Adaptive radiotherapy (up to 74 Gy) or standard radiotherapy (66 Gy) for patients with stage III non-small-cell lung cancer, according to [^{18}F]FDG-PET tumour residual uptake at 42 Gy (RTEP7–IFCT-1402): a multicentre, randomised, controlled phase 2 trial

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Summary

Background Thoracic radiation intensification is debated in patients with stage III non-small-cell lung cancer (NSCLC). We aimed to assess the activity and safety of a boost radiotherapy dose up to 74 Gy in a functional sub-volume given according to on-treatment [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET results.

Methods In this multicentre, randomised, controlled non-comparative phase 2 trial, we recruited patients aged 18 years or older with inoperable stage III NSCLC without EGFR mutation or ALK rearrangement with an Eastern Cooperative Oncology Group performance status of 0–1, and who were affiliated with or a beneficiary of a social benefit system, with evaluable tumour or node lesions, preserved lung function, and who were amenable to curative-intent radiochemotherapy. Patients were randomly allocated using a central interactive web-response system in a non-masked method (1:1; minimisation method used [random factor of 0·8]; stratified by radiotherapy technique [intensity-modulated radiotherapy *vs* three-dimensional conformal radiotherapy] and by centre at which patients were treated) either to the experimental adaptive radiotherapy group A, in which only patients with positive residual metabolism on [^{18}F]FDG-PET at 42 Gy received a boost radiotherapy (up to 74 Gy in 33 fractions), with all other patients receiving standard radiotherapy dosing (66 Gy in 33 fractions over 6·5 weeks), or to the standard radiotherapy group B (66 Gy in 33 fractions) over 6·5 weeks. All patients received two cycles of induction platinum-based chemotherapy cycles (paclitaxel 175 mg/m^2 intravenously once every 3 weeks and carboplatin area under the curve [AUC]=6 once every 3 weeks, or cisplatin 80 mg/m^2 intravenously once every 3 weeks and vinorelbine 30 mg/m^2 intravenously on day 1 and 60 mg/m^2 orally [or 30 mg/m^2 intravenously] on day 8 once every 3 weeks). Then they concomitantly received radiochemotherapy with platinum-based chemotherapy (three cycles for 8 weeks, with once per week paclitaxel 40 mg/m^2 intravenously and carboplatin AUC=2 or cisplatin 80 mg/m^2 intravenously and vinorelbine 20 mg/m^2 intravenously on day 1 and 40 mg/m^2 orally (or 20 mg/m^2 intravenously) on day 8 in 21-day cycles). The primary endpoint was the 15-month local control rate in the eligible patients who received at least one dose of concomitant radiochemotherapy. This RTEP7–IFCT-1402 trial is registered with ClinicalTrials.gov (NCT02473133), and is ongoing.

Findings From Nov 12, 2015, to July 7, 2021, we randomly assigned 158 patients (47 [30%] women and 111 [70%] men) to either the boosted radiotherapy group A (81 [51%]) or to the standard radiotherapy group B (77 [49%)]. In group A, 80 (99%) patients received induction chemotherapy and 68 (84%) received radiochemotherapy, of whom 48 (71%) with residual uptake on [^{18}F]FDG-PET after 42 Gy received a radiotherapy boost. In group B, all 77 patients received induction chemotherapy and 73 (95%) received radiochemotherapy. At the final analysis, the median follow-up for eligible patients who received radiochemotherapy (n=140) was 45·1 months (95% CI 39·3–48·3). The 15-month local control rate was 77·6% (95% CI 67·6–87·6%) in group A and 71·2% (95% CI 60·8–81·6%) in group B. Acute (within 90 days from radiochemotherapy initiation) grade 3–4 adverse events were observed in 20 (29%) of 68 patients in group A and 33 (45%) of 73 patients in group B, including serious adverse events in five (7%) patients in group A and ten (14%) patients in group B. The most common grade 3–4 adverse events were febrile neutropenia (seven [10%] of 68 in group A *vs* 16 [22%] of 73 in group B), and anaemia (five [7%] *vs* nine [12%]). In the acute phase, two deaths (3%) occurred in group B (one due to a septic shock related to chemotherapy, and the other due to haemotypsia not related to study treatment), and no deaths occurred in group A. After 90 days, one additional treatment-unrelated death occurred in group A and two deaths events occurred in group B (one radiation pneumonitis and one pneumonia unrelated to treatment).

Interpretation A thoracic radiotherapy boost, based on interim [18F]FDG-PET, led to a meaningful local control rate with no difference in adverse events between the two groups in organs at risk, in contrast with previous attempts at thoracic radiation intensification, warranting a randomised phase 3 evaluation of such [18F]FDG-PET-guided radiotherapy dose adaptation in patients with stage III NSCLC.

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Introduction

The standard treatment for inoperable, locally advanced non-small-cell lung cancer (NSCLC) is concurrent radiochemotherapy, which has shown improved survival over sequential radiotherapy and chemotherapy or radiotherapy alone,[1] followed by consolidation immunotherapy with durvalumab over the course of 1 year.[2]

Several studies have shown the value of [18F] fluorodeoxyglucose ([18F]FDG)-PET in managing patients with locally advanced inoperable stage IIA–III NSCLC, performed before, during, and after radiochemotherapy.[3–5] Additionally, although the 1-year locoregional control rate of NSCLC with radiotherapy alone was as low as 17% in 1991,[6] the locoregional control rate when adding chemotherapy was disappointing at 15%, and has subsequently been illustrated by a 28% locoregional progression at 3 years in the 2010 meta-analysis by Aupérin and colleagues,[1] as well as a median locoregional progression-free survival of only 14 months (95% CI 10–24) in a 2005 seminal phase 1 dose-escalation study.[7] In a secondary analysis of seven Radiation Therapy Oncology Group (RTOG) trials, a total of 1356 patients underwent radiochemotherapy between 1988 and 2002. The 2-year locoregional failure rate was 46%, but a 1-Gy dose-increase in radiotherapy dose intensity was significantly associated with a 3% improvement in the locoregional control rate.[8]

Research in context

Evidence before this study

We searched MEDLINE for articles published from Jan 1, 2010, to Dec 31, 2017, either in English or French, reporting the results of phase 2 and 3 studies relevant to our study. We used the terms ("stage III non-small-cell lung cancer" AND "adaptive radiotherapy") and ("PET-guided radiotherapy dose escalation" OR "image-guided radiotherapy dose escalation" AND "chemo-radiotherapy" AND "stage III non-small-cell lung cancer"). We found that the standard of care for the medical treatment of patients with stage III non-small-cell lung cancer (NSCLC), without an *EGFR* mutation or *ALK* rearrangement, currently consists of platinum-based concurrent radiotherapy and chemotherapy, using the standard radiotherapy dose of up to 66 Gy over 6·5 weeks, followed by 1 year of maintenance with anti-PD-L1 immunotherapy with durvalumab. Such standard of care is based on a 2017 phase 3 study reporting a median progression-free survival of 16·9 months with durvalumab versus 5·6 months with placebo, and an overall survival of 47·5 months with durvalumab versus 29·1 months with placebo. Previous attempts to improve locoregional tumour control by radiotherapy dose escalation to 74 Gy did not result in increased survival rates, yet it did result in higher radiation-induced toxicity and higher death rates. Several studies have supported the value of [18F]fluorodeoxyglucose ([18F]FDG)-PET with CT before or during treatment with concurrent radiochemotherapy to better define the tumour volume to treat.

Added value of this study

The findings from our study of adaptive thoracic radiation intensification in adult patients with inoperable stage III NSCLC compared with standard 66 Gy radiation, showed a high 1-year local regional control rate in both groups, without a significant difference in the adverse event rate in the group receiving a radiotherapy boost. High-dose thoracic radiotherapy has previously been reported to induce a high number of adverse events in organs at risk such as the lung, heart, and oesophagus, and an increase in cardiac toxicity-related deaths. The rate of adverse events was lower in our boost dose group than previously reported, even in trials using [18F]FDG-PET tumour uptake at diagnosis. Therefore, these data show an alternative to the currently available options that have not been improved on since the large study of thoracic radiation intensification by Bradley and colleagues a decade ago that did not report any survival benefit but instead reported high rates of radiation-induced severe adverse events.

