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ORIGINAL ARTICLE

Radiotherapy boost in patients with hypoxic lesions identified by ^{18}F-FMISO PET/CT in non-small-cell lung carcinoma: can we expect a better survival outcome without toxicity? [RTEP5 long-term follow-up]

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Abstract

Purpose Chemoradiotherapy is the reference curative-intent treatment for nonresectable locally advanced non-small-cell lung carcinoma (NSCLC), with unsatisfactory survival, partially due to radiation resistance in hypoxic tissues. The objective was to update survival and toxicity at 3 years following radiotherapy boost to hypoxic tumours in NSCLC patients treated with curative-intent chemoradiotherapy.

Methods This was an open-label, nonrandomized, multicentre, phase II clinical trial. ^{18}F-Fluoromisonidazole (^{18}F-FMISO) PET/CT was used to determine the hypoxic profile of the patients. ^{18}F-FMISO-positive patients and those without organ-at-risk constraints received a radiotherapy boost (70–84 Gy); the others received standard radiotherapy (66 Gy). Overall survival (OS), progression-free survival (PFS) and safety were assessed.

Results A total of 54 patients were evaluated. OS and PFS rates at 3 years were 48.5% and 28.8%, respectively. The median OS in the ^{18}F-FMISO-positive patients was 25.8 months and was not reached in the ^{18}F-FMISO-negative patients ($p = 0.01$). A difference between the groups was also observed for PFS (12 months vs. 26.2 months, $p = 0.048$). In ^{18}F-FMISO-positive patients, no difference was observed in OS in relation to dose, probably because of the small sample size ($p = 0.30$). However, the median OS seemed to be in favour of patients who received the radiotherapy boost (26.5 vs. 15.3 months, $p = 0.71$). In patients who received the radiotherapy boost, no significant late toxicities were observed.

Conclusion ^{18}F-FMISO uptake in NSCLC patients is strongly associated with features indicating a poor prognosis. In ^{18}F-FMISO-positive patients, the radiotherapy boost seemed to improve the OS by 11.2 months. A further clinical trial is needed to investigate the efficacy of a radiotherapy boost in patients with hypoxic tumours.

Keywords Positron emission tomography · Fluorodeoxy-D-glucose · ^{18}F-Fluoromisonidazole · Hypoxia · Lung cancer · Radiotherapy dose

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Introduction

Concomitant chemoradiotherapy (CCRT) is the reference curative-intent treatment for stage III non-small-cell lung cancer (NSCLC), although the age-standardized 5-year survival remains between 10% and 20%, with a median overall survival (OS) of 16 to 30 months [1]. More precise staging (PET, endobronchial ultrasonography, or endoscopic ultrasonography) has led to an increase in survival in the past several years. Apart from the contribution of immunotherapy to maintenance, there have been no significant changes in the therapeutic strategy in these patients [2]. One approach is to increase the dose to radioresistant areas, facilitated by image-guided radiotherapy. The findings of previous studies are contradictory, with some in favour of dose escalation [3, 4] and some not [5, 6], but none has taken into consideration the hypoxic profile of the tumour.

From 2012 to 2015, we conducted a phase II prospective study aiming to test the feasibility of performing boost radiotherapy to hypoxic tumours identified by ^{18}F-fluoromisonidazole (^{18}F-FMISO) PET/CT. Early results have been published previously and demonstrated the feasibility of delivering higher radiotherapy doses to those small target volumes without exceeding the tolerance to normal organs [7]. We showed identical local control in patients who had received an additional dose of radiotherapy (hypoxic tumour) and in patients who had received a standard dose (normoxic tumour). However, patients who received additional radiotherapy had tumours twice as large as patients who did not receive additional radiotherapy, suggesting that the radiotherapy boost was effective. This report presents additional long-term data on survival and toxicity.

Materials and methods

Study design and patients

The study was an open-label, single-arm, multicentre, nonrandomized, phase II clinical trial conducted by independent investigators from 15 academic centres in France. For a period of 3 years (2012–2015), patients with NSCLC referred to the participating centres were involved in a run-in period ($N = 79$). The design of the study, as well as inclusion and exclusion criteria, have been presented previously [7].

