Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial

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Summary

Background With increasingly precise radiotherapy and advanced medical imaging, the concept of radiotherapy target volume planning might be redefined with the aim of improving outcomes. We aimed to investigate whether target volume reduction is feasible and effective compared with conventional planning in the context of radical chemoradiotherapy for patients with locally advanced non-small-cell lung cancer.

Methods We did a multicentre, open-label, randomised, controlled trial (PET-Plan; ARO-2009-09) in 24 centres in Austria, Germany, and Switzerland. Previously untreated patients (aged older than 18 years) with inoperable locally advanced non-small-cell lung cancer suitable for chemoradiotherapy and an Eastern Cooperative Oncology Group performance status of less than 3 were included. Undergoing ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET and CT for treatment planning, patients were randomly assigned (1:1) using a random number generator and block sizes between four and six to target volume delineation informed by ^{18}F-FDG PET and CT plus elective nodal irradiation (conventional target group) or target volumes informed by PET alone (^{18}F-FDG PET-based target group). Randomisation was stratified by centre and Union for International Cancer Control stage. In both groups, dose-escalated radiotherapy (60–74 Gy, 2 Gy per fraction) was planned to the respective target volumes and applied with concurrent platinum-based chemotherapy. The primary endpoint was time to locoregional progression from randomisation with the objective to test non-inferiority of ^{18}F-FDG PET-based planning with a prespecified hazard ratio (HR) margin of 1·25. The per-protocol set was included in the primary analysis. The safety set included all patients receiving any study-specific treatment. Patients and study staff were not masked to treatment assignment. This study is registered with ClinicalTrials.gov, NCT00697333.

Findings From May 13, 2009, to Dec 5, 2016, 205 of 311 recruited patients were randomly assigned to the conventional target group (n=99) or the ^{18}F-FDG PET-based target group (n=106; the intention-to-treat set), and 172 patients were treated per protocol (84 patients in the conventional target group and 88 in the ^{18}F-FDG PET-based target group). At a median follow-up of 29 months (IQR 9–54), the risk of locoregional progression in the ^{18}F-FDG PET-based target group was non-inferior to, and in fact lower than, that in the conventional target group in the per-protocol set (14% [95% CI 5–21] *vs* 29% [17–38] at 1 year; HR 0·57 [95% CI 0·30–1·06]). The risk of locoregional progression in the ^{18}F-FDG PET-based target group was also non-inferior to that in the conventional target group in the intention-to-treat set (17% [95% CI 9–24] *vs* 30% [20–39] at 1 year; HR 0·64 [95% CI 0·37–1·10]). The most common acute grade 3 or worse toxicity was oesophagitis or dysphagia (16 [16%] of 99 patients in the conventional target group *vs* 17 [16%] of 105 patients in the ^{18}F-FDG PET-based target group); the most common late toxicities were lung-related (12 [12%] *vs* 11 [10%]). 20 deaths potentially related to study treatment were reported (seven *vs* 13).

Interpretation ^{18}F-FDG PET-based planning could potentially improve local control and does not seem to increase toxicity in patients with chemoradiotherapy-treated locally advanced non-small-cell lung cancer. Imaging-based target volume reduction in this setting is, therefore, feasible, and could potentially be considered standard of care. The procedures established might also support imaging-based target volume reduction concepts for other tumours.

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Introduction

Radiotherapy has been revolutionised by highly precise treatment applications and increasingly conformal irradiation technology. Combined with modern systemic treatments, such applications and technology allow for increased tumour control, reduced toxicity, and improved outcomes for patients with cancer. However, the beneficial effect of radiotherapy is dependent on appropriate

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Research in context

Evidence before this study

The potential clinical benefit of target volume reduction can be studied by use of a diagnostically well evaluated imaging tool. Investigating the impact of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT in the planning of chemoradiotherapy for locally advanced non-small cell lung cancer is a good model to generate prospective evidence on this topic. For randomised controlled trials of locally advanced non-small-cell lung cancer, many groups have adopted the idea of using ^{8}F-FDG PET for radiotherapy treatment planning after retrospective and single-centre analyses were published in the early 2000s. By contrast with standards for other solid tumours, it was proposed to omit prophylactic mediastinal irradiation. We searched MEDLINE (with no language restriction) for research articles published between database inception and Sept 4, 2019, using the terms "non-small cell lung cancer", "radiotherapy", "FDG-PET", and "target volume" and found only one prospective single-centre phase 1/2 trial published in 2005 investigating local outcome in 44 patients with an advantage for this approach. Using the terms "non-small cell lung cancer", "radiotherapy", and "elective nodal irradiation", one additional prospective single-centre trial from 2007 in 200 patients with an advantage in overall response and local control for the limited approach was found.

Added value of this study

To our knowledge, PET-Plan is the first multicentre, international, randomised trial that provides prospective, quality-controlled evidence showing that the restriction of target volumes based on molecular imaging information in the context of a dose-escalated chemoradiotherapy is non-inferior to conventional planning and, furthermore, might lead to improved local outcomes without increased toxicity.

Implications of all the available evidence

As ^{18}F-FDG PET/CT-based target volume reduction for chemoradiotherapy of locally advanced non-small-cell lung cancer appears to be safe and potentially beneficial for patients, it could become a new standard for clinical practice and future studies. The PET-Plan trial might therefore inspire future target volume reduction concepts for other tumours.

selection of target volume. Although this choice might be simple for small targets, it becomes challenging in expanded locoregional treatments, in which the risk of recurrence must be balanced with the risk of side-effects in increasing normal tissue volumes. Unsurprisingly, results from prospective trials have shown that adequate target volume delineation affects outcomes and toxicity.[1]

Despite their importance, many radiotherapy target volume concepts rely on long-term practice, clinical knowledge, and experience together with conventional imaging standards rather than on evidence, resulting in largely variable clinical practice.[2] Although the gross tumour volume itself as a core part of the planning target volume is clearer to define, this variability largely affects clinical target volume concepts, which, in addition to the gross tumour volume, are designed to cover assumed microscopic tumour spread.

Alongside the technical achievements in radiotherapy, major improvements have been made in medical imaging. Molecular imaging is one such improvement; by contrast with anatomical imaging, molecular imaging methods depict metabolic processes that are of great importance in radiotherapy.

While re-examining target volume standards, well evaluated modern diagnostic imaging might allow enhanced delineation of the gross tumour volume through improved imaging of primary tumours and affected nodes, and optimisation of clinical target volume concepts through improved accuracy on microscopic spread to neighbouring tissues or nodes. To tackle unmet needs, modified target volume concepts might enable precise treatment intensification along with improved protection of normal tissue.