Implications of all the available evidence

Performing an interim [18F]FDG-PET in patients with inoperable stage III NSCLC for guiding radiotherapy dose escalation on the basis of residual FDG uptake could result in a meaningful local regional control translating into an appreciable progression-free survival while avoiding an increase in radiation-induced toxicity. Such a strategy has the potential to allow for better delineation of patient subsets with a radiotherapy-resistant tumour (who would actually benefit from radiotherapy dose escalation), while preventing the overtreatment of patients sensitive to radiotherapy, thereby avoiding radiotherapy-induced severe toxicity. This strategy warrants further confirmation in larger, comparative phase 3 trials.

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See Online for appendix

Increasing the radiotherapy dose has thus been explored to improve locoregional control. In a 2015 large phase 3 randomised trial, high-dose conformational radiotherapy up to 74 Gy, given in two fractions with concurrent chemotherapy, was reported to be detrimental, as reflected by decreased overall survival rates, higher treatment-related death rates, and increased toxicity rates.[9] The additional radiotherapy dose was delivered to a target volume delineated on the pretreatment CT scan, which might have resulted in a target volume yielding the excessive irradiation of healthy organs at risk, therefore resulting in increased cardiac toxicity.

Our previous studies show the ability to perform [^{18}F]FDG-PET during radiochemotherapy without any PET image artifacts,[4,5] and identified the optimal time to perform [^{18}F]FDG-PET during radiochemotherapy being at 42 Gy (at the 5th week).[5] A phase 2 study of dose-escalation radiotherapy with concurrent chemotherapy, involving 107 patients with stage III NSCLC, delivered an escalated dose up to 77·5 Gy to the whole primary tumour volume (to 54 patients) or up to 74·2 Gy to a PET-defined subvolume (generally smaller; to 53 patients), in 24 fractions, based on [^{18}F]FDG-PET images acquired before starting radiotherapy.[10,11] Both groups had improved 1-year local control rates, but had high acute and late grade 3 toxicity (43% and 38% for acute and late toxicity, respectively, in patients treated on the primary tumour volume; and 22% and 32%, respectively, for patients boosted in the PET-defined subvolume), along with a grade 5 treatment-related event rate of 14% over both groups.

We thus hypothesised that on-treatment [^{18}F]FDG-PET, rather than pre-treatment [^{18}F]FDG-PET, would be better at refining the dose and volume of thoracic radiotherapy in patients with stage III NSCLC. To this end, we designed a prospective multicentre, randomised, controlled phase 2–3 study, comparing a control treatment group in which all patients received standard 66 Gy radiotherapy, irrespective of the residual FDG uptake after having received 42 Gy radiotherapy, versus an experimental group, in which a radiation boost of up to 74 Gy was only given to those with residual FDG uptake at 42 Gy radiotherapy. The current report presents the results of the phase 2 part of the study.

Methods

Study design and participants

RTEP7-IFCT-1402 was designed as a multicentre randomised phase 2–3 trial, conducted at 19 hospitals in France (appendix p 18). The study design is depicted in figure 1. The French National Cancer Institute grant funding the study (PHRC 2014) was only obtained for phase 2 of the study, precluding any continuation into phase 3. Therefore, the current Article provides the final results of the randomised, but yet not comparative, phase 2. The trial protocol and all amendments were approved by the French Health Authorities (Agence Nationale de Sécurité des Médicaments et des produits de Santé) and Ethics Committee (of CPP Nord Ouest I; Feb 9, 2014) and are available in the appendix (p 117). The CONSORT 2010 checklist is also provided in the appendix (pp 10–17).

We recruited patients aged at least 18 years, with an Eastern Cooperative Oncology Group performance status of 0–1, who provided a signed informed consent before enrolment, and were affiliated with or a beneficiary of a social benefit system. Sex information was obtained via electronic medical records. As per the French law, race and ethnicity data could not be collected.

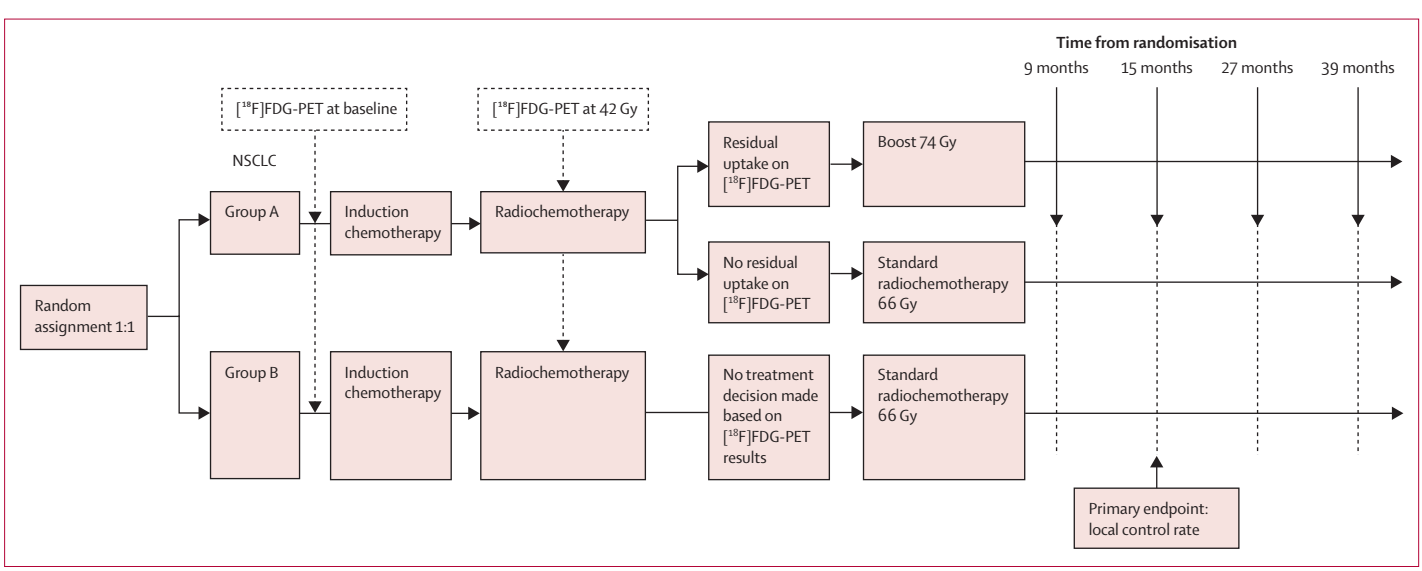

Figure 1: **Study design**
[^{18}F]FDG=[^{18}F]fluorodeoxyglucose. NSCLC=non-small-cell lung cancer.

Eligible patients had inoperable histologically proven stage III NSCLC, determined using the 7th TNM classification, and without an *EGFR* mutation or *ALK* rearrangement. Patients had to have measurable tumour or node lesions according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 and were eligible candidates for curative-intent radiochemotherapy, with the absence of pleural involvement or a comorbidity contraindicating radiochemotherapy. In the case of an [^{18}F]FDG-PET result suggestive of N2 or N3 involvement, a mediastinoscopy or an endobronchial ultrasonography was done to confirm the histological stage N2 or N3; in the case of bulky N2 on [^{18}F]FDG-PET or T4 disease, for each patient, a thorax multidisciplinary board validated the treatment. The patients had to have preserved lung function with a forced expiratory volume in the first second of 40% or more of the theoretical value, and partial pressure of oxygen of 60 mm Hg or more. The patients had to have adequate haematological, hepatic, and renal function, measured within 14 days of enrolment. A provisional radiotherapy plan had to confirm that the dose objectives (a minimal dose of 62·7 Gy [95% of the prescribed dose] in 98% of target volumes, and 70·3 Gy [95% of the prescribed dose] for the boosted volume at 74 Gy) and dose constraints (ie, for lungs and spinal cord) were met, according to the International Commission on Radiation Units.[12] Finally, one cycle of induction chemotherapy could be administered before inclusion, to avoid recruitment bias by selecting patients with slow-progressing tumours, provided patients had undergone [^{18}F]FDG-PET at diagnosis. Exclusion criteria are listed in the study protocol (appendix).