The main inclusion criteria were histological proof of NSCLC with a measurable tumour (RECIST1.1), with a World Health Organization performance status of ≤1 and patients eligible for curative-intent CCRT. The primary endpoints were the OS and progression-free survival (PFS) at 1, 2 and 3 years. The secondary endpoint was late toxicity. Of the 79 patients, 54 who had at least one lesion showing fluorodeoxyglucose (FDG) uptake were included. Subsequently, if the FDG-avid lesion showed ^{18}F-FMISO uptake on PET/CT performed before CCRT within 8 days of the initial FDG PET/CT scan, the lesion was considered hypoxic.

The protocol and the consent form were approved by the Ethics Committee Nord-Ouest 1. All patients gave their written informed consent. The study was registered in the Clinical Trials Protocol Registration System (NCT01576796; RTEP5 study). The clinical, biological, imaging and toxicity data were monitored by a certified clinical research unit.

PET imaging

^{18}F-FDG PET/CT and ^{18}F-FMISO PET/CT were performed using the same type of machine and under identical operational conditions in each centre, ensuring centrally supervised quality control to secure homogeneity in image quality among all centres [7]. ^{18}F-FDG PET/CT was performed with the patient in the treatment position (arms over the head, free breathing) at least 15 days after the last administration of neoadjuvant chemotherapy. ^{18}F-FMISO PET/CT was scheduled 48 h after ^{18}F-FDG PET/CT. The ^{18}F-FMISO PET/CT acquisitions were reviewed visually by three independent experts (of the nine experts) after training and validation [9] who decided on the presence (hypoxia) or absence (no hypoxia) of uptake. The CT images were used to register all PET/CT acquisitions, delineate target volumes and plan radiotherapy.

In each patient, the ^{18}F-FDG and ^{18}F-FMISO images were first coregistered to the planning CT images on an Oncoplanet workstation, v. 1.4 (DOSIsoft, Villejuif, France). The volumes of interest for ^{18}F-FDG (metabolic biological target volume, BTV_m) were defined as the sum of the pixels with greater than 40% of the maximum standardized uptake value (SUVmax) inside the primary tumour or nodes [8]. The volumes of interest for ^{18}F-FMISO (hypoxic biological target volume, BTV_h) were defined as the sum of the pixels with SUV ≥1.4 as previously validated [9]. The regions with increased ^{18}F-FDG and ^{18}F-FMISO uptake were compared with the anatomical findings from the CT scans. Quantitative analysis was not used to define positivity or negativity of ^{18}F-FMISO PET/CT, but only to define the BTV_h (^{18}F-$FMISO_{BTV}$). The coregistered ^{18}F-FDG and ^{18}F-FMISO PET/CT images (DICOM), as well as BTV_m (^{18}F-FDG_{BTV}) and BTV_h (^{18}F-$FMISO_{BTV}$) (DICOM-RT), were transferred back to the local radiation oncologist using the same network.

Radiochemotherapy protocol

The chemoradiotherapy protocol applied in this study complied with French and international guidelines [10, 11]. All dose calculations were corrected for heterogeneity, and intensity-modulated radiotherapy was not performed. The total dose was prescribed by the International Commission on Radiation Units point. The maximum dose to the spinal cord

was strictly less than 46 Gy, and no more than 30% of the total lung volume (excluding the gross tumour volume) received more than 20 Gy. Furthermore, no more than 30% of the oesophagus or heart could receive more than 50 or 35 Gy, respectively.

Patients received the standard dose of 66 Gy (five daily fractions of 2 Gy weekly). Higher radiation doses to the BTV were achieved by increasing the overall treatment time. CCRT was cisplatinum and etoposide or cisplatinum and vinorelbine after two neoadjuvant chemotherapy courses using the same protocol.

Statistical analysis

The analysis was conducted on an intention-to-treat basis. The statistical analysis was performed using R software, version 3.5.0 [12]. The entire database was held and the analysis was performed at the Clinical Trial Research Unit of the Henri Becquerel Cancer Centre.

Variables relating to hypoxic status and the total radiotherapy dose received were compared using Fisher's exact test for categorical data and analysis of variance for continuous data. Groups with continuous variables were compared using independent samples *t* tests. OS and PFS were considered from the first radiotherapy administration to death or progression and death, respectively. The statistically significant threshold was fixed at a two-tailed *p* value of less than 0.05.