One such clinically unmet need is chemoradiotherapy for locally advanced non-small-cell lung cancer. The poor outcomes of chemoradiotherapy for locally advanced non-small-cell lung cancer, in which local recurrence is a main issue,[3] mandates more effective local treatment.[4] Conversely, safe application of chemoradiotherapy with highly radiation-sensitive normal tissues involved[5] is a technical challenge. The relatively high diagnostic accuracy of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT compared with historical CT imaging[6] makes it possible to tailor down target volumes. After retrospective and single-centre analyses in the 2000s[7,8] demonstrated an improvement of the inter-observer agreement on target volumes,[9] many clinical and research groups adopted the idea of using ^{18}F-FDG PET, which was originally established for staging, in radiotherapy treatment planning. However, standard procedures for use of ^{18}F-FDG PET in radiotherapy treatment planning have not been defined yet.

Independent from PET scans and in contrast to the standards of target volume delineation for other solid tumours, it was simultaneously proposed to omit elective nodal irradiation in favour of involved-field radiotherapy.[10] This approach was supported by three single-centre, randomised trials[11–13] with no or limited PET scanning and three smaller cohort studies[14–16] (one with PET scanning) together with a meta-analysis showing no difference in terms of elective nodal failure.[17]

Experts therefore favoured the omission of elective nodal irradiation, but recommended prospective trials on ^{18}F-FDG PET-based dose escalation.[10] Despite remaining risks,[18] this approach was recommended by clinical guidelines,[19] but no prospective, multicentre, benefit–risk assessment is available investigating

outcome and toxicity after the use of both PET scans and the reduction of target volumes together with dose escalation.

We previously reported that dose-escalated chemoradiotherapy with target volumes restricted by ^{18}F-FDG PET for locally advanced non-small-cell lung cancer showed a favourable and safe outcome.[20] Here, we aimed to compare this ^{18}F-FDG PET-based treatment planning versus standard treatment using target volumes not restricted by PET in patients with locally advanced non-small-cell lung cancer.

Methods

Study design and participants

In this multicentre, open-label, randomised, controlled trial (PET-Plan; ARO 2009-09), patients were recruited from 24 centres in Austria, Germany, and Switzerland (appendix pp 8–9). Eligible patients were older than 18 years; had histologically or cytologically proven inoperable stage II or III non-small-cell lung cancer; had an Eastern Cooperative Oncology Group performance status of less than 3; had adequate pulmonary, cardiac, renal, and haematological function (as assessed according to local standards); and were judged to be suitable for chemoradiotherapy by interdisciplinary consensus (detailed criteria are in the appendix p 1). The main exclusion criteria were supraclavicular lymph node metastasis, previous surgical resection or chemotherapy, and signs of distant metastasis or inflammation on ^{18}F-FDG PET. Staging had to be done within the 6 weeks before study entry, including a diagnostic whole-body ^{18}F-FDG PET or PET/CT.

For radiotherapy planning, a planning CT, which could have been done during planning PET/CT within 3 weeks before start of radiotherapy, was obtained during shallow breathing, and, if available, a four-dimensional scan (the mid-position scan to be used for contouring) was done. The planning PET (or PET/CT) also needed to be done with the patient lying in radiotherapy treatment position within 3 weeks before the start of radiotherapy, with image acquisition taking place at least 60 min after intravenous ^{18}F-FDG was administered in the fasting state. Co-registration of PET and CT datasets was checked using anatomical landmarks, and procedures were defined for the case of insufficient registration. Invasive mediastinal staging was left to the choice of the treating physician and documented accordingly.

The trial was done in accordance with the Declaration of Helsinki. The protocol and its amendments were approved by the ethics committees, and the protocol (appendix p 10) is available at the German Clinical Trials Register website. All patients provided written, informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to the conventional target group or the ^{18}F-FDG PET-based target group. If radiotherapy planning with conventional target volumes was not possible, patients were excluded from randomisation and documented in an observational group (not further referred to in this Article). Allocation sequences were generated at IMBEI Mainz (Mainz, Germany) with a random number generator, using block sizes varying between four and six within strata defined by the centre and Union for International Cancer Control (UICC; version 7)) stage (four levels). Upon registration, centres were informed about the allocation with a central randomisation unit via fax. Patients and study staff who applied the interventions, assessed the outcomes, or analysed the data were not masked to group assignment.

Procedures

For target volume definition, the gross tumour volume of the primary tumour was delineated in the planning CT based on co-registered ^{18}F-FDG PET (figure 1, circled in red). Study staff were encouraged to use a semi-automatic algorithm.[21] Manual adjustments to enlarge but not to reduce the tumour contour according to CT morphology were allowed.

For the ^{18}F-FDG PET-based target group, this gross tumour volume was then expanded into all directions by 2 mm to the primary tumour clinical target volume, and the rationale for this relatively small margin was the wide interpretation of the PET signal by the automatic contouring, which, derived from three-dimensional PET, also included movement blurring. For nodal irradiation, affected lymph nodes were allocated to the respective Mountain-Dressler lymph node levels, were then delineated in accordance with a contouring atlas[22] with respect to any anatomical changes by enlarged nodes. Lymph node levels with ^{18}F-FDG-positive nodes or bioptically affected nodes (ie, if a biopsy sample had confirmed tumour from optional mediastinal staging, even if not positive on PET scan) were included in the lymph node clinical target volume (figure 1, circled in orange). Both nodal and primary tumour clinical target volumes were then expanded by 8–10 mm to the escalation planning target volume, subject to dose escalation.

See Online for appendix

For the conventional target group, the PET-based gross tumour volume of the primary tumour, as described previously, was expanded to include up to 3 cm of an eventual tumour-associated atelectasis, if applicable (figure 1, circled in green). The resulting volume was then expanded to the primary tumour clinical target volume according to the same procedure as for ^{18}F-FDG PET-based contouring. For nodal irradiation, affected lymph nodes were delineated as done for ^{18}F-FDG PET-based contouring. In addition, lymph node levels with CT-positive (short axis diameter >1 cm) but ^{18}F-FDG-negative nodes were included (figure 1, circled in blue). Both the respective nodal and primary tumour clinical target volumes were again expanded to the escalation planning target volume, being subject to dose escalation.

