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Prognostic Value of FDG PET Metabolic Parameters Before and After 42 Gy of Radiochemotherapy in Patients with Inoperable Stage III Nonsmall Cell Lung Cancer

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The purpose of this study was to assess the prognostic value of ^{18}F-FDG PET parameter variation between baseline and 42 Gy (PET2) of radiochemotherapy at 6 mo and 1 y of evaluation in patients with stage III inoperable nonsmall cell lung cancer based on RECIST 1.1. **Methods:** In total, 158 patients in a prospective multicenter phase II/III study were analyzed. Patients were randomized into 2 groups: an experimental arm (group A) and a standard arm (group B). Patients from group A with residual metabolism on PET2 (group A+) at 42 Gy received a radiation boost (74 Gy). Patients without residual uptake on ^{18}F-FDG PET at 42 Gy (group A−) and patients in group B received a standard radiotherapy dose (66 Gy). We compared group A with group B. The ^{18}F-FDG PET parameters SUV_{max}, SUV_{mean}, SUV_{peak}, peak SUV normalized on lean body mass, mean SUV normalized on lean body mass, total lesion glycolysis, total metabolic tumor volume (MTV) (tumor and nodes), and tumor MTV were measured. All patients were evaluated with RECIST 1.1 using CT at 6 mo and 1 y after radiochemotherapy. Progression-free survival and overall survival were evaluated. **Results:** Except for the radiotherapy dose ($P < 0.001$), patient demographic characteristics were similar between the 2 groups (A vs. B). All ^{18}F-FDG PET uptake and volume parameter measurements were correlated. Therefore, only the change in SUV_{max} (ΔSUV_{max}) and total MTV were selected for the analysis. There was no significant difference in any variable between the 2 groups. In the multivariate analysis, ΔSUV_{max} appeared to be the most important prognostic factor for overall survival, and SUV_{max} of PET2 appeared to be the most important prognostic factor for progression-free survival. **Conclusion:** ^{18}F-FDG PET at 42 Gy can be used to identify good responders to radiochemotherapy in patients with inoperable stage III nonsmall cell lung cancer. The SUV_{max} of PET2 and ΔSUV_{max} are independent prognostic factors.

Key Words: ^{18}F-FDG PET; nonsmall cell lung cancer; radiochemotherapy

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Concurrent radiochemotherapy is the standard of care before consolidative durvalumab for patients with inoperable stage III nonsmall cell lung cancer (NSCLC). In parallel, the use of molecular imaging (PET) combined with technical improvements in radiotherapy delivery has resulted in major changes in the definition of

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target volumes in recent decades (*1*). PET with ^{18}F-FDG has become the reference examination for staging lung cancers and also for defining target volumes. It has been shown that irradiated volumes, particularly in the mediastinal area, can be defined by PET (*2*).

Numerous studies have demonstrated the value of ^{18}F-FDG PET in the management of patients with locally advanced inoperable stage IIA/III NSCLC before (*3*), during (*4–7*), and after treatment (*7–11*). Several studies have shown that ^{18}F-FDG PET can be performed during radiochemotherapy without artifacts (*12*). The prospective multicenter RTEP2 study (*4*) showed the prognostic value of ^{18}F-FDG PET at a radiotherapy dose of 42 Gy with a specificity of 92% for predicting tumor progression 1 y after radiochemotherapy in patients with residual tumor uptake.

Therefore, a prospective randomized multicenter phase II/III study was developed to increase the dose of radiotherapy in patients with NSCLC receiving radiochemotherapy and showing residual uptake at 42 Gy of radiochemotherapy.

In this article, we present data evaluating the prognostic value of metabolic parameters measured by ^{18}F-FDG PET before and after 42 Gy of radiochemotherapy in a cohort of 158 patients and focused on ^{18}F-FDG PET performed at baseline and during radiochemotherapy (*13*). The present article focuses on the comprehensive analysis of all ^{18}F-FDG PET parameters, the comparison of ^{18}F-FDG PET analysis methods, and the prognostic value of ^{18}F-FDG PET parameters on overall survival (OS).

MATERIALS AND METHODS

The RTEP7/IFCT-1402 study was designed as a multicenter randomized phase II/III trial conducted at 19 sites in France (NCT02473133). The trial protocol was approved by French health authorities (Agence Nationale de Sécurité du Médicament) and by the ethics committee.