Survival probabilities were estimated using the Kaplan-Meier method. Univariate and multivariate analyses using Cox models and log-rank tests were performed to evaluate the effects of several variables on survival. Since this phase II trial was initially planned as not randomized, we observed that the sample characteristics differed according to ^{18}F-FMISO uptake and initial tumour size. Because the latter was a non-negligible confounding factor strictly related to hypoxia and prognosis, we performed a survival analysis on data adjusted according to the propensity score weighting method [13], which has been shown to be appropriate for studies with small sample sizes [14]. This method allows the estimation of a propensity score by adjusting the logistic regression model containing influencing covariates. Adjusted samples are then created by weighting on the propensity score to establish balance between groups (with a reduction in the standardized mean difference). Survival can therefore be reevaluated using the adjusted samples to reduce selection bias.

Sample size and follow-up procedures

The study design followed Gehan's method; the sample size calculation has been presented previously [7]. Efficacy and toxicity assessments were planned for 3 months, and for 1, 2 and 3 years after the end of the treatment.

Results

Study flow chart and patient characteristics

Between 2012 and 2015, 79 patients willing to participate were involved in the run-in period. From among these patients, 54 were included and participated in the study, and of these, 34 were considered to have a hypoxic lesion. The study flow chart and the reasons for noneligibility are presented in Fig. 1.

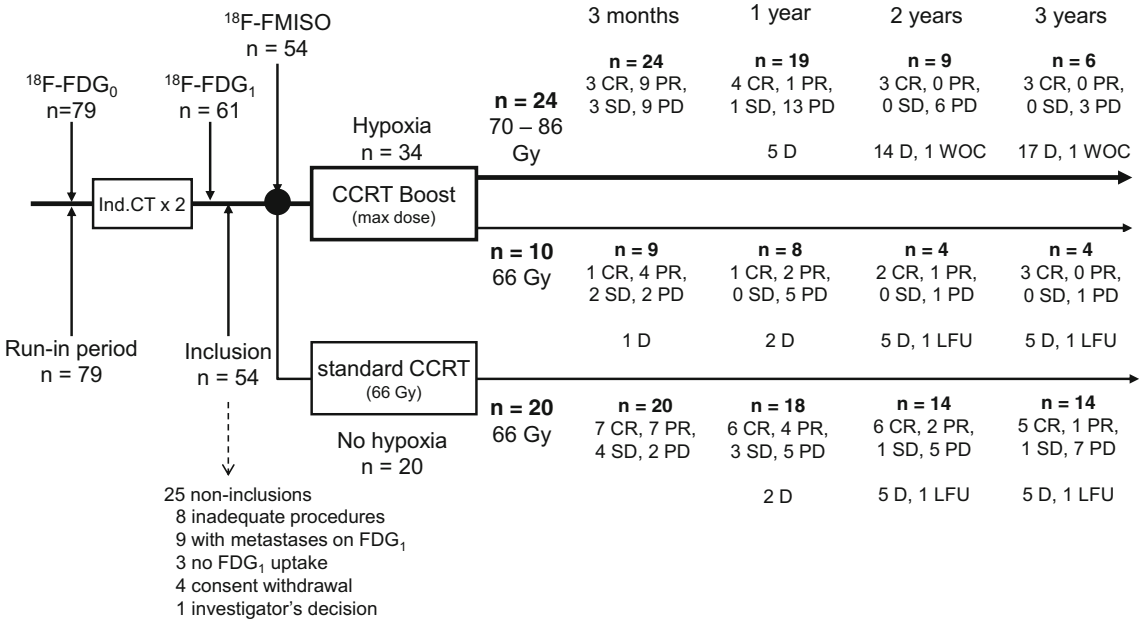


Fig. 1 Study design/study flow. *CCRT* radiochemotherapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease (RECIST 1.1), *D* death, *LFU* lost to follow-up, *WOC* withdrawal of consent, *Ind.* induction