Randomisation and masking

A central interactive web-response computer system was used to generate random, non-masked treatment allocation. Patients enrolled by investigators were randomly assigned 1:1 to each group, according to dynamic minimisation randomisation algorithm, to receive either standard 66 Gy radiotherapy regardless of on-treatment [^{18}F]FDG-PET results (group B) or radiotherapy plus a boosted dose up to 74 Gy in the case of residual [^{18}F]FDG-PET tumour uptake at 42 Gy (hereafter referred to as the radiotherapy plus boost group; group A). The minimisation method for random assignment was designed to minimise the imbalance between treatments by taking stratification factors into account (radiotherapy technique: intensity-modulated radiotherapy *vs* three-dimensional [3D] conformal radiotherapy and the investigating site [hospital] that enrolled the patient). A random factor of 0·8 was applied for concealment.

Procedures

All patients received two induction chemotherapy cycles (paclitaxel 175 mg/m² intravenously once every 3 weeks and carboplatin area under the curve [AUC]=6 once every 3 weeks, or cisplatin 80 mg/m² intravenously once every 3 weeks and vinorelbine 30 mg/m² intravenously on day 1 and 60 mg/m² orally [or 30 mg/m² intravenously] on day 8 once every 3 weeks). Patients were administered radiotherapy concomitantly with platinum-based chemotherapy (for three cycles) for 8 weeks with once per week paclitaxel 40 mg/m² intravenously and carboplatin AUC=2, or cisplatin 80 mg/m² intravenously once every 3 weeks and vinorelbine 20 mg/m² intravenously on day 1 and 40 mg/m² orally (or 20 mg/m² intravenously) on day 8 once every 3 weeks. Complete blood and platelet counts and serum biochemistry with bilirubin, hepatic enzymes, creatinine, and creatinine clearance were measured at baseline and weeks 1, 2, 4, and 5 of the induction chemotherapy, and subsequently once per week during the radiochemotherapy period. Chemotherapy dose adjustments were based on the lowest blood counts since the last chemotherapy administration, following the study protocol recommendations (appendix). Radiotherapy techniques, consisting of either intensity-modulated radiotherapy or 3D conformal radiotherapy, depended on local centre equipment.

Patients in the experimental group (group A; radiotherapy plus boost) received an individualised radiotherapy prescription of up to 74 Gy in 33 fractions (in the case of intensity-modulated radiotherapy) or 41 fractions (in the case of 3D radiotherapy) over 6·6 weeks in the case of a positive [^{18}F]FDG-PET result at 42 Gy. Patient who had a negative result received standard radiotherapy (66 Gy) in 33 fractions. A 66 Gy dose was delivered onto the whole tumour volume as defined by a CT scan and pretreatment [^{18}F]FDG-PET, followed by an additional boost dose of up to 74 Gy on the uptake volume persisting on [^{18}F]FDG-PET during radiotherapy.[13] A second simulation CT scan using the same method used in the initial simulation CT scan was to be performed, in which the [^{18}F]FDG-PET at 42 Gy had to be realigned and coregistered with the simulation CT scan. To keep the total treatment time constant, for hospitals using 3D radiotherapy, a twice per day fractionated radiotherapy dose of 2·0 Gy to the initial planning target volume plus 1·0 Gy fraction at least 6 h later to the biological target volume, as measured by [^{18}F]FDG-PET at 42 Gy, was applied. For patients treated with intensity-modulated radiotherapy, a simultaneous integrated boost was used, with the subvolume being established by a radiation oncologist according to 50–60% of the maximum standardised uptake value (SUVmax).[13] Patients in the standard group (group B) received a single prescription of 66 Gy in 33 fractions over 6·6 weeks, with 2 Gy fractions given once per day, 5 days a week, without target volume reduction or adaptation, irrespective of [^{18}F]FDG-PET results at 42 Gy. In both groups, the total dose prescribed for the total mean lung dose was 20 Gy or less, and the volume of lung receiving 20 Gy was less than 30%, with doses to other organs at risk (oesophagus, heart, and spine) meeting dose constraints.

Local investigators scored adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), categorised as acute (occurring at 90 days or less after the start of radiochemotherapy) or late (occurring later than 90 days after the start of radiochemotherapy). Adverse events were assessed once per week during treatment and at 1, 3, 6, 12, 24, and 6 months thereafter, and then once per year until death. In the case of a grade 3 radiation pneumonitis or pulmonary infiltrate secondary to radiotherapy, all treatment was stopped and corticosteroids started. Radiotherapy was interrupted for grade 4 oesophagitis toxicity until it was grade 2 or less. For grade 3 oesophagitis, radiotherapy was not interrupted but the chemotherapy dose was reduced or stopped. Nutritional support via oral supplements or a gastric tube were initiated upon the development of grade 3 oesophagitis, according to local procedures and the mutual preference of the treating physician and patient. For dermatitis at grade 4 toxicity in-field, radiotherapy was discontinued until it was grade 2 or less. In the case of an interruption of treatment lasting more than 7 consecutive days, the patient was withdrawn from the study and did not receive a boost dose.

Because durvalumab became a part of the standard care for stage III inoperable NSCLC after the trial was initiated,[3] an amendment was proposed on May 24, 2018, stating that consolidation therapy could be given to all eligible patients with no disease progression after radiochemotherapy completion at 10 mg/kg bodyweight intravenously once every 2 weeks for up to 12 months. The quality controls for [18F]FDG-PET and radiotherapy (delineation and dosimetry) were that centres only qualified after they successfully completed a series of dummy runs, and are detailed in the appendix (pp 3–4).

We did a baseline disease assessment with a CT body scan (thorax, abdomen, and pelvis) and brain MRI or a CT scan (if an MRI was not possible), and then again at 9, 15, 27, and 39 months for response assessment (local control rate) with Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, as evaluated by local thoracic radiologists. A central response review using thoracic CT scans was performed by a radiation oncologist panel, all of whom were masked to treatment group allocation, to assess the precise location of a progression site, as compared with the radiation dose volume histograms. Clinical status was assessed once per week during treatment and 1, 3, 6, 12, 24, and 6 months thereafter, then yearly until death. All included patients were to be followed up until progression or death.

Outcomes

The primary endpoint was to establish the local control rate at 15 months from randomisation (the proportion of patients without progression in the primary tumour or any mediastinal lymph node) when the tumour dose was escalated up to 74 Gy in 6·6 weeks, given only to eligible patients with residual active disease assessed by [18F]FDG-PET, via adapting the radiotherapy target volume (to both the primary tumour and node) to the metabolic persisting active volume after 42 Gy of concomitant radiochemotherapy.

The secondary endpoints were: the local control rate at 9, 27, and 39 months; overall survival (the time from random assignment to death from any cause) at 9, 15, 27, and 39 months; and progression-free survival (the time from the date of random assignment to the date of first documented progression or death due to any cause) rates at 9, 15, 27, and 39 months; a toxicity assessment with the percentage of severe adverse events (grade 3 or worse events as per the Common Terminology Criteria for Adverse Events version 4.0), and radiation-induced toxicity affecting the lung and oesophagus at 3 months after radiochemotherapy (acute adverse events) as well as after 3 months (late toxicity); the percentage of group A patients for whom the radiotherapy dose intensification (boost) was possible; the prognostic value of [18F]FDG-PET at baseline on locoregional progression rates at the aforementioned timepoints (9, 15, 29, and 39 months from randomisation); the prognostic value of SUVmax and metabolic tumour volume (MTV) of [18F]FDG-PET at 42 Gy; the effect of the relative change in [18F]FDG-PET uptake (SUVmax) and MTV on the local control prognosis between baseline and [18F]FDG-PET at 42 Gy; and the time to locoregional progression. Exploratory analyses were performed to explore the prognostic value of clinical, radiotherapeutic, and [18F]FDG-PET variables (appendix p 5). The results of the ongoing ancillary, exploratory biomarker study will be reported elsewhere.

