose (EQD2 α/β = 3 Gy) (Gy)	17.3 (14.5 – 19.1)	16.5 (13.1–18.7)
V5 (%)	64.7 (56.2 – 71.9)	61.8 (51.0 – 76.4)
V20 (%)	28.7 (23.1 – 32.8)	28.6 (22.6 – 35.3)
OAR – mediastinal envelope PRV		
Max dose D0.1 % (physical) (Gy)	74.2 (70.5–75.2)	74.4 (71.2–75.3)
OAR - oesophagus		
Mean dose (EQD2 α/β = 10 Gy) (Gy)	25.5 (19.0 – 33.0)	25.3 (18.6 – 33.0)
V36 (%)	36.2 (27.2 – 46.9)	35.7 (19.5 – 46.6)
Max dose D0.1 % (EQD2 α/β = 10 Gy) (Gy)	69.5 (67.4 – 75.8)	69.4 (66.0 – 75.2)
OAR – heart		
Mean dose (EQD2 α/β = 3 Gy) (Gy)	8.1 (3.1 – 17.8)	11.0 (2.7 – 17.2)
Max dose D0.1 % (EQD2 α/β = 3 Gy) (Gy)	67.2 (52.5 – 75.3)	68.0 (40.5 – 72.8)
OAR – nervous system		
Brachial plexus max dose D0.1 % (EQD2 α/β = 2 Gy)	74.9 (54.5 – 77.4)	57.5 (10.8 – 73.8)
Spinal cord max dose D0.1 % (EQD2 α/β = 2 Gy)	46.8 (41.8 – 49.0)	48.3 (36.7 – 50.3)

Data are median (IQR) or number (%). PTV = planning tumour volume. IMRT = intensity-modulated radiation therapy. VMAT = volumetric modulated arc therapy. MV = megavolt. OAR = organ at risk. PRV = planning risk volume. EQD2 = equivalent dose delivered in 2 Gy fractions. Vx = volume (%) receiving $\geq$ x prescribed dose. D0.1 % = highest dose delivered to 0.1 % of volume, i.e. near maximum dose.