Patients were included if they met the following criteria (*1*): had histologic evidence of invasive NSCLC (*2*), had significant ^{18}F-FDG uptake (i.e., higher than twice the background level) in either the primary tumor or mediastinal lymph nodes at the time of inclusion (*3*), had evaluable tumor or node lesions according to RECIST 1.1 (*4*), were candidates for curative-intent radiochemotherapy (*5*), were older than 18 y of age, and (*6*) provided informed written consent. The main exclusion criteria were (*1*) histology other than primary NSCLC (*2*), uncontrolled diabetes (glycemia level $\geq$ 10 mmol).

The study design is shown in Figure 1. Patients were stratified according to the type of radiation method used, namely, intensity-modulated radiation therapy arm or 3-dimensional radiotherapy.

Procedures

Chemotherapy protocols are in the supplemental materials (available at http://jnm.snmjournals.org).

Arm A. Patients in the experimental arm received an individualized radiotherapy prescription up to a total dose of 74 Gy over 6.6 wk in the case of a positive ^{18}F-FDG PET at 42 Gy (group A+). ^{18}F-FDG PET positivity was defined as tumor or node uptake greater than or equal to mediastinum uptake. An initial dose of 66 Gy was delivered on the initial volume defined by the CT scan and ^{18}F-FDG PET pretreatment, followed by an additional boost of up to 74 Gy based on ^{18}F-FDG PET per radiotherapy. For 3-dimensional radiotherapy, we applied a twice-daily fractionated radiotherapy dose of 2.0 Gy in the initial planning target volume plus a 1.0-Gy fraction at least 6 h later in the biologic target volume. For intensity-modulated radiation therapy, a simultaneous integrated boost was used. An example is given in Figure 2. The treatment duration was the same for all patients, with no major hypofractionation. Patients who did not receive an additional radiation boost were classified as group A−.

Arm B. Patients in the standard arm received a single prescription of 66 Gy in 33 fractions for 6.6 wk, with 2 Gy fractions given once daily, 5 d a week, without target volume reduction or adaptation, regardless of the ^{18}F-FDG PET at 42 Gy (group B).

In both arms, the total dose was prescribed so that the total mean lung dose was no more than 20 Gy. The volume of lung at or exceeding 20 Gy was less than 30%, the heart volume receiving 40 Gy should be less than 30%, and doses to other organs at risk (esophagus and spine) met the standard limits (*14*). As durvalumab became part of standard care for stage III inoperable NSCLC (*15*), an amendment was proposed thereafter stating that consolidation therapy could be given to all eligible patients with no disease progression after radiochemotherapy completion.

Quality Control Procedure and Dummy Run

Before inclusion in the trial, each investigating center performed a dummy run (PET image reconstruction, SUV control, ^{18}F-FDG PET pathologic uptake segmentation), image registration (^{18}F-FDG PET with planning CT), and radiotherapy (delineation and dosimetry) process control to ensure that the center was suitable for inclusion according to the protocol (description in supplemental materials). No additional dummy runs were performed later.

^{18}F-FDG PET/CT Acquisition and Analysis

PET1 was the ^{18}F-FDG PET/CT performed at baseline (before induction CT), and PET2 was the ^{18}F-FDG PET/CT at 42 Gy. PET3 at 6 mo after radiochemotherapy was not mandatory in the protocol. ^{18}F-FDG PET/CT acquisition is described in the supplemental materials. The ^{18}F-FDG PET images from the 19 centers were anonymized and transferred to an online storage system (OncoPlace version 4.8.9; Aquilab) and then extracted for analysis.

Three nuclear physicians performed ^{18}F-FDG PET image analyses at the Henri Becquerel Cancer Center (Rouen, France). For each patient, the same nuclear physician selected volumes of interest in the tumor and nodes on the baseline before radiochemotherapy ^{18}F-FDG PET images (PET1) and pasted them on the PET2 using PETVCARE software on the Advantage Window workstation (version 3.2;