Statistical analysis

The primary study endpoint and secondary endpoints were evaluated in all eligible patients who received at least one dose of concomitant radiochemotherapy. For the locoregional progression endpoint, the events considered were patients with locoregional progression or who died (from any cause). Other patients were censored at the date of last follow-up or distant progression. The safety population comprised all patients who received at least one dose of concomitant radiochemotherapy. On the basis of the results observed in hypoxic radio-resistant tumors[14,15] we assumed that 51% local control rate or less at 1 year (null hypothesis) would be a level at which the [18F]FDG-PET CT-guided radiotherapy boost would not be therapeutically useful in the experimental group A (ie, if the local control rate was 51% or less, treatment would be deemed inactive), whereas a targeted local control rate of more than 66% (alternative hypothesis), based on the results of the RTOG 0617 trial,[9] would indicate clinical activity. Using this hypothesis, with a one-sided α error of 0·10 and 90% power, the calculation led to the accrual of 71 eligible patients in each group (with a total of 142 patients) to allow for the detection of a primary outcome effect.

Assuming that 5% of patients would be ineligible, we had to recruit 75 patients into each group. On the basis of these assumptions, at least 42 patients had to be without locoregional progression at 15 months, established using a one-step binomial proportion test, to enable conclusions to be made regarding the experimental regimen's activity. Taking account of such a phase 2 design, no direct comparison between the two groups was performed, since they were underpowered. A post-hoc analysis evaluated the 15-month local control rate and progression-free survival in patients with or without adjuvant durvalumab. Post-hoc analyses evaluated the median radiotherapy dose to the heart and to the lung in patients (from both groups) who did not receive a boost, the median dose to the heart in boosted patients, the median total radiotherapy duration, median number of radiotherapy interruption days, oesophagus volume receiving 35% of the prescribed radiotherapy dose, and the volume of lung receiving 20 Gy in both treatment groups measured using non-parametric tests, including a Mann–Whitney test.

An independent safety committee decided whether to continue the study when safety interim analyses had been conducted on every 14 patients (with no more than three patients presenting grade 3–5 adverse reactions related to treatments excluding haematological events, nausea, and vomiting).

For patients without progression events, the cutoff point was their last tumour assessment. We plotted progression-free survival and overall survival using Kaplan–Meier curves, with follow-up censored on Nov 1, 2022 (database lock). The median follow-up time was calculated via the reverse Kaplan–Meier method. The prognostic value of clinical, radiotherapeutic, and [^{18}F]FDG-PET variables on progression-free survival was assessed using a univariate Cox regression model. A multivariable model was tested with all the variables of the univariable model, and a stepwise-type step-by-step selection was used with variable durvalumab consolidation as a time-dependent variable. For statistical analyses, SAS software version 9.4 was used, providing two-sided p values and 95% CIs. This trial was registered on ClinicalTrials.gov (NCT02473133) and a specific French registration number from Agence Nationale de Sécurité du Médicament et des produits de santé for clinico-biological research (IDRCB 2014-A01628–39).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Nov 12, 2015, to July 7, 2021, 158 patients with locally advanced stage III NSCLC were prospectively enrolled at the 19 participating centres in France, of whom 81 patients were randomly assigned to group A

	All patients (N=158)	Group A (chemoradiotherapy plus boost; n=81)	Group B (chemoradiotherapy alone; n=77)
Sex			
Male	111 (70%)	60 (74%)	51 (66%)
Female	47 (30%)	21 (26%)	26 (34%)
Age, years			
Median (IQR)	62·9 (57·2–68·8)	61·9 (57·7–68·9)	62·9 (56·7–68·6)
Smoking status			
Yes	150 (95%)	76 (94%)	74 (96%)
No	8 (5%)	5 (6%)	3 (4%)
ECOG performance status			
0	95 (60%)	49 (60%)	46 (60%)
1	63 (40%)	32 (40%)	31 (40%)
Histology			
Adenocarcinoma	83 (53%)	39 (48%)	44 (57%)
Squamous cell carcinoma	60 (38%)	32 (40%)	28 (36%)
Others	15 (9%)	10 (12%)	5 (6%)
Cancer TNM stage			
IIIa	84 (53%)	48 (59%)	36 (47%)
IIIb	72 (46%)	32 (40%)	40 (52%)
Other	2 (1%)	1 (1%)	1 (1%)
Method of confirmation of [^{18}F]FDG-PET N2 or N3 involvement			
Not applicable	77/156 (49%)	44/80 (55%)	33/76 (43%)
By endobronchial ultrasonography	52/156 (33%)	25/80 (31%)	27/76 (36%)
By mediastinoscopy	27/156 (17%)	11/80 (14%)	16/76 (21%)
Missing	2	1	1
Induction chemotherapy type			
Paclitaxel–carboplatin	82/157 (52%)	46/80 (57%)	36 (47%)
Vinorelbine–cisplatin	71/157 (45%)	32/80 (40%)	39 (51%)
Other*	4/157 (3%)	2/80 (3%)	2 (3%)
Not received	1	1	0
Radiochemotherapy type			
Paclitaxel–carboplatin	73/141 (52%)	37/68 (54%)	36/73 (49%)
Vinorelbine–cisplatin	56/141 (40%)	26/68 (38%)	30/73 (41%)
Other†	12/141 (9%)	5/68 (7%)	7/73 (10%)
Not received	17	13	4
Number of radiochemotherapy cycles			
0	17 (11%)	13 (16%)	4 (5%)
1	5 (3%)	3 (4%)	2 (3%)
2	54 (34%)	24 (30%)	30 (39%)
3	82 (52%)	41 (51%)	41 (53%)
Radiotherapy method			
Three-dimensional conformal radiotherapy	24/141 (17%)	13/68 (19%)	11/73 (15%)
Intensity-modulated radiotherapy	117/141 (83%)	55/68 (81%)	62/73 (85%)
Radiotherapy dose			
Median (range)	66·0 (14·0–74·1)	74·0 (14·0–74·1)	66·0 (60·0–66·0)
Durvalumab consolidation therapy			
Yes	76 (48%)	39 (48%)	37 (48%)
No	82 (52%)	42 (52%)	40 (52%)

Data are n (%), unless otherwise specified. There was no significant difference between groups A and B, except for radiotherapy dose (p<0·001). *Vinorelbine–carboplatin in three patients, and cisplatin alone in one patient. †Vinorelbine–carboplatin in 11 patients, and carboplatin alone in one patient.