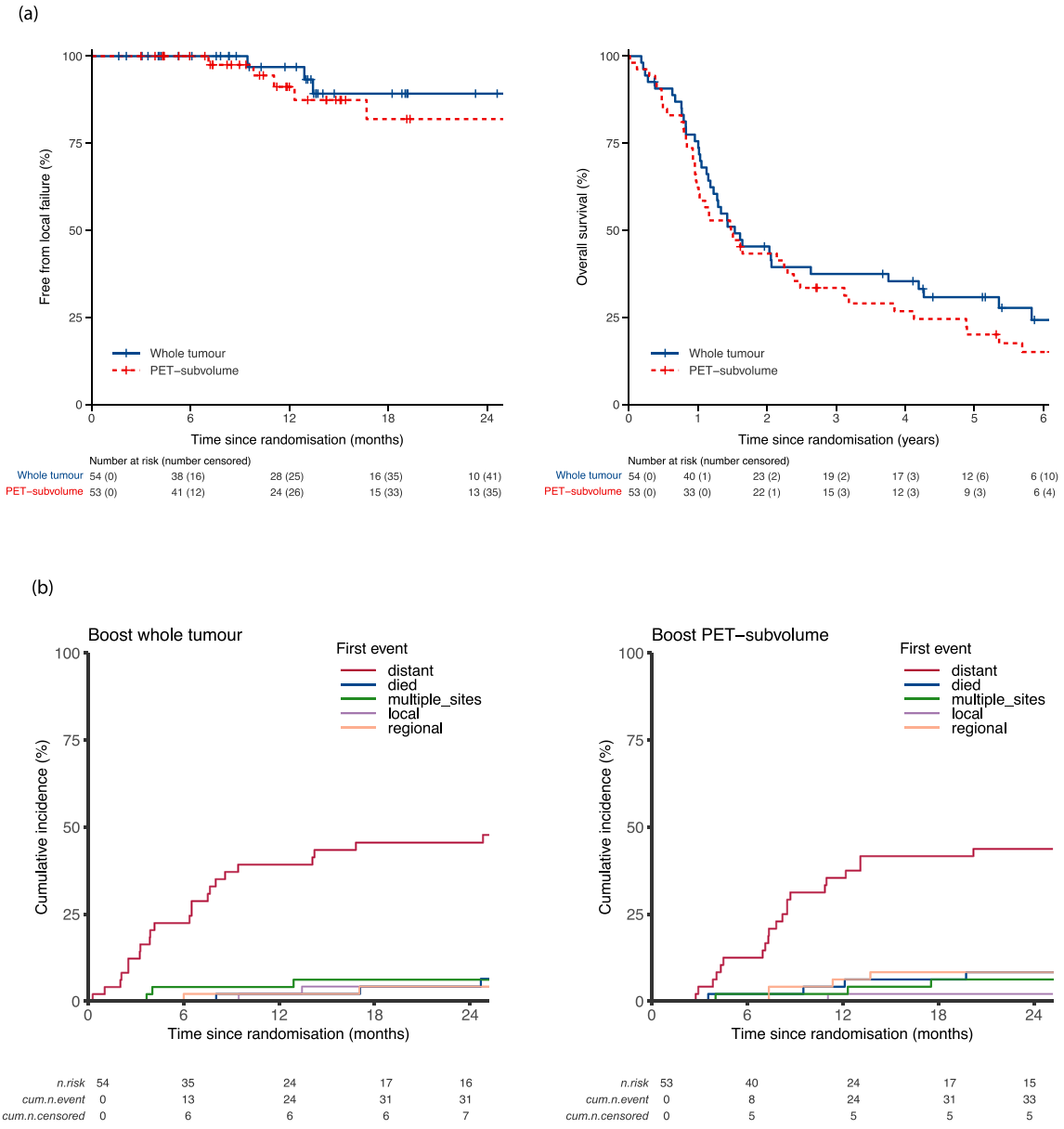

Fig. 3. The top left panel shows Kaplan-Meier curve for freedom from local failure per treatment arm. Local progression was recorded in three patients in the whole tumour group, and in five in the PET-subvolume group. The top right panel shows overall survival per treatment arm. At time of analysis, 39(72%) and 44(83%) deaths had occurred in whole tumour and PET-subvolume group, respectively. The bottom plots show the cumulative incidence for competing risk of local failure, regional failure, distant metastasis, multiple sites of simultaneous recurrence and death as first observed event. The bottom left panel shows results of the whole tumour group, and the right panel shows results the PET-subvolume group.

Appendix Table B.9 reports dose to OARs, in patients with $\geq$ G3 toxicity, and visualises association with change in protocol amendments.

Discussion

Local control is an important outcome associated with survival after radiotherapy for LA-NSCLC.[18,19] In addition to homogeneously increasing radiation dose, it was hypothesised that increasing the radiation dose to areas at high risk of local relapse defined by ^{18}F-FDG-PET subvolumes could improve the cure rate. We investigated the efficacy and safety of a personalised, integrated escalation of radiotherapy dose delivered either to the primary tumour as a whole or to the PET-subvolume. In our study, both treatment strategies led to high rates of local control, acceptable rates of distant metastasis and survival, but high rates of grade five adverse events.

In our study, 1-year FFLF rate was 97 % in the whole tumour group, and 91 % in the PET-subvolume group. In the RTOG-0617 trial, treatment with 60 Gy and 74 Gy resulted in 1-year local control rates of 84 % and 75 %, respectively.[4] Recently, RTOG-1106 showed that the use of mid-treatment ^{18}F-FDG-PET to escalate dose up to 80.4 Gy (median BED_{10} 104 Gy) led to 2-year in-field local control of 76 %, compared to 59 % with standard dose.[20].

The high rates of local control in both groups may be explained by the high doses delivered, whilst at the same time limiting overall treatment time.[7] This combination is thought to minimise tumour cell repopulation, increasing the likelihood of tumour control.[21] Our results are consistent with SBRT studies, which have

modelled > 100 Gy BED is required to achieve local control rates of > 90 %.[22] The finding that the local control rates were high in both groups in our study may be explained by the similarly high mean tumour dose in both groups, where in the PET-subvolume group the higher dose to the PET-subvolume is levelled out to a similar average dose to the whole tumour.

We report favourable 2-year distant metastasis rates (±43 %), when compared to RTOG-0617 (47 % vs 51 %, respectively), and PET-Plan studies (±43 %).[3,4] We also report worse 2-year OS (±44 %) to that reported in the PET-Plan (±56 %), Proclaim (±52 %), and the standard dose arm of RTOG-0617 studies (58 %).[1] However, the large tumour volumes in our study should be considered when interpreting the survival data (median GTV_{total} ± 130-cm^3), which is a known prognostic factor associated with inferior outcome.[23] In comparison, median GTV_{total} in RTOG-0617 was ± 100cm^3. Furthermore, it is noteworthy that the mean heart dose was only 10 Gy in our study. Lowering the heart dose further may improve OS.[24].

Our study reports ≥ G3 AEs in 54 % and 53 % in in the whole tumour and PET-subvolume group, respectively. More specifically, we report ≥ G3 dysphagia/oesophagitis in 19 % and 17 %, and ≥ G3 pulmonary events in 19 % and 32 %. In RTOG-0617, standard dose vs high-dose treatment was associated with ≥ G3 toxicity in 76 % vs 79 %, dysphagia/oesophagitis in 7 % vs 21 %, and pulmonary events in 21 % vs 19 %, respectively.[4] In RTOG-1106, ≥G3 respiratory events were reported in 23.8 % vs 14.3 % in the adaptive radiotherapy and control arm, respectively.[20].

Despite the applied dose constraints, we report 15(14 %) (possibly) treatment-related grade 5 events, consisting mainly of haemorrhage, oesophageal fistula and respiratory insufficiency. This is higher than in the high-dose arm of the RTOG-0617 (4.3 %),[2] but similar to the PET-Plan (9.8 %),[3] and the dose-escalation trial NCCTG-N0028 (16 %).[25] This is consistent with SBRT studies for centrally located tumours.[26,27] A description of patients who suffered fatal haemorrhage in current trial has previously been published. Briefly, all patients described had ≥ 50 % or complete encasement of large vessels. The maximum dose to planned risk volume (mediastinal envelope) ranged from 74.4 Gy to 76.8 Gy.[17].