Table 1 Baseline characteristics of the 54 included patients

Characteristic	Total	Hypoxia ($n = 34$)		No hypoxia ($n = 20$)	p value[a]
		Boost ($n = 24$)	66 Gy ($n = 10$)	66 Gy	
Sex ratio (M:F)	6.71	5	4	19	0.38
Age (years), mean ± SD	59.91 ± 7.59	59.92 ± 8.35	56.8 ± 9.31	61.45 ± 5.28	0.29
Tumour histology, *n* (%)					
Squamous cell carcinoma	26 (48.15)	14 (58.3)	2 (20)	10 (50)	0.078
Adenocarcinoma	24 (44.44)	7 (29.2)	7 (70)	10 (50)	
Undifferentiated	4 (7.41)	3 (12.5)	1 (10)	0 (0)	
Tumour stage, *n* (%)					
IIB	4 (7.41)	2 (8.30)	1 (10)	1 (5)	0.85
IIIA	17 (31.48)	8 (33.30)	2 (20)	7 (35)	
IIIB	26 (48.15)	12 (50.00)	6 (60)	8 (40)	
IIIC	7 (12.96)	2 (8.30)	1 (10)	4 (20)	
Tumour size (mm), mean ± SD	47.33 ± 29.05	61.17 ± 32.47	49.10 ± 24.35	29.85 ± 15.24	<0.001
Radiotherapy dose (Gy), mean ± SD	71.00 ± 6.59	77.25 ± 5.17	66.00 ± 0	66.00 ± 0	<0.001
^{18}F-FDG					
PET1 SUV_{max}, mean ± SD	12.26 ± 9.58	13.77 ± 7.80	16.40 ± 12.44	8.38 ± 9.01	0.054
PET1 BTV_m (cm^3), mean ± SD	45.00 ± 60.32	58.99 ± 84.81	46.82 ± 24.86	27.32 ± 23.92	0.22
^{18}F-FMISO					
PET SUV_{max}, mean ± SD	2.09 ± 0.83	2.40 ± 0.61	2.68 ± 0.96	1.41 ± 0.48	<0.001
PET BTV_h (cm^3), mean ± SD	–	34.13 ± 58.11	32.00 ± 37.95	–	

For comparisons between the three groups : hypoxic boosted, hypoxic nonboosted and nonhypoxic groups

[a] For comparisons between hypoxic (both boosted and nonboosted) and nonhypoxic groups

In the ^{18}F-FMISO uptake assessment, Cohen's kappa for agreement between investigator and expert was 0.88, considered a strong level of agreement [15]. Of the 34 patients, 24 (70.6%) were eligible to receive an increased total radiotherapy dose (86 Gy in five patients, 80 Gy in two patients, 76 Gy in nine patients, 74 Gy in four patients, 72 Gy in two patients, and 70 Gy in two patients). In the other 10 patients (29.4%), the dose was limited to 66 Gy because of organ-at-risk constraints. The 20 ^{18}F-FMISO-negative patients exclusively received 66 Gy (standard treatment). The baseline characteristics of the 54 included patients are presented in Table 1.

There were significant differences in tumour size ($p < 0.001$) and ^{18}F-FMISO SUV_{max} ($p < 0.001$) between the three groups (Table 1). ^{18}F-FDG SUV_{max} also showed a slight but not significant difference ($p = 0.054$). A significant difference in tumour size between hypoxic and nonhypoxic tumours was also seen on CT (RECIST 1.1; 57.62 mm vs. 29.85 mm, $p < 0.001$). A difference in tumour size of the hypoxic tumours was seen between the boosted and nonboosted patients (61.17 mm and 49.10 mm, respectively), but this was not significant ($p = 0.30$).