For the **protocol** see http://www.drks.de/DRKS00002178

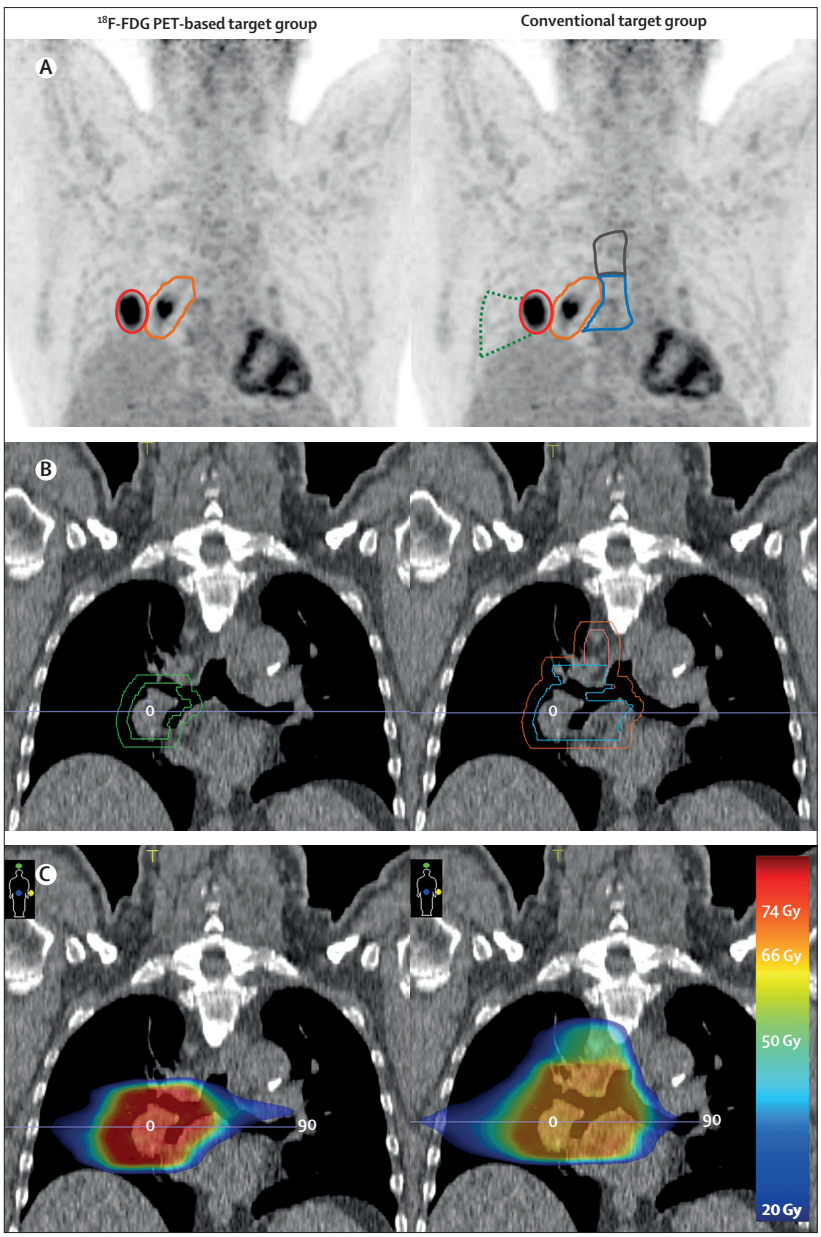

Figure 1: **Schematic illustration of PET-Plan target volume delineation (A), exemplified contours (B), and dose distribution (C)**

(A) Maximum-intensity projection of ^{18}F-FDG PET with schematic illustrations are shown. A ^{18}F-FDG PET-based clinical target volume of tumour (red line) and ^{18}F-FDG-positive nodes (orange line) were delineated for all patients; for the ^{18}F-FDG PET-based target group, this was the volume targeted for dose escalation. For the conventional target group, in addition to the PET-based clinical target volumes, if present, ^{18}F-FDG-negative lymph node stations with nodes enlarged in CT (blue line) and dystelectasis or atelectasis (dotted green line, not applicable in this example case) were included in the dose-escalated clinical target volume, and nodal stations with a probability of involvement of more than 10% (grey line) were treated up to 50 Gy. (B) Coronal CT scan with clinical target volume (inner green line) and planning target volume (outer green line) as for radiotherapy planning in the ^{18}F-FDG PET-based target group. Coronal CT scan with escalated clinical target volume (inner blue line), elective clinical target volume (inner red line), and total planning target volume (outer red line) as for radiotherapy planning according to the conventional target group. (C) Subsequent dose distributions after dose-escalated planning according to study protocol. ^{18}F-FDG=^{18}F-fluorodeoxyglucose.

Patients in the conventional target group also received elective nodal irradiation up to a total dose of 50 Gy in 2 Gy fractions. This volume (figure 1, circled in grey) included unaffected lymph node levels with a more than 10% likelihood of lymph node metastases, informed by a table in the protocol using information from Giraud and colleagues,[23] who tabulated likelihoods of nodal spread for locally advanced non-small-cell lung cancer related to the primary tumour position from pathology data.

For both study groups, by isotoxic escalation, doses between 60 Gy and 74 Gy (2 Gy per fraction) were prescribed to the respective escalation planning target volume (at least including the primary tumour and the affected nodal stations), giving highest possible doses while adhering to predefined normal tissue constraints (appendix p 1). If any constraint was exceeded, the highest safe dose level below (in 2 Gy steps) was used. In the conventional target group, constraints had to be adhered to for the whole radiotherapy series.

Radiotherapy planning for intensity-modulated radiation therapy or three-dimensional conformal radiation therapy used type-b algorithms in the routine planning systems of the respective study centres. Dose specifications for planning were according to the International Commission on Radiation Units and Measurements (ICRU) article 50[24] with the aim of a minimum dose of 95% and a maximum dose 107% in the planning target volume.

Concurrent chemotherapy consisted of a platinum-based doublet, according to clinical guidelines. A choice of five published regimens are allowed in the protocol: two different regimens containing cisplatin plus vinorelbine;[25,26] two different regimens containing cisplatin plus etoposide;[27,28] and one regimen containing carboplatin plus vinorelbine.[26]

Treatment duration was 6–8 weeks, depending on the total dose prescribed. The trial was closed after the last included patient had reached 6 months of follow-up. Until then, all patients were followed-up for as long as possible. Treatment response, toxicity, and survival were assessed within 1 week after the end of radiotherapy, then every 3 months from randomisation during the first year, every 6 months up to year 5, and annually thereafter. Treatment response was assessed by CT. ^{18}F-FDG PET/CT was mandatory when locoregional or distant disease progression was suspected. According to predefined criteria and Response Evaluation Criteria in Solid Tumors, the primary tumour and all affected lymph nodes were separately assessed in relation to Mountain-Dressler stations. As initial imaging and target volumes were also related to those, the localised outcome parameters were defined in relation to this grid.

The trial included extensive quality assurance of various components, partly published previously.[21,29,30] Quality assurance included phantom calibration of the PET-based target volume contouring, dummy run for target volume delineation, expert panel review of initial PET reading, and blinded expert support for response assessment by this panel.

Quality assurance also included prospective and retrospective assessments of target volume and normal tissue delineation as well as of radiotherapy planning and dose escalation together with radiotherapy. A list of required parameters was provided in the protocol with minor and major deviations predefined for radiotherapy quality assurance (appendix pp 2–3). After initial central prospective radiotherapy quality assurance, randomly selected radiotherapy plans were subject to mutual radiotherapy quality assurance by the study group. All radiotherapy plans finally underwent retrospective central quality assurance.