Protocol amendments lowering dose to oesophagus, and excluding patients with encasement of large vessels, led to a decrease in occurrence of severe adverse events in our study. Additionally, we found higher oesophageal doses were associated with higher grades of oesophageal toxicity.

This study was performed prior to the addition of immune checkpoint inhibitors (ICI) in the treatment of locally advanced NSCLC. Recently, the PACIFIC trial reported 5-year 43 % vs 33 % OS, and 33 % vs 19 % PFS, in patients treated with durvalumab or placebo after concurrent chemoradiation, respectively.[28] Several studies have suggested there may be a synergistic effect between radiotherapy and ICI. Where ICI promotes T cell activation, radiotherapy may increase tumour antigen presentation and cytokine production, and modulate the tumour microenvironment – this combination is likely to enhance patients' antitumour immune response.[29,30] As pre-clinical studies suggest higher radiotherapy doses have an immunostimulatory effect, combining dose intensification strategies and ICI may result in improved cure rates.[29] However, concerns exist about increased rates of pulmonary toxicity reported in prospective studies with radiotherapy and ICI combinations.[31,32] Currently, much is unknown about the optimal timing, dose and fractionation of radiotherapy dose when combined with ICI.[29,33] For patients with locally-advanced NSCLC, ongoing trials combining hypofractionated radiotherapy and ICI include NCT04351256, NCT03801902 and NCT04245514.

The strengths of our study include the personalised, isotoxic-dose-escalation strategies, utilising advanced radiotherapy techniques in a multi-institutional setting, and explicit aim to improve local control. Our study was, however, limited by its comparison to historical data, early closure and smaller sample size, heterogeneity in patient characteristics, and uneven enrolment distribution across centres. Due to the small sample size, meaningful subgroup analyses were not feasible. Our study may have been improved by extending the follow-up period. A 1-year endpoint was selected for our study as it was calculated sufficient power could be achieved, and longer follow-up periods require more included patients. However, considering the low number of events found in current study, longer follow-up periods may be considered by new clinical trials. Especially with increasing survival times and the advent of immunotherapy, a 1-year endpoint may not reflect the true effect of dose on long-term tumour control.

We also acknowledge the radiotherapy-related radiographic pulmonary changes could have impacted response assessment and therefore the measurement of our primary endpoint. However, this was mitigated by the central review of CT-scans. Follow-up ^{18}F-FDG-PET imaging is thought to aid in response evaluation, although its role after high dose radiotherapy remains unclear.[34] Also, the current knowledge and understanding of pathologic response assessment after (high dose) radiotherapy in LA-NSCLC is limited.[35].

Although our trial did not reach target inclusion, both dose-escalation strategies met the primary objective to improve FFLF at 1-year. Due to the "pick-the-winner" design, in which each arm is evaluated separately, no formal statistical tests were performed to assess if one strategy was more effective in achieving local control than the other. The study was designed to potentially select a treatment strategy to be tested in large-scale future trial. Due to high rates of grade 5 events, neither is selected in its current form. However, with improved patient selection (excluding patients with vascular invasion), a patient-tailored radiotherapy strategy utilising dose differentiation, delivering a higher dose to the primary tumour, whilst sparing mediastinal structures, particularly the oesophagus and heart, is likely to improve outcome.

Further studies should focus on safe delivery of high doses hypofractionated or mildly hypofractionated radiotherapy. We note in our study 14 % of included patients were not eligible to receive an escalated fraction within healthy dose limits, mostly in patients with large volume. Targeting smaller volumes, including sub-volumes, may better spare healthy tissue. Furthermore, current developments in technology, including online adaptive, MRI-guided and proton radiotherapy, hold promise as they may allow for higher delivery accuracy and lower doses to healthy tissue. [36].

In our study, dose escalation by high mean tumour doses resulted in high rates of local control, whether homogeneously or ^{18}F-FDG-PET based given. However, both treatment strategies led to high rates of grade 5 toxicity. Our results suggest this may be reduced with improved patient selection and stricter healthy tissue dose constraints.

Role of the funder/sponsor

The EC and KWF had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful for funding by the European Commission's Seventh Framework Programme (ARTFORCE, grant agreement no 257144) and the Dutch Cancer Society (KWF) (project no 2010-4675).

The content of this report is the sole responsibility of the authors and does not necessarily reflect the official views of the EC or KWF.

Professor Sonke is supported by a grant from Elekta AB.

Professor Faivre-Finn is supported by a grant from the NIHR Manchester Biomedical Research Centre.

We thank the patients and their families; all investigators, involved physicians, physicists, RTTs, planners, site staff and data managers. We also thank Pietje Muller as study project coordinator, and the members of the independent monitoring committee. Further acknowledgments to Harry Bartelink and Gunnar Westman for their invaluable contributions.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109492.

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