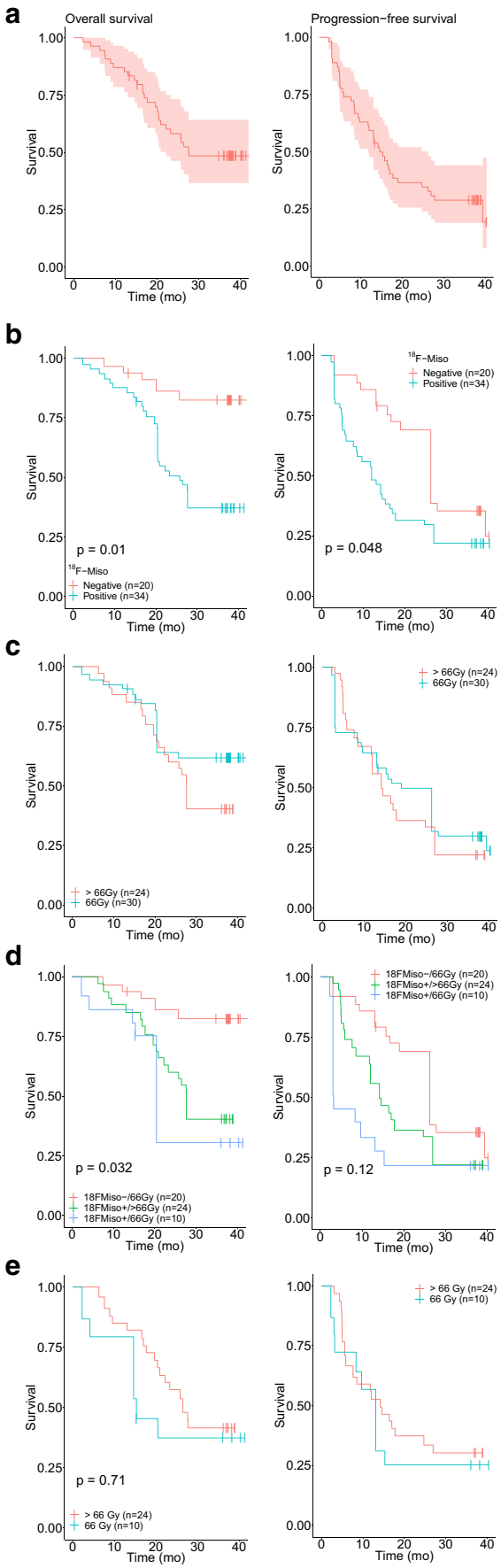
Survival analysis

Survival curves are presented in Fig. 2. The OS rates at 1, 2 and 3 years after radiotherapy in the entire sample were 87%, 58.2% and 48.5%, respectively (median OS 27.7 months), and the PFS rates were 59.3%, 36.4% and 28.8%, respectively (median PFS 14.5 months; Fig. 2a).

Survival analysis based on adjusted samples

To compare survival distributions according to ^{18}F-FMISO uptake and radiotherapy dose, an adjusted sample was created using the inverse probability of treatment weighting (IPTW) method to reduce selection bias between the arms. Propensity scores were computed using tumour size, age, stage and histology as confounding variables. The IPTW method resulted in adjusted samples whose characteristics were well balanced between those with and without a hypoxic tumour. Survival curves are shown in Fig. 2. Regarding ^{18}F-FMISO uptake, OS was significantly different between ^{18}F-FMISO-positive and ^{18}F-FMISO-negative patients, with a median OS of 25.8 months in positive patients and median not reached in negative patients ($p = 0.01$; Fig. 2b). A slight difference was observed for PFS, with a median PFS of 12 months in positive patients and 26.2 months in negative patients ($p = 0.048$; Fig. 2b).

Fig. 2 Kaplan-Meier curves for OS and PFS. **a** For the entire sample (the shaded areas represent the 95% confidence intervals). **b** In relation to ^{18}F-FMISO status on PET/CT. **c** In relation to the administered radiation dose. **d** In relation to ^{18}F-FMISO status on PET/CT and the administered radiation dose. **e** In relation to the administered radiation dose in the ^{18}F-FMISO PET/CT subgroup



Analysis of survival distributions according to the received dose led to crossing survival curves, showing that the hypothesis of the proportional hazards required for the Cox model and log-rank test was not satisfied. However, OS and PFS did not seem to vary according to dose. The OS rates at 1, 2 and 3 years after radiotherapy were 88.3%, 60.0% and 40.3%, respectively, in patients who received the radiotherapy boost and 92.3%, 64.0% and 61.7% in those who received the standard dose of 66 Gy (Fig. 2c). The PFS rates at 1, 2 and 3 years after radiotherapy were 55.7%, 36.3% and 22.0%, respectively, in patients who received the radiotherapy boost and 64.4%, 49.7% and 29.9%, respectively, in those who received the standard dose (Fig. 2c).

Combining ^{18}F-FMISO uptake and radiotherapy dose, OS remained higher in ^{18}F-FMISO-negative patients ($p = 0.032$; Fig. 2d). Conversely, PFS became not significantly different between the groups ($p = 0.12$), most likely because of a potential difference in survival in relation to dose in ^{18}F-FMISO-positive patients (Fig. 2d). To go further, we performed a second adjusted survival analysis using the IPTW method focused on this subgroup.