Table 1: **Baseline and study treatment characteristics**

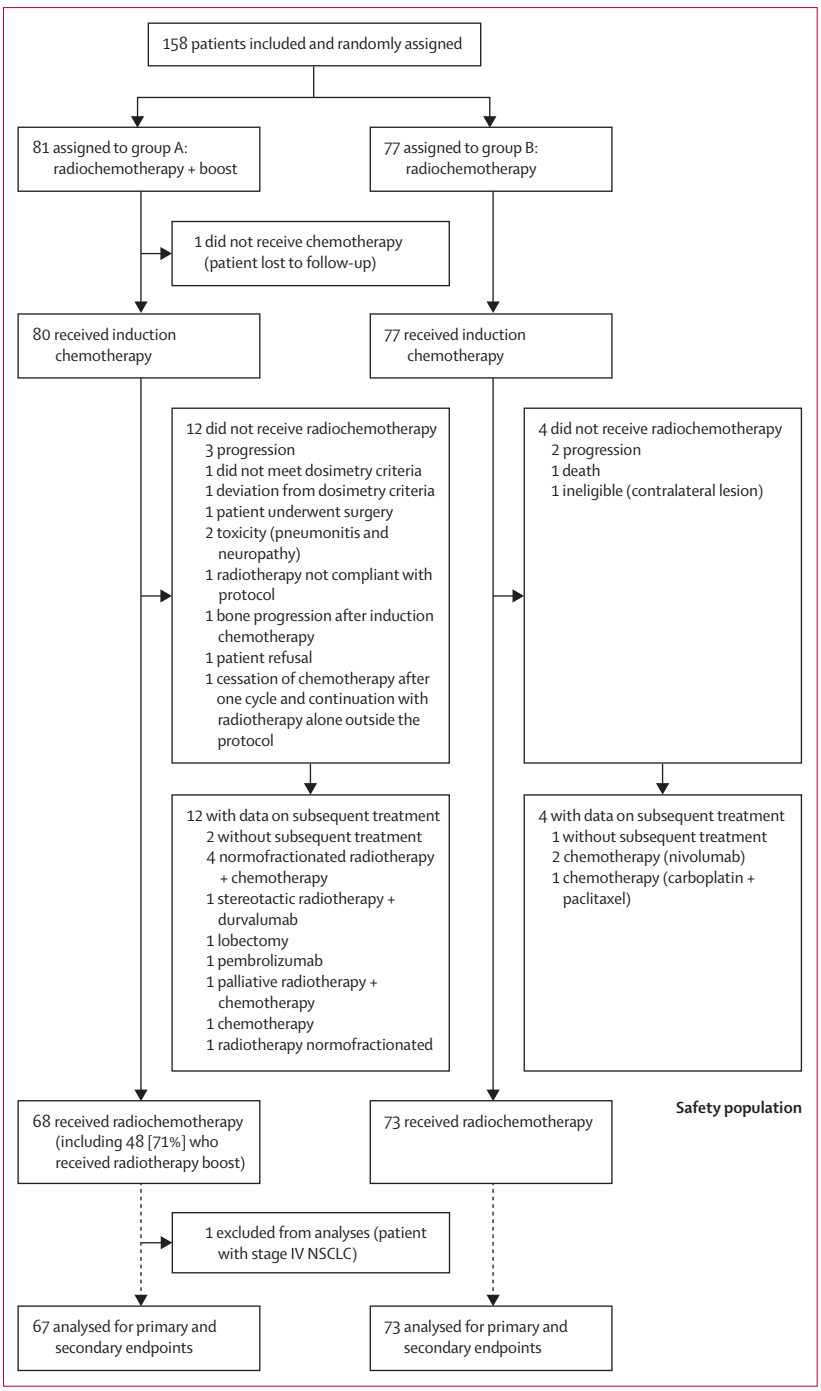

Figure 2: **Study flowchart**
NSCLC=non-small-cell lung cancer.

and 77 patients to group B. Demographic data were similar between the two groups and are presented in table 1. Briefly, the study population consisted of 47 (30%) women and 111 (70%) men; the median age was 62·9 years (IQR 57·2–68·8); 150 (95%) of patients were current or former smokers; 95 (60%) had an ECOG performance status of 0; 60 (38%) had squamous cell carcinoma; and 84 (53%) had cancer stage IIIa and 72 (46%) had cancer stage IIIb. Figure 2 provides the study flowchart.

The number of concurrent chemotherapy cycles was similar in both groups (table 1). The chemotherapy dose intensity, evaluated as the percentage of theoretical doses actually administered, was similar in both groups for each drug, including carboplatin, cisplatine, paclitaxel, or vinorelbine (data not shown). All except two patients in group A received more than 90% of the planned radiotherapy dose. Of these two patients, one refused to continue any further treatment and died 11 months after inclusion, and the second was progressing at [^{18}F]FDG-PET at 5 weeks on mediastinal nodes and received second-line nivolumab and was alive at the date of follow-up censoring.

The mean total radiotherapy duration for both groups was 47 days (SD 5·4). The median planning target volume was 368·8 mL (IQR 238·65–533·21) in group A and 372·36 mL (225·22–545·56) in group B. The median dose to planning target volume was 73·77 Gy (66·52–73·97) for group A and 65·94 Gy (65·79–66·02) for group B ($p<0·0001$; Mann–Whitney post-hoc analysis).

The median follow-up for patients who met the eligibility criteria and received radiochemotherapy (n=140; 67 in group A and 73 in group B) was 45·1 months (95% CI 39·3–48·3). The primary endpoint was reached in both groups: at 15 months, the local control rate was 77·6% (95% CI 67·6–87·6) in group A and 71·2% (95% CI 60·8–81·6) in group B, both higher than the 66% rate assumption for clinical activity. The local control rate at 9 months was 88·1% (95% CI 80·3–95·8) in group A versus 79·5% (70·2–88·7) in group B; at 27 months, 68·7% (57·5–79·8) in group A versus 65·8% (54·9–76·6) in group B; and at 39 months, 61·2% (49·5–72·9) in group A versus 57·5% (46·2–68·9) in group B. In patients who did not receive durvalumab, the 15-month local control rate was still 71·4% (95% CI 54·7–88·2) in group A and 61·1% (45·2–77·0) in group B (post-hoc analysis). In patients who received durvalumab, the 15-month local control rate was 82·1% (95% CI 70·0–94·1) in group A and 81·1% (68·5–93·7) in group B.

During induction chemotherapy, grade 3 adverse events occurred in nine (13%) of 68 patients in group A and 17 (23%) of 73 patients in group B; and grade 4 adverse events occurred in six (9%) patients in group A and six (8%) patients in group B (table 2). During radiochemotherapy, the incidence of grade 4 or worse adverse events (both acute and late) was three (4%) of 68 in group A (with one grade 5 pneumonitis not linked to radiotherapy that occurred after 90 days) and eight (11%) of 73 patients in group B (with four grade 5 events: one haemoptysis [in the acute phase], one cardiac failure not linked to radiotherapy, one septic shock [in the acute phase], and one radiation pneumonitis linked to radiotherapy or chemotherapy). The most common grade 3–4 adverse events were febrile neutropenia (seven

	Group A: radiochemotherapy + boost (N=68)					Group B: radiochemotherapy (N=73)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Induction										
Any adverse event	63 (93%)	48 (71%)	9 (13%)	6 (9%)	0	71 (97%)	48 (66%)	17 (23%)	6 (8%)	0
Serious adverse event	4 (6%)	1 (1%)	2 (3%)	1 (1%)	0	2 (3%)	0	2 (3%)	0	0
Chemotherapy-related adverse event*	48 (71%)	36 (53%)	6 (9%)	6 (9%)	0	60 (82%)	42 (58%)	12 (16%)	6 (8%)	0
Oesophageal event†	3 (4%)	3 (4%)	0	0	0	2 (3%)	2 (3%)	0	0	0
Atrial fibrillation	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0
Acute (≤90 days after the beginning of radiochemotherapy)										
Any adverse event	67 (99%)	47 (69%)	18 (26%)	2 (3%)	0	73 (100%)	38 (52%)	29 (40%)	4 (5%)	2 (3%)‡
Serious adverse event	7 (10%)	2 (3%)	3 (4%)	2 (3%)	0	15 (21%)	3 (4%)	9 (12%)	1 (1%)	2 (3%)
Chemotherapy-related adverse event§	52 (76%)	37 (54%)	15 (22%)	0	0	67 (92%)	42 (58%)	21 (29%)	4 (5%)	0
Oesophageal event¶	51 (75%)	49 (72%)	2 (3%)	0	0	57 (78%)	53 (73%)	3 (4%)	1 (1%)	0
Radiation skin injury	9 (13%)	9 (13%)	0	0	0	17 (23%)	16 (22%)	1 (1%)	0	0
Cardiac event‖	1 (1%)	1 (1%)	0	0	0	2 (3%)	0	2 (3%)	0	0
Radiation pneumonitis	3 (4%)	2 (3%)	0	1 (1%)	0	0	0	0	0	0
Haemoptysis	2 (3%)	2 (3%)	0	0	0	1 (1%)	0	0	0	1 (1%)‡
Septic shock	0	0	0	0	0	1 (1%)	0	0	0	1 (1%)
Late (>90 days after the beginning of radiochemotherapy)										
Any adverse event	32 (47%)	26 (38%)	5 (7%)	0	1 (1%)	30 (41%)	24 (33%)	4 (5%)	0	2 (3%)
Serious adverse event	0 (0%)	0	0	0	0	2 (3%)	0	2 (3%)	0	0
Chemotherapy-related adverse event**	2 (3%)	0	2 (3%)	0	0	1 (1%)	1 (1%)	0	0	0
Oesophageal event††	9 (13%)	9 (13%)	0	0	0	4 (5%)	4 (5%)	0	0	0
Radiation skin injury	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Atrial fibrillation	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0
Radiation pneumonitis	6 (9%)	4 (6%)	1 (1%)	0	1 (1%)	11 (15%)	8 (11%)	2 (3%)	0	1 (1%)
Bronchitis	1 (1%)	1 (1%)	0	0	0	1 (1%)	1 (1%)	0	0	0
Cardiac failure	0	0	0	0	0	1 (1%)	0	0	0	1 (1%)