Outcomes

The primary outcome of the study was time to locoregional progression (progressive disease in the primary tumour or any mediastinal lymph nodes) from randomisation in the per-protocol set. Secondary endpoints included time to out-of-field progression (progressive disease in mediastinal lymph nodes outside the target volume), time to in-field progression (progressive disease in primary tumour or mediastinal lymph nodes within the target volume), time to distant progression (appearance of metastases elsewhere), overall survival (time from randomisation to death from any cause), progression-free survival (time to locoregional progression, distant progression, or death), acute treatment-related toxicity (up to 90 days after start of radiotherapy, prospectively classified according to Common Terminology Criteria [CTC], version 3), late treatment-related toxicity (according to Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer [RTOG/EORTC] Scoring Scheme), escalated doses reached in the planning target volume, and size of planning target volume. Serious adverse events as defined by the study protocol were reported according to Good Clinical Practice guidelines and assessed in the form of line listings by a data and safety monitoring committee on an annual basis.

Statistical analysis

We considered the primary endpoint of locoregional progression in a competing risk framework together with distant metastases and death as competing risks. The non-inferiority hypothesis was that the ratio of cause-specific hazards for the primary endpoint for the ^{18}F-FDG PET-based target group versus the conventional target group would be less than or equal to the non-inferiority margin of 1·25, with the type I error fixed at the one-sided level of 0·10. In case of confirmation, non-inferiority was to be tested at the one-sided level 0·025 and if confirmed again, the superiority hypothesis (hazard ratio [HR] <1) was to be tested at the same level. Treatment effects were reported as HRs with 95% CIs (and 80% CI for the primary endpoint in the per-protocol set). We checked the proportional hazards assumption by visual inspection of Schoenfeld residuals (appendix p 8).

Sample size was finally calculated as 95 per group, with a power of 0·80 for the rejection of the primary non-inferiority hypothesis under the assumption that the true HR was 0·75, only considering administrative censoring, and was fixed at 100 to allow for attrition. Because of initially low recruitment, the protocol was amended (amendment 4 on Jan 30, 2013) to include a sample size adjustment and an adaption of the primary endpoint (from locoregional progression-free survival to time to locoregional progression).

For data analysis, the intention-to-treat set included all randomly assigned patients. The per-protocol set included those patients who were treated according to protocol for radiotherapy (no treatment-relevant protocol deviations in radiotherapy planning identified by central radiotherapy quality assurance, full prescribed dose given). Because the primary objective was to demonstrate non-inferiority, the per-protocol analysis was fixed as primary in order to avoid false positive conclusions based on effects that might have been diluted by the inclusion of non-compliers. The definition of the per-protocol set and the decision to use it for the primary analysis was fixed in a statistical analysis plan before disclosing the treatment group allocation. The safety set was defined as all patients receiving any study-specific treatment.

For the primary analysis, Cox proportional hazards models were fitted using three UICC stage categories (IIa/IIb, IIIa, and IIIb) as strata and centre (centres with less than five patients were grouped into one category) as a covariable. We show the results using cumulative incidence curves for competing risk endpoints, which show the probability of having locoregional progression by the given time, as opposed to having any other or no events. We defined numbers at risk for cumulative incidence curves by adapting the definition generally used for Kaplan-Meier curves as follows: patients were removed from the at-risk set in case of a censoring event and in case of the primary endpoint, but not at any event with a competing cause (ie, distant metastasis or death). This definition is specific to the displayed endpoint and allows qualitative judgment of random errors in the cumulative incidence as with those reported for Kaplan-Meier curves. Notably, these numbers do not describe, and might therefore be greater than, the number of patients still at risk for any competing endpoint.

We estimated the follow-up time for the primary endpoint by the (reverse) Kaplan-Meier method, with last available assessment of progress as the event of interest and with progress (locoregional progression or distant metastasis) and death as censoring events.

We analysed secondary endpoints similarly with the same covariables and stratification factors as for the primary analysis. For overall survival and progression-free survival, observations were censored at date of last contact or end of the study. For the endpoints in-field and out-of-field progression, the same

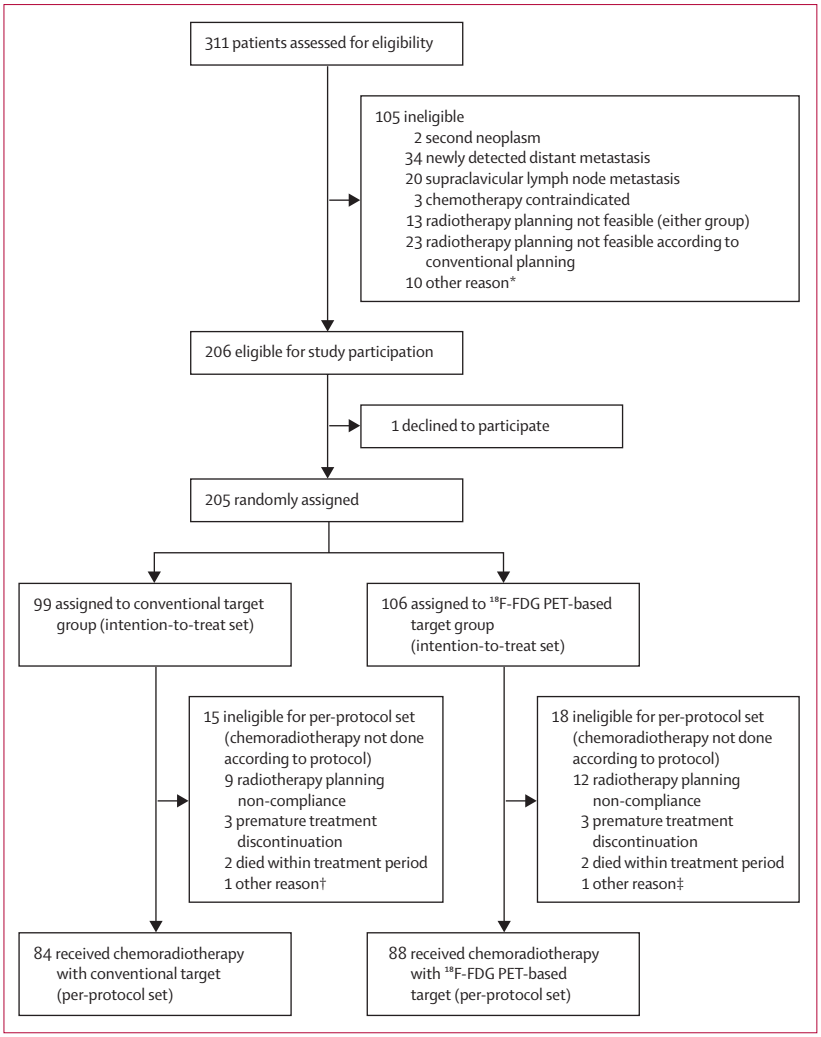

Figure 2: **Trial profile**
^{18}F-FDG=^{18}F-fluorodeoxyglucose. *Includes apoplectic insult, induction chemotherapy, planning obstacle (pleural effusion), and pleural empyema (one patient each), and six patients with infection, inflammation, or superior vena cava syndrome. †Distant metastasis before treatment with consecutive change of concept. ‡Early death before treatment.

competing risk framework was used as for the primary endpoint with out-of-field and in-field progression, distant progression, and death as competing risks. In addition, we did post-hoc sensitivity analyses for locoregional progression and overall survival. We evaluated a number of prognostic factors (age, gross tumour volume, planning target volume, atelectasis, number of irradiated nodal stations, and study centres) by fitting univariable and multivariable Cox models. We had fixed the list of factors but not the models in the statistical analysis plan. In an exploratory analysis, we estimated the treatment effect with various adjustment variables sets.