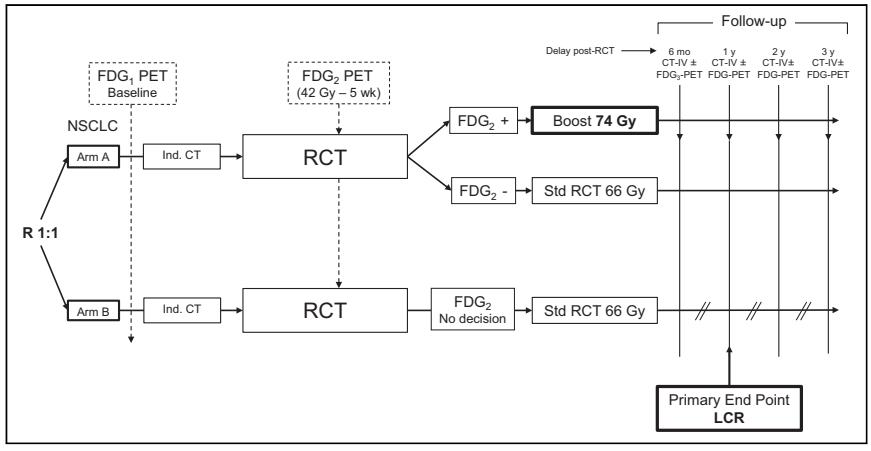

FIGURE 1. Study design. CT-IV = contrast-enhanced CT scan; Ind. CT = induction chemotherapy; LCR = locoregional recurrence; R = randomization; RCT = radiochemotherapy; Std = standard.

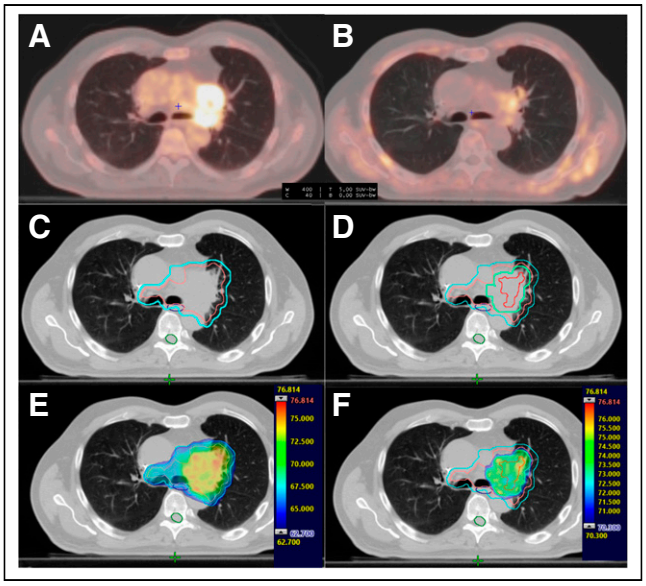

FIGURE 2. Example of radiotherapy planning based on FDG PET. (A) Initial planning PET/CT. (B) Planning PET/CT at 42 Gy. (C) Target volume: clinical target volume at 66 Gy with pink line and planning target volume at 66 Gy with light blue line and organs at risk. Esophagus with dark blue line and spinal cord with dark green. (D) Biologic target volume with red line and planning target volume at 74 Gy with light green line and same organs at risk as (C). (E) Initial dosimetry at 66 Gy with visible dose above 95% of prescribed dose (62.7 Gy) and same volumes as (C). (F) Dosimetry at 74 Gy with visible dose above 95% of prescribed dose (70.3 Gy) and same volumes as (D).

GE HealthCare). The volumes of interest were delineated with a threshold of SUV_{max} defined by the physician on the basis of an adaptive method for tumors (~40% SUV_{max}) and approximately 50%–60% of the SUV_{max} for nodes, as previously validated (*16*).

Several variables were analyzed: SUV_{max}, SUV_{mean}, SUV_{peak}, peak SUV normalized on lean body mass (SUL_{peak}), mean SUV normalized on lean body mass (SUL_{mean}), tumor metabolic tumor volume (MTV), total MTV (MTV including nodes), and total lesion glycolysis (TLG), which were calculated with the total MTV based on the SUV_{mean} or the SUL_{peak}.

When more than 1 volume of interest was delineated (tumor and nodes), the highest value was selected for the SUV_{max}, SUV_{peak}, and SUL_{peak}. The metabolism of the tumor or node is considered positive if it is greater than the metabolism of the mediastinum.

We analyzed the tumor response evaluated by the PETVCARE software module using the European Organization for Research and Treatment of Cancer (EORTC) (*17*) and PERCIST (*18*) and by visual analysis (VA) by physicians. All physicians who performed the analyses of ^{18}F-FDG PET responses were masked to the CT scan and clinical data follow-up.

Statistical Analysis

This open, double-arm, randomized phase II of a phase II/III study was designed to include 71 patients (+10%) in groups A and B. Statistical analysis was performed using SAS 9.4 software and R software, version 4.0.4. Between-group comparisons of continuous data were performed using independent sample *t* tests. Categoric data were compared using the Pearson χ^2 test or the Fisher exact test, as appropriate. Agreement between the 3 methods of response evaluation (EORTC, PERCIST, and VA) was assessed by Cohen κ. A 2-tailed *P* value of less than 0.05 was considered to indicate statistical significance. Pearson correlation tests were performed for ^{18}F-FDG PET functional parameters.