*Decreased neutrophil count, nausea, diarrhoea, constipation, increased blood creatinine, vomiting, anaemia, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, febrile neutropenia, leukopenia, lymphopenia, or thrombocytopenia. †Gastro-oesophageal reflux disease, dyspepsia, or oesophagitis. ‡Not treatment related. §Nausea, constipation, diarrhoea, vomiting, decreased neutrophil count, decreased platelet count, increased blood creatinine, increased γ-glutamyltransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, increased aspartate aminotransferase, decreased lymphocyte count, decreased white blood cell count, anaemia, lymphopenia, leukopenia, febrile neutropenia, thrombocytopenia, or neutropenia. ¶Radiation oesophagitis, oesophagitis, dysphagia, gastro-oesophageal reflux disease, or dyspepsia. ||Angina pectoris, atrial fibrillation, or myocardial ischaemia. **Increased blood creatinine, anaemia, or lymphopenia. ††Oesophagitis, dysphagia, and odynophagia.

Table 2: **All causality adverse events**

[10%] of 68 in group A *vs* 16 [22%] of 73 in group B), and anaemia (five [7%] *vs* nine [12%]; appendix pp 120–122). Acute (within 90 days from radiochemotherapy initiation) grade 3–4 adverse events were observed in 20 (29%) of 68 patients in group A and 33 (45%) of 73 patients in group B, including serious adverse events in five (7%) patients in group A and ten (14%) patients in group B. Table 3 shows all treatment-related serious adverse events observed during the study.

One (1%) patient of 68 in group A and five (7%) patients of 73 in group B had a transitory interruption of treatment, which lasted for 4 days in the group A patient, and lasted for a median of 6·0 days (range 3–9) in group B. The cause for the transitory interruption was adverse events in only two patients, both in group B.

The median progression-free survival was 22·3 months (95% CI 14·8–33·7) in group A and 12·3 months (9·4–23·3) in group B (figure 3A). The progression-free survival at 9, 15, 27 and 39 months are shown in the appendix (p 123).

39-month local or regional progression rates were 58% (41·1–71·6) in group A and 52·2 (36·8–65·6) in group B (appendix p 1). Time to locoregional progression is shown in the appendix (p 1). Post-hoc analysis of progression-free survival according to durvalumab maintenance treatment is shown in the appendix (p 2).

Overall, 56 (40%) of 140 eligible patients died at database lock (Nov 1, 2022). The median overall survival was not reached (NR; 95% CI 40·9–NR) in group A, and was 43·3 months (33·4–NR) in group B, with a 39-month overall survival of 67·8% (95% CI 53·9–78·3) in group A and 55·8% (43·0–66·8) in group B (figure 3B). The overall survival at 9, 15, and 27 months are shown in the appendix (p 123). Causes of all deaths until the follow-up censoring date are provided in the appendix (p 7).

	Group A: radiotherapy + boost (N=68)					Group B: radiotherapy (N=73)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Induction										
Serious treatment-related adverse event*	2 (3%)	0	1 (1%)	1 (1%)	0	0	0	0	0	0
Febrile neutropenia	1 (1%)	0	1 (1%)	0	0	0	0	0	0	0
Anaphylactic shock	1 (1%)	0	1 (1%)	0	0	0	0	0	0	0
Hypokalaemia	1 (1%)	0	0	1 (1%)	0	0	0	0	0	0
Acute (≤90 days after the beginning of radiochemotherapy)										
Serious treatment-related adverse event*	4 (6%)	1 (1%)	2 (3%)	1 (1%)	0	6 (8%)	1 (1%)	3 (4%)	1 (1%)	1 (1%)
Radiation oesophagitis	1 (1%)	0	1 (1%)	0	0	3 (4%)	0	2 (3%)	1 (1%)	0
Anaemia	1 (1%)	0	1 (1%)	0	0	1 (1%)	0	1 (1%)	0	0
Febrile neutropenia	0	0	0	0	0	1 (1%)	0	1 (1%)	0	0
Catheter site infection	0	0	0	0	0	1 (1%)	0	1 (1%)	0	0
Septic shock	0	0	0	0	0	1 (1%)	0	0	0	1 (1%)
Acute kidney injury	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0
Radiation pneumonitis	1 (1%)	0	0	1 (1%)	0	0	0	0	0	0
Erythema	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Late (>90 days after the beginning of radiochemotherapy)										
Serious treatment-related adverse event*	0	0	0	0	0	1 (1%)	0	1 (1%)	0	0
Radiation pneumonitis	0	0	0	0	0	1 (1%)	0	1 (1%)	0	0
Pulmonary embolism	0	0	0	0	0	1 (1%)	0	1 (1%)	0	0

*Number of patients, one patient having had two adverse events.

Table 3: **Patients with treatment-related serious adverse events**

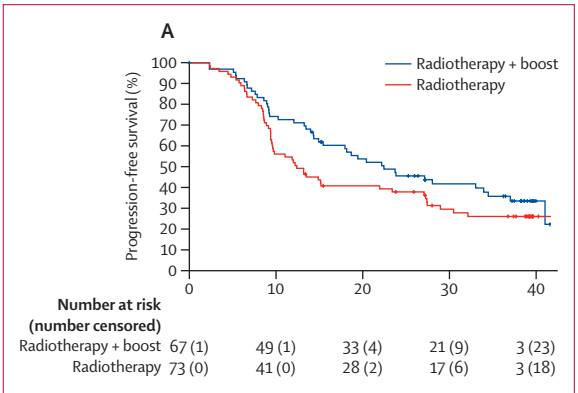

Figure 3: **Progression-free survival (A) and overall survival (B) from randomisation**

Subsequent treatments at disease progression are listed in the appendix (pp 8–9), and were similar between the two groups.

In the prespecified analyses, SUVmax, MTV, change in SUVmax, and change in MTV did not differ significantly between groups A and B in terms of [^{18}F]FDG-PET at baseline, at 42 Gy, and at 6 months (appendix p 6). The correlation between SUVmax and MTV for FDG-PET at baseline was 0·31 (p<0·001). The time to locoregional progression is also shown in the appendix (p 1).

A prespecified exploratory univariable regression analysis assessed whether clinical variables, radiotherapy boost, or [^{18}F]FDG-PET variables could predict patient progression-free survival after radiochemotherapy completion (table 4). Prespecified Cox regression multivariable analysis revealed that a median SUVmax ([^{18}F]FDG-PET at 42 Gy) of 5·4 or less (p=0·0079) was the only [^{18}F]FDG-PET variable that significantly predicted progression-free survival along with 3D conformal radiotherapy and durvalumab, with similar hazard ratios for these three variables.

For patients (from both groups) who did not receive a boost, the median dose to the lung was 15·34 Gy (IQR 12·56–19·26), versus 14·83 Gy (12·46–19·08) in the 48 patients who did receive a boost. Volume of lung receiving 20 Gy was 27·36% (22·01–33·05) in group A versus 26·28% (20·38–32·13) in group B. The median dose to the heart was 9·60 Gy (4·91–15·84) in group A and 10·78 Gy (6·27–17·30) in group B. The median dose to the heart in patients (from both groups) who did not

receive a boost was 10·92 Gy (6·68–17·42), whereas the median dose to the heart in boosted patients was 9·09 Gy (4·67–13·61; p=0·04; Mann–Whitney post-hoc analysis). Finally, the oesophagus volume receiving 35% of the prescribed radiotherapy dose was higher for group A patients, at 19·30% (11·89–32·95), versus 12·68% (9·20–16·59) for group B patients (p<0·0001; Mann–Whitney post-hoc analysis). The median total radiotherapy duration did not differ significantly between group A and B patients (47·0 and 46·0 days, respectively), nor did the median number of radiotherapy interruption days (six and four days, respectively).