In a post-hoc analysis, we assessed the association between mean heart dose and total escalation dose by Pearson's coefficient of correlation.

Because of the development of research questions during the recruitment time of our trial, the treatment effect in the subgroup of patients with UICC stage III disease, a possible correlation of mean heart dose with total escalated dose and its effect on locoregional progression and overall survival was investigated post hoc.

The quantitative variables in treatment groups were characterised by medians and IQR, in case of skewed distributions, or otherwise by means and SD, and by Mann-Whitney *U* test for statistical comparisons of treatment groups. For comparisons with respect to categorical variables, we report odds ratios (ORs) and 95% CIs and Pearson's χ^2 test. All p values are two-sided and are referred to as significant if less than or equal to 0·05 unless otherwise specified. For statistical analyses, we used the statistical software packages SAS (version 9.4), and R (version 3.4.2).

The trial is registered with ClinicalTrials.gov, NCT00697333.

Role of the funding source

The funder reviewed and approved the study design, but had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 13, 2009, and Dec 5, 2016, 311 patients were recruited and provided informed consent, of whom 105 were ineligible and one declined to participate (figure 2). Of 205 eligible patients, 99 patients were randomly assigned to the conventional target group and 106 patients to the ^{18}F-FDG PET-based target group (intention-to-treat set). For 33 patients, chemoradiotherapy was not done in accordance with protocol. Thus, 172 patients were included in the per-protocol set (84 patients in the conventional target group and 88 in the ^{18}F-FDG PET-based target group; figure 2). One patient in the intention-to-treat set did not receive study-specific treatment in the ^{18}F-FDG PET-based target group. Therefore, 204 patients were analysed for safety.

Demographic and clinical details are shown in table 1 for the intention-to-treat set and in the appendix (p 11) for the per-protocol set, and treatment-related parameters are shown in table 2. The mean escalated total radiotherapy reference dose was significantly higher in the ^{18}F-FDG PET-based target group (67·3 Gy [SD 5·2]) than in the conventional target group (65·3 Gy [5·3]; appendix p 7). Doses of 68 Gy or more were more frequently achieved with ^{18}F-FDG PET-restricted volumes (41 [47%] of 88 patients) than conventional ones (28 [33%] of 84 patients). The OR for receiving more than 65 Gy was significantly higher in the ^{18}F-FDG PET-based target group than in the conventional target group (p=0·0070; appendix p 7).

	Conventional target group (n=99)	^{18}F-FDG PET-based target group (n=106)
Age, years	64·0 (58·0–72·0)	65·5 (60·0–71·8)
Sex		
Male	71 (72%)	78 (74%)
Female	28 (28%)	28 (26%)
ECOG performance status at study inclusion		
0	20 (20%)	15 (14%)
1	72 (73%)	79 (75%)
2	7 (7%)	12 (11%)
Weight loss		
<5%	64 (55%)	73 (69%)
≥5%	25 (25%)	26 (25%)
Missing	10 (10%)	7 (7%)
UICC (7th edition) stage at study inclusion		
IIA	3 (3%)	4 (4%)
IIB	5 (5%)	4 (4%)
IIIA	37 (37%)	41 (39%)
IIIB	54 (55%)	57 (54%)
UICC (8th edition) stage at study inclusion*		
IIA	1 (1%)	0
IIB	5 (5%)	8 (8%)
IIIA	28 (28%)	21 (20%)
IIIB	48 (48%)	52 (49%)
IIIC	17 (17%)	25 (24%)
Histologic classification of non-small-cell lung cancer		
Squamous cell carcinoma	60 (61%)	62 (58%)
Adenocarcinoma	31 (31%)	31 (29%)
Large cell carcinoma	1 (1%)	5 (5%)
NOS or other subtypes	7 (7%)	7 (7%)
Missing	0	1 (1%)
Number of PET-positive lymph node stations	3·1 (2·0)	3·5 (2·1)
SUV_{max} (primary tumour) in planning ^{18}F-FDG-PET	16·5 (7·5)	14·8 (5·6)
Imaging method used for radiotherapy planning		
PET/CT	83 (84%)	90 (85%)
Stand-alone PET and CT	16 (16%)	16 (15%)

Data are n (%), median (IQR), or mean (SD). ECOG=Eastern Cooperative Oncology Group. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. UICC=Union for International Cancer Control. NOS=not otherwise specified. SUV_{max}=maximum standardised uptake value. *Retrospectively assigned.

Table 1: **Baseline characteristics**

	Conventional target group	^{18}F-FDG PET-based target group
Intention-to-treat set	n=99	n=106
GTV (primary), mL	56·8 (27·0–112·0)	71·6 (37·2–136·0)
PTV_{esc}, mL	519 (336–706)	526 (338–725)
Radiation technique (escalated volume)		
IMRT	54 (55%)	56 (53%)
3D-RT	44 (44%)	49 (46%)
Missing	1 (1%)	1 (1%)
Applied chemotherapy regimen		
Cisplatin plus vinorelbine[25]*	19 (19%)	16 (15%)
Cisplatin plus vinorelbine[26]	52 (53%)	49 (46%)
Other cisplatin regimens†	9 (9%)	11 (10%)
Carboplatin plus vinorelbine[26]	13 (13%)	22 (21%)
Other carboplatin regimen‡	2 (2%)	6 (6%)
Vinorelbine monotherapy	1 (1%)	0
None	3 (3%)	2 (2%)
Complete administration of respective chemotherapy regimen		
Cycle 1	74 (75%)	81 (76%)
Cycle 2	68 (69%)	71 (67%)
Per-protocol set	n=84	n=88
GTV (primary), mL	56·4 (26·6–96·7)	77·6 (40·4–158·0)
PTV_{esc}, mL	506 (336–686)	551 (369–775)
Radiation technique (escalated volume)		
IMRT	43 (51%)	43 (49%)
3D-RT	41 (49%)	45 (51%)
Applied chemotherapy regimen		
Cisplatin plus vinorelbine[25]*	17 (20%)	14 (16%)
Cisplatin plus vinorelbine[26]	47 (56%)	45 (51%)
Other cisplatin regimens†	8 (10%)	6 (7%)
Carboplatin plus vinorelbine[26]	9 (11%)	19 (22%)
Other carboplatin regimen‡	1 (1%)	4 (4%)
Vinorelbine monotherapy	1 (1%)	0
None	1 (1%)	0
Complete administration of respective chemotherapy regimen		
Cycle 1	66 (79%)	72 (82%)
Cycle 2	61 (73%)	63 (72%)

Data are n (%) or median (IQR). 3D-RT=three-dimensional conformal radiation therapy. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. GTV=gross tumour volume. IMRT=intensity-modulated radiation therapy. PTV_{esc}=escalation planning target volume. *Regimen according to the third study group,[25] without induction phase as specified in PET-Plan study protocol. †Including maintenance treatment according to the GILT trial[31] (three in the conventional target group *vs* two in the ^{18}F-FDG PET-based target group in the per-protocol set, and four *vs* three in the intention-to-treat set) and ad-hoc modifications. ‡Including the combination with paclitaxel (two in the ^{18}F-FDG PET-based target group in the per-protocol set, and one in the conventional target group *vs* four in the ^{18}F-FDG PET-based target group in the intention-to-treat set) and individual ad-hoc modifications (one in the conventional target group *vs* two in the ^{18}F-FDG PET-based target group in the per-protocol set and one *vs* two in the intention-to-treat set).