Survival analysis in the ^{18}F-FMISO-positive subgroup As shown in Table 1, tumour size differed according to ^{18}F-FMISO uptake but also according to the dose of radiotherapy received. Moreover, patients with organ-at-risk constraints did not receive a radiotherapy boost. In the same manner as its use for balancing the ^{18}F-FMISO-positive and ^{18}F-FMISO-negative patient groups, we also applied the IPTW method to the subgroup of ^{18}F-FMISO-positive patients to balance the characteristics between those receiving 66 Gy and those receiving a radiotherapy boost. The survival curves (Fig. 2e) still did not show any significant differences between those receiving the different doses ($p = 0.71$ for OS, and not applicable for PFS because of nonproportional hazards). The median survival times may nevertheless indicate a potential benefit of the boost on OS, with median survivals of 26.5 months in patients receiving the radiotherapy boost and 15.3 months in those not receiving the boost (Fig. 2e). The OS rates at 1, 2 and 3 years after radiotherapy were 85.0%, 57.4% and 41.4%, respectively, in patients who received the radiotherapy boost and 79.3%, 37.3% and 37.3%, respectively, in those who received the standard dose (Fig. 2e). The PFS rates at 1, 2 and 3 years after radiotherapy were 52.7%, 37.3% and 30.2%, respectively, in patients who received the radiotherapy boost and 56.8%, 25.2% and 25.2%, respectively, in those who received the standard dose (Fig. 2e).

Toxicity

Acute toxicities have been discussed previously [7]. and late toxicities are listed in Table 2. No grade 4 or 5 late radiotherapy-related adverse events or late cardiac toxicities were reported in the entire sample at 1, 2 or 3 years.

Table 2 Late toxicities in the 54 included patients at 1, 2 and 3 years. No grade 4 or 5 toxicities were observed

Late adverse event	Hypoxia ($n = 34$)												No hypoxia ($n = 20$)					
	Boost ($n = 24$)						66 Gy ($n = 10$)						66 Gy					
	1 year		2 years		3 years		1 year		2 years		3 years		1 year		2 years		3 years	
	Grade ½	Grade 3	Grade ½	Grade 3	Grade ½	Grade 3	Grade ½	Grade 3	Grade ½	Grade 3	Grade ½	Grade 3	Grade ½	Grade 3	Grade ½	Grade 3	Grade ½	Grade 3
Asthenia	2				1				1				2		1			
Pain	1		3				1	1							2		3	
Dyspnoea	6				2		4		2		2		5		1		3	
Radiation pneumonitis	3	2							1		1		1					
Cough	2		1				5		1				1		1		2	
Expectoration	1								1				1					
Myocardial infarction										1								
Laryngitis	1														1			
Dysphagia	2		1		1								1					
Vomiting	1																	
Constipation	1																	
Neuropathy	2											1	1		1			
Infection			1				1				1		1				1	
Dermatitis			1										1					
Other	1		2						2						1		1	

Discussion

The purpose of this work was to update the survival analysis and toxicity at 3 years after an increased total radiotherapy dose to hypoxic tumours in NSCLC patients treated with curative-intent chemoradiotherapy. To our knowledge, this is the largest series of patients with NSCLC receiving a radiotherapy boost to hypoxic tumours identified by ^{18}F-FMISO PET/CT in the context of a multicentre and prospective study. Hypoxia was identified in 34 of 54 patients (15 centres) and higher radiotherapy doses (70 to 86 Gy) could be delivered without excessive early toxicity [7] and without significant late toxicity in 24 patients with hypoxic areas. Although not significant, a difference in median survival times between those with and without a radiotherapy boost may nevertheless indicate a potential benefit of the boost on OS, with a median OS of 26.5 months in patients receiving a radiotherapy boost of >66 Gy versus 15.3 months in those without a boost (11.2 months OS benefit).

Our results confirmed the difference previously shown in OS and PFS between ^{18}F-FMISO-positive and ^{18}F-FMISO-negative patients ($p = 0.01$ and $p = 0.048$, respectively; Fig. 2) [16]. This strengthens the hypothesis that treatment might need to be selected according to the ^{18}F-FMISO profile. However, there was no difference in either OS or PFS between those receiving the radiotherapy boost and those receiving the standard dose (Fig. 2), probably because the standard-dose radiotherapy group included both patients with hypoxic and patients with nonhypoxic profiles, while the increased-dose radiotherapy group included only patients with a hypoxic profile.

The previous study demonstrated a response rate of ≥40% with acceptable early toxicity [7]. The measurement of ^{18}F-FMISO and the definition of BTV_h have been previously validated [9]. ^{18}F-FMISO uptake in NSCLC patients is strongly associated with a poor prognosis that cannot be reversed by radiotherapy doses up to 86 Gy. Since there was no significant gain in survival in patients who received a radiotherapy boost, this trial was considered negative. However, this trial was not a randomized phase III trial. The radiotherapy boost might have had an important effect on hypoxic tumours, but we were not able to assess the effect of the boost because of the small sample size. Nevertheless, the study was designed as a phase II clinical trial, and it met to its objectives. Because patients were selected on the basis of the presence of hypoxia identified by ^{18}F-FMISO uptake, we selected patients who received a radiotherapy boost and who had a tumour volume twice as large as patients without hypoxia. In this study, there was an important difference in tumour size (measured on CT scan) between the two populations: 61.17 mm in hypoxic tumours (that received a radiotherapy boost) and 29.85 mm in nonhypoxic tumours ($p < 0.001$).