Discussion

This prospective, multicentre, randomised non-comparative phase 2 study involving 158 patients with inoperable stage III NSCLC showed that increasing the radiotherapy dose depending on an [18F]FDG-PET sub-volume result at 42 Gy was safe, and led to encouraging local control of the tumour at 15 months. The study findings show that increasing the radiotherapy dose in patients with inoperable stage III NSCLC is not always deleterious, provided it is restricted to patients with persisting active disease after the initial 42 Gy of radiotherapy, is based on metabolic imaging during treatment, and the radiotherapy boost volume is adapted to the residual metabolic tumour sub-volume. This customised strategy could result in an improved local control rate without increased toxicity, and local control rate has previously been shown to be significantly associated with overall survival.[15,16]

Our trial used intensity-modulated radiotherapy technique for the majority of patients, including an extensive quality control of technical radiotherapy (ie, a dummy run before centre inclusion and controlling treatment plans) and [18F]FDG-PET procedures (ie, a dummy run, [18F]FDG-PET qualification, specific image reconstruction for multicentre analysis, to ensure that all radiotherapy centres used the same specification for the PET definition of the radiation volumes, and centralised [18F]FDG-PET analysis). Therefore, we cannot exclude the notion that the favourable disease control and survival data observed in both groups, compared with historical study data, could have benefited from progress in radiotherapy techniques.[15,17]

During the course of this trial, the PACIFIC phase 3 trial[2] results were published, and led to the marketing authorisation of adjuvant durvalumab after radio-chemotherapy for patients with stage III NSCLC with tumour control after the completion of radiotherapy, and no radiation pneumonitis.[2] We subsequently amended our trial protocol to allow durvalumab use. However, the 15-month local control rate was still 71·4% in the group of patients who did not receive durvalumab, suggesting that the effect of the customised radiotherapy boost was also observed in patients who did not receive adjuvant immunotherapy.

	Number of patients	Univariable analysis (all; N=140)		Multivariable analysis (all; N=136)	
		HR (95% CI)	p value	HR (95% CI)	p value
Radiotherapy method					
Intensity-modulated radiotherapy	116	1	..	1	..
Three-dimensional conformal radiotherapy	24	0·62 (0·34–1·12)	0·11	0·46 (0·25–0·87)	0·0197
Age in years, continuous variable	140	1·01 (0·99–1·04)	0·28	..*	..*
Sex					
Female	40	1	..	..*	..*
Male	100	1·41 (0·88–2·28)	0·15	..*	..*
Eastern Cooperative Oncology Group performance status					
0	88	1	..	..*	..*
1	52	0·98 (0·65–1·50)	0·94	..*	..*
Histology					
Squamous cell carcinoma	54	1	..	..*	..*
Non-squamous cell carcinoma, including adenocarcinoma, large cell, and undifferentiated carcinoma	86	1·03 (0·68–1·57)	0·87	..*	..*
TNM stage					
IIIa	75	1	..	..*	..*
IIIb	65	1·43 (0·96–2·15)	0·0795	..*	..*
Durvalumab consolidation					
No	64	1	..	1	..
Yes	76	0·59 (0·39–0·88)	0·0099	0·51 (0·33–0·79)	0·0032
SUVmax ([18F]FDG-PET at baseline) <14·20, median					
No	70	1	..	..*	..*
Yes	69	1·08 (0·72–1·62)	0·70	..*	..*
MTV ([18F]FDG-PET at baseline) <33·9 cm³, median					
No	70	1	..	..*	..*
Yes	69	0·84 (0·56–1·25)	0·38	..*	..*
SUVmax ([18F]FDG-PET at 42 Gy) ≤5·4, median					
No	67	1	..	1	..
Yes	69	0·59 (0·39–0·89)	0·0130	0·57 (0·37–0·86)	0·0079
MTV ([18F]FDG-PET at 42 Gy) <3·55 cm³, median					
No	68	1	..	..*	..*
Yes	68	0·77 (0·51–1·16)	0·22	..*	..*
Change in SUVmax <–59·21%, median					
No	68	1	..	..*	..*
Yes	68	0·73 (0·48–1·10)	0·13	..*	..*
Change in MTV <–88·10%, median					
No	68	1	..	..*	..*
Yes	68	0·70 (0·46–1·06)	0·0912	..*	..*
Radiotherapy boost					
No	93	1	..	..*	..*
Yes	47	0·70 (0·45–1·08)	0·11	..*	..*

All subset analyses were prespecified. HR=hazard ratio. MTV=metabolic tumour volume. SUVmax=maximum standardised uptake value. TNM=tumour node metastasis. *Variable not selected by the stepwise model.

Table 4: **Univariable and multivariable analyses of progression-free survival**

The absence of a significant difference in adverse events between the two groups that we observed in this study, based on the interim [18F]FDG-PET and radiotherapy sub-volume adaptation to metabolic tumour

volume at 42 Gy, actually contrasts with the results of the RTOG 0617 study by Bradley and colleagues.[9] The RTOG 0617 trial reported that increasing the planned radiation dose to 74 Gy before radiotherapy to the whole initial tumour volume, without [18F]FDG-PET targeting, did not improve overall survival, potentially because of cardiac toxicity. Our data also contrasts with the results of the PET-boost trial,[10,11,18,19] where [18F]FDG-PET was done at diagnosis rather than on-treatment to escalate the radiotherapy dose up to 74–77 Gy, while targeting the initial metabolically active volume.[17]

Notably, our data show that [18F]FDG-PET imaging can be used during radiotherapy to better target the residual tumour volume, thus reducing the volume of healthy tissue irradiated. Before our prospective study, Guberina and colleagues[20] and Pöttgen and colleagues[21] conducted a [18F]FDG-PET retrospective analysis before, during, and after treatment, confirming the value of [18F]FDG-PET when applied before radiotherapy.[19,20]

Over the last 10 years, the PET-boost trial[10,18,19] and the RTOG 1106 trial[19] based on a phase 2 clinical trial[22] prospectively tested the possibility of using [18F]FDG-PET to increase radiotherapy dosing in patients with lung cancer, but reported higher rates of radiotherapy-related adverse events. Subsequently, in the PET-Plan study,[23] the authors did not report any major toxicity when the radiotherapy boost was administered, depending on the residual tumour uptake on [18F]FDG-PET. Taken together, these data favour precise PET targeting in the attempt to increase the radiotherapy dose. However, these studies reported higher acute and late toxicity than conventional radiochemotherapy. In contrast to these latest published studies, our findings indicate, as previously suggested,[4,19] that a radiation boost of 8 Gy, regardless of the radiotherapy technique applied (3D or intensity-modulated radiotherapy), on a controlled sub-volume in patients with NSCLC does not increase grade 3 and 4 acute and late radiotherapy-related toxicity.

In this RTEP7–IFCT-1402 trial, the median radiation dose to the heart did not differ significantly between the two groups. Notably, the dose to the heart was slightly higher in patients (from either group) who did not receive any boost compared with patients who did receive a boost from the experimental group, potentially because of the results of the on-treatment PET-based strategy, leading to a radiation volume reduction to the heart. The median dose to the lung and the volume of lung receiving 20 Gy did not differ substantially either between the two groups, or in patients in group A who received the radiation boost and those who did not.

Regarding [18F]FDG-PET variables, in a prespecified multivariable analysis, the SUVmax of [18F]FDG-PET at 42 Gy predicted a longer progression-free survival, as did durvalumab treatment. The SUV cutoff would have to be explored in future [18F]FDG-PET studies or radiotherapy studies, or both, using [18F]FDG-PET for tumour volume delineation, with an adequate sample size for predictive analyses and interaction tests.