Table 2: **Treatment-related parameters**

For the per-protocol set, the median gross tumour volume was higher in the ^{18}F-FDG PET-based target group than in the conventional target group; however, there was no significant difference in the median planning target volume (p=0·18; table 2).

Median follow-up time for the primary endpoint was 29 months (per-protocol set: IQR 9–54); end of follow-up time was May 31, 2017. Until the fixed end of follow-up, 120 patients died (57 in the conventional target group *vs* 63 in the ^{18}F-FDG-based target group). Causes of death were mainly tumour related (38 in the conventional target group *vs* 37 in the ^{18}F-FDG-based target group), treatment related (six *vs* 13), other causes (nine *vs* seven), or cause unknown (four *vs* six).

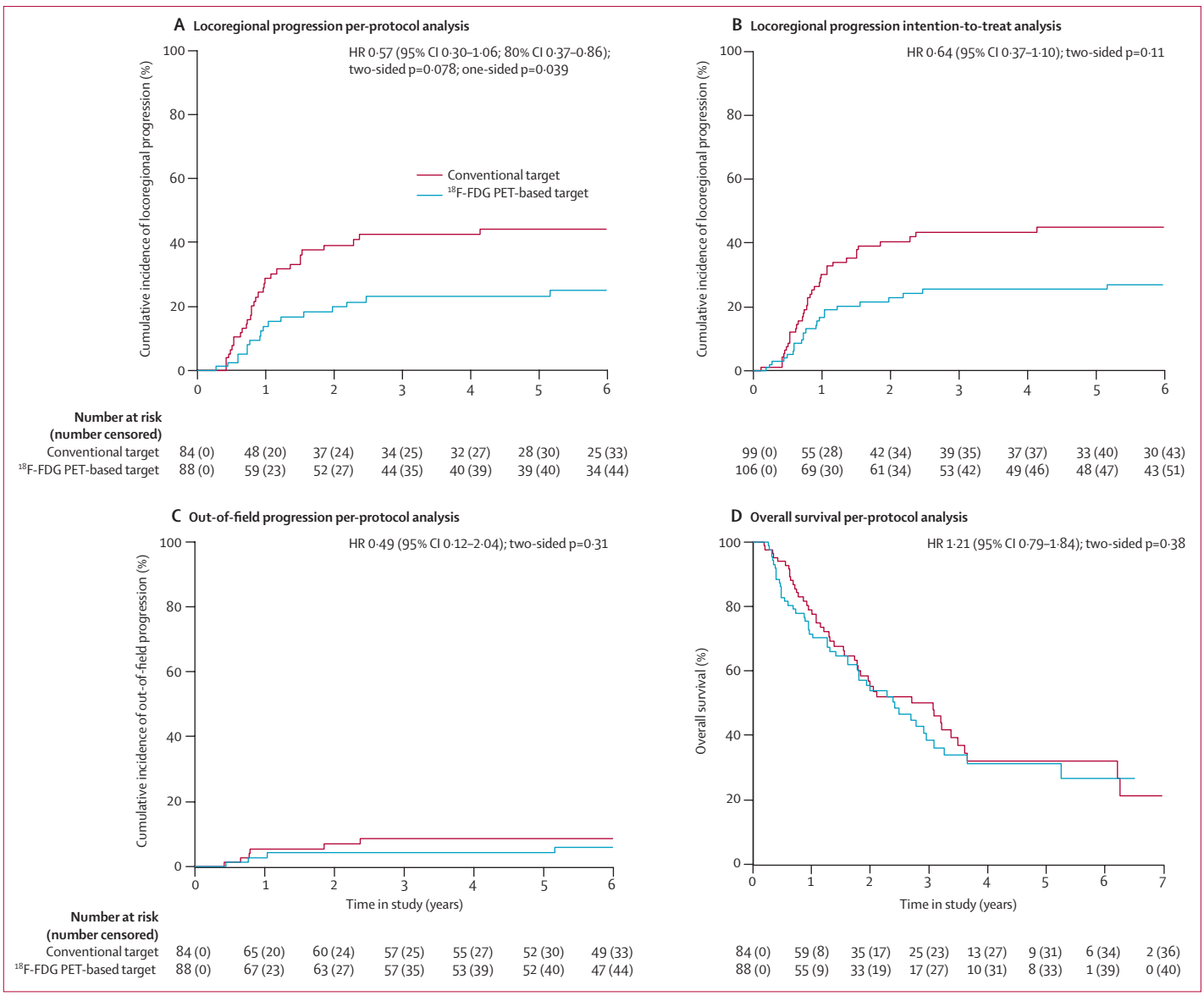

Figure 3: **Cumulative incidence of locoregional progression, out-of-field progression, and overall survival**
(A) Cumulative incidence curves of locoregional progression as the primary endpoint competing with distant failure and death in the per-protocol analysis set. (B) Cumulative incidence curves of locoregional progression as the primary endpoint competing with distant failure and death in the intention-to-treat analysis set. (C) Cumulative incidence curves for out-of-field progression evaluated as a risk competing with in-field progression, distant failure and death. (D) Kaplan-Meier curves for overall survival. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. HR=hazard ratio.

For the per-protocol set, the primary outcome of cumulative incidence for locoregional progression in the ^{18}F-FDG-based target group was 14% (95% CI 5–21) at 1 year, 20% (10–29) at 2 years, and 23% (12–32) at 3 years (17 events) compared with 29% (17–38) at 1 year, 39% (27–50) at 2 years, and 42% (30–53) at 3 years in the conventional target group (32 events; figure 3). The HR in the per-protocol set was 0·57 (95% CI 0·30–1·06, 80% CI 0·37–0·86), confirming non-inferiority with respect to the margin 1·25, both at the one-sided level 0·10 and one-sided level 0·025 (cumulative incidence 17% [95% CI 9–24] *vs* 30% [20–39] at 1 year; HR 0·64 [95% CI 0·37–1·10] in the intention-to-treat set; figure 3; appendix p 3).

The risk for out-of-field recurrence was low overall and similar in both groups (figure 3; appendix p 4), whereas in-field progression was higher in both groups (HR 0·60 [95% CI 0·30–1·15], p=0·13; appendix p 4). The distant metastasis risk (recorded as first site of progression) was not significantly different between the groups (HR 1·29 [95% CI 0·79–2·15]; p=0·31; appendix p 4).