Regarding ^{18}F-FMISO uptake, OS was found to be significantly different between ^{18}F-FMISO-positive and ^{18}F-FMISO-negative patients (median OS 25.8 months and not reached, respectively; $p = 0.01$). A slight difference was observed for PFS (median PFS 12 months and 26.2 months, respectively; $p = 0.048$). We thus applied the IPTW method to the subgroup of ^{18}F-FMISO-positive patients to balance characteristics between those receiving 66 Gy and those receiving a radiotherapy boost. Using this method, we took into consideration tumour size as a confounding variable in the construction of a propensity score, which has been shown to be a better predictor of survival than the TNM classification in NSCLC [17]. Survival curves (Fig. 2e) still did not show any significant difference in survival between patients receiving and not receiving the radiotherapy boost, with $p = 0.71$ for OS. However, a difference in median survival times may nevertheless indicate a potential benefit of the boost on OS, with an increase in median survival time of 11.2 months in patients who received the radiotherapy boost. This statistical method allowed the use of age, tumour size, stage and histology as confounding variables to rule out possible bias related to differences in hypoxic tumour profile.

Radiobiological and clinical data suggest that total doses greater than 80 Gy are required to achieve tumour control in NSCLC [18]. The RTOG 0617 randomized trial showed reduced OS in patients receiving 74 Gy (versus 60 Gy) to a target volume (median 90 cm^3) defined on ^{18}F-FDG PET/CT [5]. Phase I/II studies have shown that doses in excess of 80 Gy can be delivered only to small tumours [19, 20]. Our BTVs delineated on ^{18}F-FMISO PET/CT were approximately 40% smaller than those delineated on ^{18}F-FDG PET/CT. Our results indicate that ^{18}F-FMISO uptake is associated with a worse outcome, regardless of the total radiotherapy dose. Increased ^{18}F-FMISO uptake was correlated with other features associated with a poor prognosis (larger tumour size, higher ^{18}F-FDG SUV_{max}), and hypoxia might not be the sole reason for treatment failure.

The absence of ^{18}F-FMISO uptake identified a group of tumours associated with a better prognosis. Our OS and PFS at 1 year compare favourably with those found in the RTOG 0617 trial (OS 80%, range 74–85%; PFS 49%, range 42–56%) in patients treated with 60 Gy [5]. Similar approaches are being assessed in clinical trials, such as increasing total dose to smaller subvolumes considered at higher risk of failure (high ^{18}F-FDG uptake subvolumes on preradiotherapy ^{18}F-FDG PET/CT, PET boost NCT01024829) or evaluating the residual tumour at midtreatment by ^{18}F-FDG PET/CT (RTOG-110, NCT01507428; RTEP-7, NCT02473133). For the latter, Kong et al. confirmed the possibility of increasing the radiotherapy dose with survival rates similar to those in our study (25 months) [21]. In this study, the tumours received an accelerated dose, while in the RTEP5 trial, the dose remained at 2 Gy with an increase in the duration of treatment. An accelerated approach is surely preferable, as we proposed in our last study (RTEP-7, NCT02473133).

Conclusion

This prospective phase II study demonstrates the feasibility of delivering higher radiotherapy doses to small target volumes based on the ^{18}F-FMISO uptake, without exceeding the tolerance to normal organs and with no significant toxicity in patients with NSCLC. With a 3-year follow-up, boost radiotherapy seemed to improve OS by 11.2 months in patients with a hypoxic tumour, but the difference was not statistically significant ($p = 0.71$), probably because of the small sample size. A future phase III clinical trial devoted to hypoxic tumours will determine the efficacy of boost radiotherapy.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol and the consent form were approved by the Ethics Committee Nord-Ouest 1. The study was registered in the Clinical Trials Protocol Registration System (NCT01576796; RTEP5 study). The clinical, biological, imaging and toxicity data were monitored by a certified clinical research unit.

Informed consent Informed consent was obtained from all individual participants included in the study.

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