One of the issues raised by our study is whether such a strategy could be generalisable to routine practice, taking into account all technical and organisational constraints. However, after qualification of the centres for the study (including a dummy run test) to ensure a maximum homogenisation of techniques across these centres, they did not face further difficulty in accruing patients, suggesting that using [18F]FDG-PET at 42 Gy for adapting radiotherapy dosing could be implemented in most radiotherapy and nuclear medicine departments. In this randomised phase 2 study, the small sample size was the main limitation of this study.

Large-scale randomised trials are now needed, with long-term survival and safety results, before this metabolic-response-based customised strategy could actually modify the current radiotherapy treatment framework, by selectively increasing radiotherapy dosing in patients with stage III NSCLC with radiotherapy-resistant tumours on interim [18F]FDG-PET.

Contributors

PV, ST, PC-R, ALan, GZ, and PGi conceptualised the study. PV, ST, FLT, SH, HK-G, EM, AB-R, NP, JMB, PB, SGuillem, NS, IB-R, CLP, CB, EG-L, DM, SGuiller, KB, LT, CA-V, DL, EQ, CM, FC, PM, AL, RM, PGo, NG, GZ, and PGi conducted the investigations (recruited and treated patients and collected data; did the central review of imaging, quality controls, and dummy run for centres qualification; and reviewed the radiotherapy data). PGo and EA were responsible for project administration. PV, ST, PC-R, ALan, GZ, and PGi analysed and interpreted the data. PV, ST, PGi, and GZ wrote the original draft. All authors had full access to all the data in the study, reviewed and approved the final version, and accept responsibility for the decision to submit for publication. PV, PGi, ST, ALan, and GZ accessed and verified the data.

Declaration of interests

EM declared payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Varian Medical Systems, AstraZeneca, MSD, Janssen, and Sanofi; support for attending meetings or travel, or both, from Ipsen, Janssen, and AstraZeneca; and participation on a data safety monitoring board or advisory board for AstraZeneca and Janssen. IB-R declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis 3A and Curium; payment for expert testimony from Curium; and support for attending meetings or travel, or both, from Novartis 3A. CLP declares payment or honoraria to her institution for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca and Amgen; support for attending meetings or travel, or both, paid to her institution from Janssen and Roche; and participation on a data safety monitoring board or advisory board paid to her institution for AstraZeneca, Varian, MSD, and Roche. EG-L declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, AstraZeneca, Ipsen, Janssen, Lilly, MSD, Novartis, Pfizer, Sanofi, and Takeda; and support for attending meetings or travel, or both, from Takeda, MSD, AstraZeneca, and Roche. CA-V declares support for attending meetings or travel, or both, from Roche, Sanofi, MSD, BMS, Lilly, Pfizer, AstraZeneca, Janssen, and Abbvie; and participation on a data safety monitoring board or advisory board for Roche, Sanofi, MSD, BMS, Lilly, Pfizer, AstraZeneca, Janssen, and Abbvie. ALan and EA are employees of the French Intergroup (Intergroupe Francophone de Cancérologie Thoracique). GZ declares consulting fees paid to his institution from AstraZeneca, BMS, Takeda, and Roche; payment or honoraria to his institution for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Inventiva, BMS, and Pfizer; support for

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Data sharing

The individual participant data that underlie the results reported in this Article, as well as the study protocol and statistical analysis plan, will be made available after deidentification immediately after publication and for 3 years subsequently. Researchers who provide a methodologically sound proposal for any purpose can direct proposals to contact@ifct.fr. To gain access, data requestors will need to sign a data access agreement that requires approval by the French Cooperative Thoracic Intergroup and Henri Becquerel Centre.

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References

1 Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28:** 2181–90.

2 Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; **377:** 1919–29.

3 Vaz SC, Adam JA, Delgado Bolton RC, et al. Perspective paper about the joint EANM/SNMMI/ESTRO practice recommendations for the use of 2-[^{18}F]FDG-PET/CT external beam radiation treatment planning in lung cancer. *Radiother Oncol* 2022; **168:** 37–39.

4 Edet-Sanson A, Dubray B, Doyeux K, et al. Serial assessment of FDG-PET FDG uptake and functional volume during radiotherapy (RT) in patients with non-small cell lung cancer (NSCLC). *Radiother Oncol* 2012; **102:** 251–57.

5 Vera P, Mezzani-Saillard S, Edet-Sanson A, et al. FDG PET during radiochemotherapy is predictive of outcome at 1 year in non-small-cell lung cancer patients: a prospective multicentre study (RTEP2). *Eur J Nucl Med Mol Imaging* 2014; **41:** 1057–65.

6 Arriagada R, Le Chevalier T, Quoix E, et al. ASTRO (American Society for Therapeutic Radiology and Oncology) plenary: effect of chemotherapy on locally advanced non-small cell lung carcinoma: a randomized study of 353 patients. GETCB (Groupe d'Etude et Traitement des Cancers Bronchiques), FNCLCC (Féderation Nationale des Centres de Lutte contre le Cancer) and the CEBI trialists. *Int J Radiat Oncol Biol Phys* 1991; **20:** 1183–90.

7 Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005; **63:** 324–33.

8 Machtay M, Bae K, Movsas B, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 2012; **82:** 425–34.

9 Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; **16:** 187–99.

10 van Elmpt W, De Ruysscher D, van der Salm A, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiother Oncol* 2012; **104:** 67–71.

11 van Diessen J, De Ruysscher D, Sonke JJ, et al. The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial). *Radiother Oncol* 2019; **131:** 166–73.

12 Hodapp N. The ICRU report 83: prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT). *Strahlenther Onkol* 2012; **188:** 97–99 (in German).

13 Mahasittiwat P, Yuan S, Xie C, et al. Metabolic tumor volume on PET reduced more than gross tumor volume on CT during radiotherapy in patients with non-small cell lung cancer treated with 3DCRT or SBRT. *J Radiat Oncol* 2013; **2:** 191–202.

14 Ganem J, Thureau S, Gardin I, Modzelewski R, Hapdey S, Vera P. Delineation of lung cancer with FDG PET/CT during radiation therapy. *Radiat Oncol* 2018; **13:** 219–26.

15 Vera P, Thureau S, Chaumet-Riffaud P, et al. Phase II study of a radiotherapy total dose increase in hypoxic lesions identified by ^{18}F-Misonidazole PET/CT in patients with non-small cell lung carcinoma (RTEP5 Study). *J Nucl Med* 2017; **58:** 1045–53.

16 Machtay M, Paulus R, Moughan J, et al. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *J Thorac Oncol* 2012; **7:** 716–22.

17 Weber DC, Hurkmans CW, Melidis C, et al. Outcome impact and cost-effectiveness of quality assurance for radiotherapy planned for the EORTC 22071-24071 prospective study for head and neck cancer. *Radiother Oncol* 2014; **111:** 393–99.

18 Cooke SA, de Ruysscher D, Reymen B, et al. ^{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. *Radiother Oncol* 2023; **181:** 109492–99.

19 La Fontaine M, Vogel W, van Diessen J, et al. A secondary analysis of FDG spatio-temporal consistency in the randomized phase II PET-boost trial in stage II-III NSCLC. *Radiother Oncol* 2018; **127:** 259–66.

20 Guberina M, Pöttgen C, Metzenmacher M, et al. Prognostic value of postinduction chemotherapy volumetric PET/CT parameters for stage IIIA or IIIB non–small cell lung cancer patients receiving definitive chemoradiotherapy. *J Nucl Med* 2021; **62:** 1684–91.

21 Pöttgen C, Gauler T, Bellendorf A, et al. Standardized uptake decrease on [18F]-fluorodeoxyglucose positron emission tomography after neoadjuvant chemotherapy is a prognostic classifier for long-term outcome after multimodality treatment: secondary analysis of a randomized trial for resectable stage IIIA/B non-small-cell lung cancer. *J Clin Oncol* 2016; **34:** 2526–33.

22 Kong FM, Ten Haken RK, Schipper M, et al. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non-small-cell lung cancer: a phase 2 clinical trial. *JAMA Oncol* 2017; **3:** 1358–65.

23 Nestle U, Schimek-Jasch T, Kremp S, et al. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. *Lancet Oncol* 2020; **21:** 581–92.