In the per-protocol set (and intention-to-treat set; appendix p 4), overall survival and progression-free survival were similar in both groups (progression-free survival HR 1·07 [95% CI 0·75–1·53]; p=0·70; figure 3; appendix p 4). Median overall survival was 3·08 years (95% CI 1·80–3·61) in the conventional target group and

2·41 years (1·80–3·26) in the ^{18}F-FDG PET-based target group. Median progression-free survival was 0·85 years (95% CI 0·73–1·02) in the conventional target group and 0·92 years (0·73–1·40) in the ^{18}F-FDG PET-based target group.

Results of prespecified Cox analyses adjusted for variables and post-hoc sensitivity analyses are shown in the appendix (pp 5–7). For the purpose of comparability to other studies, the treatment effect in the subgroup of patients with UICC stage III was analysed post hoc. The HR comparing the ^{18}F-FDG PET-based target group with the conventional target group with respect to locoregional progression was 0·50 (95% CI 0·25–0·97; p=0·041).

Treatment-related toxicities were generally mild to moderate (table 3). Grade 3 or worse acute toxicities were mainly oesophagitis or dysphagia (16 [16%] of 99 patients in the conventional target group *vs* 17 [16%] of 105 patients in the ^{18}F-FDG PET-based target group) and haematological (20 [20%] *vs* 32 [30%]). Late grade 3–4 toxicities (RTOG/EORTC) were mainly lung related (12 [12%] of 99 patients in the conventional target group *vs* 11 [10%] of 105 patients in the ^{18}F-FDG PET-based target group), and grade 3 oesophageal and cardiac toxicities were rare. Treatment-related serious adverse events were infrequent (14 in the conventional target group *vs* 15 in the ^{18}F-FDG PET-based target group), and were mainly infections (nine *vs* nine). Eight (8%) of 99 patients in the conventional target group and ten (10%) of 105 patients in the ^{18}F-FDG PET-based target group had relevant dose reductions in radiotherapy (seven *vs* five) or chemotherapy (three *vs* eight). Two patients (both died) in the conventional target group and four (one died, two had oesophagitis, and one had pneumonitis) patients in the ^{18}F-FDG PET-based target group discontinued treatment for toxicity. 20 deaths potentially related to study treatment were reported by treating physicians (seven in the conventional target group and 13 in the ^{18}F-FDG PET-based target group); 17 were of pulmonary origin (six *vs* 11, including nine pneumonias (four in the conventional target group and five in the ^{18}F-FDG PT-based target group), and three were due to other reasons (one in the conventional target group due to systemic inflammatory response syndrome *vs* two in the ^{18}F-FDG PET-based target group due to oesophageal stenosis with tracheobronchial fistula and acute liver failure), but none was related to cardiac events.

The mean heart dose, which weakly correlated with the total escalated dose (r=0·13; p=0·079), did not affect locoregional progression (HR per Gy 1·00, 95% CI 0·95–1·05) or overall survival (HR per Gy 1·02 [95% CI 0·99–1·04]; appendix p 5).

	Conventional target group (n=99)			^{18}F-FDG PET-based target group (n=105)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Worst grade of haematological parameters during chemoradiotherapy						
Decreased haemoglobin	36 (36%)	3 (3%)	0	45 (43%)	5 (5%)	2 (2%)
Decreased leucocytes	51 (52%)	13 (13%)	1 (1%)	45 (43%)	20 (19%)	2 (2%)
Decreased platelets	6 (6%)	2 (2%)	1 (1%)	15 (14%)	2 (2%)	1 (1%)
Other acute toxicity (≤90 days after start of radiotherapy)*						
Oesophagitis, dysphagia	54 (55%)	15 (15%)	1 (1%)	53 (50%)	17 (16%)	0
Dyspnoea	21 (21%)	2 (2%)	4 (4%)†	29 (28%)	5 (5%)	3 (3%)†
Pneumonitis	8 (8%)	1 (1%)	0	10 (10%)	1 (1%)	0
Any cardiac toxicity	9 (9%)	3 (3%)	0	7 (7%)	3 (3%)	2 (2%)
Rash (dermatitis associated with radiotherapy)	34 (34%)	3 (3%)	0	35 (33%)	0	0
Late toxicity (>91 days after start of radiotherapy)‡						
Oesophagus	11 (11%)	2 (2%)	0	19 (18%)	1 (1%)	0
Lung	48 (48%)	11 (11%)	1 (1%)	48 (46%)	8 (8%)	3 (3%)§
Heart	14 (14%)	3 (3%)	0	13 (12%)	5 (5%)	0
Skin	7 (7%)	0	0	7 (7%)	0	0
Subcutaneous tissue	0	0	0	1 (1%)	0	0
Spinal cord	3 (3%)	0	0	2 (2%)	0	0
Blood						
Haemoglobin	5 (5%)	0	0	5 (5%)	2 (2%)	0
Leucocytes	2 (2%)	1 (1%)	0	2 (2%)	0	1 (1%)¶
Thrombocytes	0	0	0	2 (2%)	0	0
Other treatment-related serious adverse events (any time)						
Infection	..	4 (4%)	5 (5%)	..	8 (8%)	1 (1%)
Chemotherapy related‖	..	2 (2%)	0	..	1 (1%)	1 (1%)
Haemorrhage	..	0	0	..	0	2 (2%)
Other	..	2 (2%)**	1 (1%)††	..	1 (1%)‡‡	1 (1%)§§

Data are n (%). ^{18}F-FDG=^{18}F-fluorodeoxyglucose. *According to Common Terminology Criteria, version 3. †One of each with consecutive treatment related death. ‡According to Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer scoring scheme. §All three with consecutive treatment-related deaths. ¶Grade 4 leucocytes after palliative chemotherapy for recurrence. ‖Related to volume or devices needed for chemotherapy. **One reversible renal insufficiency and one decrease in performance status. ††Systemic inflammatory response syndrome, consecutive treatment-related death. ‡‡ Arrhythmia. §§Dislocation of trachea stent.

Table 3: **Treatment-related toxicity in the safety set**

Discussion

To our knowledge, this is the first randomised, international, multicentre trial on imaging-based target volume reduction in radiation oncology, in relation to outcome. In the context of dose-escalated chemoradiotherapy for locally advanced non-small-cell lung cancer, our data show that the restriction of volumes informed by ^{18}F-FDG PET might be beneficial for patients in terms of a halved incidence of locoregional tumour progression, and does not confer an increased risk of out-of-field progression or toxicity.

By using ^{18}F-FDG PET/CT in radiotherapy planning for locally advanced non-small-cell lung cancer, a concept that is unique in comparison to the concepts followed for other solid tumours, our results support current guidelines[19] and practice. Furthermore, our data support the conclusions of earlier trials that elective irradiation of mediastinal lymph nodes is not beneficial. As concluded from the non-inferiority of the^{18}F-FDG PET-based target group, this is also the case for irradiation of tumour-related atelectasis.