Survival times were defined as the number of months from the date of inclusion to the date of death (OS) or to the date of progression or death (progression-free survival [PFS]). We estimated univariate Cox regression models for survival outcomes (OS and PFS). A multivariate model was estimated with retained significant PFS variables in univariate models, and the same variables were used for the OS multivariate analysis.

RESULTS

Demographic Data

Demographic data are presented in Table 1, and the flowchart is shown in Figure 3. From November 2015 to July 2021, 158 patients with locally advanced stage III NSCLC were prospectively included, 81 in arm A and 77 in arm B. In Table 1, the only significant differences between the 2 groups were the dose of radiation therapy (74 [interquartile range, 8.0] in group A vs. 66 [interquartile range, 8.0] in group B; $P < 0.001$) as expected.

PET/CT Functional Parameters

No statistically significant difference was observed in the PET1 and PET2 parameters between groups A and B (Tables 2 and 3). There was no statistically significant difference between the A− and A+ groups (Supplemental Tables 1 and 2).

Correlations between ^{18}F-FDG PET functional parameters were tested. Particularly strong correlations (Pearson correlation coefficients > 0.85) emerged between SUV_{mean}, SUV_{peak}, SUV_{max}, and SUL_{peak}. Furthermore, the volumetric parameters of TLG (SUV and SUL) and MTV (total and tumoral) were strongly correlated (Pearson correlation coefficients ≥ 0.85). Therefore, only the SUV_{max} and total MTV were selected for further analysis. The change in SUV_{max} (ΔSUV_{max}) and the change in MTV were not significantly different between the 2 groups (Table 3).

^{18}F-FDG PET Response Evaluation

PET3 conducted at 6 mo after radiochemotherapy offers important early indications regarding the treatment response. The evaluation of the response between PET1 and PET3 involved 57 patients. The nuclear physicians performed 3 successive ^{18}F-FDG PET response evaluations between PET1 and PET3: (i) EORTC, (ii) PERCIST, and (iii) VA (Supplemental Table 3). The agreement between the EORTC and PERCIST was measured with Cohen κ at 0.95 (95% CI, 0.90–1.0), and that between the EORTC and VA was measured at 0.94 (95% CI, 0.87–1.0). The agreement between PERCIST and VA was 0.98 (95% CI, 0.95–1.0). For the VA, the readers were not hampered in their interpretation of tumor evolution by artifacts related to radiation pneumonitis.

Prognostic Factors: Survival

The PFS and OS curves for phase II of this phase II/III study are presented separately for each group in Figures 4 and 5. According to our exploratory analysis, the median OS was not reached (95% CI, 40.9 mo to not reached) in experimental arm A and was 43.3 mo (95% CI, 33.4 mo to not reached) in arm B; however, according to our exploratory analysis, the median PFS and OS were not significantly different between groups A and B.

Univariate and multivariate analyses were performed for different variables, namely, PFS (Table 4) and OS (Table 5). According to the univariate analysis of PFS, the durvalumab dose, ΔSUV_{max}, and SUV_{max} of PET2 were significantly associated with survival outcome. In the multivariate analysis, only durvalumab ($P = 0.008$) and SUV_{max} of PET2 ($P = 0.007$) remained significantly associated with improved PFS. Regarding OS, only ΔSUV_{max} was