With PET staging and image-guided treatment for all patients, overall survival results compared favourably with other trials in similar patient populations.[4,32]

However, overall survival was not improved by target volume reduction. Other studies on chemoradiotherapy in locally advanced non-small-cell lung cancer showed that in principle local control is significantly linked to overall survival.[3]

Post-hoc sensitivity analyses suggested the importance of tumour volume (gross tumour volume) as an independent prognostic factor for locoregional control, as previously shown.[33] Although the gross tumour volume was larger in the ^{18}F-FDG PET-based target group, the positive effect of the volume-restricted planning on locoregional progression was not affected. Additionally, the number of affected lymph node stations in ^{18}F-FDG PET was identified as a potential prognostic factor, which affected overall survival, whereas N stage itself did not. These two imaging-related factors might help in the stratification of patients in future trials.

The favourable overall results of this trial might also be related to the rigorous quality assurance, which led to helpful standardisation of imaging and planning procedures,[21,29] of ^{18}F-FDG PET/CT scan reading for use in radiotherapy planning,[30] of physical radiotherapy planning and application, and of reading of follow-up imaging. Illustrated by the encouragingly low proportion of radiotherapy quality assurance non-compliance as compared with the literature,[1] our results corroborate the crucial role of institutional and multicentre quality assurance for good radiotherapy practice.

Toxicities were mild to moderate and overall similar to other trials of curative-intent chemoradiotherapy for this patient population.[32] An influence of mean heart dose on outcome was not detected. Further analysis of pulmonary and cardiac toxicity is ongoing.

This trial was designed around the same time and done in a largely similar population to RTOG 0617,[32] although the study question, systemic treatment component used, and the imaging policy during follow up were different. In RTOG 0617, combined chemoradiotherapy with a radiotherapy dose escalation to 74 Gy did not lead to an improved outcome.[32] Dose range and normal tissue constraints were similar between both trials. However, although in the RTOG trial investigators were obliged to prescribe a given dose to their patients as randomised with optional normal tissue constraints, in our setting a stepwise isotoxic dose escalation was done, where investigators (using the randomised target volumes) prescribed the highest dose for each case that could be planned adhering to mandatory constraints. Consequently, the range of doses delivered in our study was broad, and doses of 68 Gy or more were only prescribed in about a third of patients. This difference might be of importance for the discussion if radiotherapy planning issues are part of the explanation for the unexpected results of the RTOG 0617 trial. Overall, in the PET-Plan trial, negative effects of high radiotherapy treatment doses on survival or toxicity were not observed, but improved local control was not shown to be related to dose.

Recently, authors of a pooled retrospective analysis of concurrent chemoradiotherapy in a large cohort of patients from 16 cooperative group trials[34] investigated the effect of radiotherapy doses and field design strategy on toxicity and outcomes. Involved-field radiotherapy was associated with less toxicity, higher radiotherapy doses with more toxicity, and involved-field radiotherapy with 60 Gy was associated with more favourable survival and less toxicity than elective nodal irradiation or higher radiotherapy doses. Unfortunately, PET was required in only one more recent trial using involved-field radiotherapy; therefore, the impact of PET scanning on outcome was not assessed. Our results are in line with this analysis in terms of improved local control by dose-escalated involved-field radiotherapy without a difference in overall survival. But, by contrast with these data, we did not see a disadvantage of higher doses, and, as PET-guided involved-field radiotherapy (resulting in a superior outcome in our trial) enabled somewhat higher dose escalation, we cannot exclude a positive dose effect.

Our trial has some limitations. The relatively small sample size and the non-inferiority design means results of the post-hoc analyses can only be hypothesis generating. Furthermore, in the experimental setting chosen, the statistical power was not high enough to prove that the experimental treatment was better, so there is still uncertainty regarding superiority. However, when taking into account the non-inferiority together with the lack of increased toxicity, and clinical plausibility, we believe that recommendations based on these results are more reliable than those based on evidence available before.

Despite randomisation, there were imbalances (gross tumour volume size and number of affected lymph nodes) in favour of the conventional target group. However, adjusting the analysis of the primary endpoint to those did not lead to qualitatively different results.

Although the concurrent chemotherapy used here is still recommended in recent guidelines, molecular testing, tyrosine kinase inhibitors, and the newest standard maintenance immunotherapy[35] were not used. In view of the importance of local control for survival in non-small-cell lung cancer,[3] we can only speculate that with the introduction of another systemic treatment, the improved local control might have translated into a better overall outcome.

Although the inclusion of patients with stage II disease in this study might impair its comparability with some other trials, less than 8% of patients included were in UICC stage II. The exploratory evaluation of the subgroup of stage III patients showed similar overall survival results to those of the whole cohort and also revealed an advantage for ^{18}F-FDG PET-based planning.

In conclusion, imaging-based reduction of radiotherapy target volumes is feasible and not inferior to conventional target volume planning. In locally advanced

non-small-cell lung cancer, quality-assured ^{18}F-FDG PET-based target volume reduction with isotoxic dose escalation might lead to improved local control without increased toxicity. We, therefore, believe that the target volume delineation established in the PET-Plan trial could be considered standard of care and could be used in future trials aiming to improve systemic treatment along with optimum radiotherapy. Furthermore, as the irradiation of unaffected draining lymph nodes might decrease the radiotherapy-related immune response,[36] this trial might encourage other clinical trials on imaging-based target volume reduction for other solid tumours, especially in the context of radioimmunotherapy.

Contributors

UN, SK, ASS, MMix, SME, JF, and A-LG conceived the study concept and initiated the study design. TS-J, MMix, AK, MT, TH, SME, Y-PB, PH, JF, AT, MS, KD, MMie, GH, HCR, EG, and SA helped with the implementation. UN is the grant holder. UN, TS-J, SK, AS-S, MMix, SME, MMie, GH, and HCR were involved in quality assurance and quality assurance of radiotherapy. JK provided statistical expertise. JK, UN, TS-J, and A-LG analysed and interpreted the data. UN, TS-J, and JK wrote the manuscript (with the main draft written by UN). All authors reviewed the manuscript, made the decision to submit the manuscript for publication, and assured the completeness and accuracy of the data and analyses and of the fidelity of this report to the trial protocol. All authors approved the final manuscript.

Declaration of interests

UN, TS-J, and JK report grants from the German Cancer Aid (Deutsche Krebshilfe) during the conduct of the study. PH reports reimbursement for travel and accommodation from Braun-Stiftung and personal fees from Bristol-Myers-Squibb, outside the submitted work. SA reports personal fees from German consortium of translational cancer research (DKTK) during the conduct of the study. All other authors declare no competing interests.

Data sharing

From publication of the main results, de-identified data collected for the PET-Plan trial and dictionaries can be made available with investigator support for other research projects upon the approval by the study group and ethics committee. For this, please contact the principal investigator of the trial (UN) with your project proposal.

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