TABLE 1
Patient Characteristics

Characteristic	Total patients (n = 158)	Group A (n = 81)	Group B (n = 77)
Sex			
Male	111 (70.3%)	60 (74.1%)	51 (66.2%)
Female	47 (29.7%)	21 (25.9%)	26 (33.8%)
Age (y)			
Mean ± SD	62.3 ± 8.5	62.5 ± 8.7	62.1 ± 8.4
Range	38.0–76.7	38.0–76.7	40.9–76.4
Smoking			
Yes	150 (94.9%)	76 (93.8%)	74 (96.1%)
No	8 (5.1%)	5 (6.2%)	3 (3.9%)
Performance status			
0	95 (60.1%)	49 (60.5%)	46 (59.7%)
1	63 (39.9%)	32 (39.5%)	31 (40.3%)
Histology			
Adenocarcinoma	83 (52.5%)	39 (48.1%)	44 (57.1%)
Epidermoid carcinoma	60 (38%)	32 (39.5%)	28 (36.4%)
Other	15 (9.5%)	10 (12.4%)	5 (6.5%)
Stage			
IIIA	85 (53.8%)	49 (60.5%)	36 (46.8%)
IIIB	73 (46.2%)	32 (39.5%)	41 (53.2%)
Certainty of N2/N3			
Not applicable	77 (49.4%)	44 (55.0%)	33 (43.4%)
By bronchoscopy	52 (33.3%)	25 (31.2%)	27 (35.5%)
By mediastinoscopy	27 (17.3%)	11 (13.8%)	16 (21.1%)
Missing	2	1	1
Induction CT type			
Paclitaxel–carboplatin	82 (52.2%)	46 (57.5%)	36 (46.8%)
Vinorelbine–cisplatin	71 (45.2%)	32 (40.0%)	39 (50.6%)
Other	4 (2.6%)	2 (2.5%)	2 (2.6%)
Not received	1	1	0
Radiochemotherapy type			
Paclitaxel–carboplatin	73 (51.8%)	37 (54.4%)	36 (49.3%)
Vinorelbine–cisplatin	56 (39.7%)	26 (38.2%)	30 (41.1%)
Other	12 (8.5%)	5 (7.4%)	7 (9.6%)
Missing	17	13	4
Radiochemotherapy cycles			
0	17 (10.7%)	13 (16.1%)	4 (5.2%)
1	5 (3.2%)	3 (3.7%)	2 (2.6%)
2	54 (34.2%)	24 (29.6%)	30 (39.0%)
3	82 (51.9%)	41 (50.6%)	41 (53.2%)
Radiotherapy method			
3D	27 (19.2%)	13 (19.1%)	14 (19.2%)
IMRT	114 (80.8%)	55 (80.9%)	59 (80.8%)
Radiotherapy dose*			
Median ± IQR	66.0 ± 8.0	74.0 ± 8.0	66.0 ± 0.0
Range	14–74.1	14–74.1	60–66
Durvalumab†			
Yes	76 (48.1%)	39 (48.1%)	37 (48.1%)
No	82 (51.9%)	42 (51.9%)	40 (51.9%)

*$P < 0.001$ (test student) for radiotherapy dose between group A and group B.

†10 mg/kg body weight intravenous every 2 wk for up to 12 mo.

CT = chemotherapy; 3D = 3-dimensional; IMRT = intensity-modulated radiation therapy; IQR = interquartile range.

significant in the univariate analysis, and it remained significant in the multivariate analysis ($P = 0.005$) with adjustment of durvalumab and SUV_{max} of PET2.

DISCUSSION

Our clinical trial (RTEP7/IFCT-1402) is a prospective multicenter study with extensive quality control of technical procedures regarding radiotherapy and ^{18}F-FDG PET. We demonstrated that durvalumab and the SUV_{max} of ^{18}F-FDG PET performed during radiochemotherapy at 42 Gy (PET2) are independent predictors of PFS and that the ΔSUV_{max} of ^{18}F-FDG PET performed between PET1 and PET2 is the only predictor of OS.

Between 2011 and 2024, the use of ^{18}F-FDG PET to manage radiotherapy or radiochemotherapy in patients with NSCLC was explored by 85 clinical trials or randomized controlled trials (only 12 prospective trials) with various numbers of patients (ranging from 10 to 598 patients).

Regarding radiation therapy, many radiation doses have been used (*6–8*,*11*,*19*), ranging from 45 to 86 Gy, but few have been used in prospective trials. In the RTOG 0617 trial (*20*), Bradley et al. showed that an increase in the radiotherapy dose up to 74 Gy planned before radiotherapy in a large field did not improve OS and might be potentially harmful, especially for patients with cardiac disease.

The 74-Gy boost seemed to have had a positive impact on PFS and OS (the median OS was not reached in experimental arm A and was 43.3 mo in arm B; P not significant). Therefore, these analyses need to be performed in a phase III study to determine whether there is a significant difference. The main objective of this phase II/III study was to test the possible toxicity of a radiation boost based on ^{18}F-FDG PET results. Our study did not show additional toxicity in patients in the 2 groups and suggests that a boost performed on a limited functional pathologic volume at mid treatment is not toxic (*13*).

However, in the prospective RTEP5 study, our group (*6*) did not observe any significant acute or late toxicity when a radiotherapy boost (up to 84 Gy) was delivered on a small target volume based on FMISO PET. In PET-Plan studies (*2*), the authors considered that ^{18}F-FDG PET–based planning with a potential dose increase up to 74 Gy could improve local control and did not appear to increase toxicity compared with the standard irradiation method. In agreement with the PET-Plan trial, large retrospective studies have shown that the use of ^{18}F-FDG PET in radiation planning has a positive effect on OS (*21*).

The PET-Boost study demonstrated that escalating the dose (≥72 Gy in 24 fractions) to either the whole primary pulmonary tumor or a known ^{18}F-FDG PET–defined subvolume within the primary tumor improved locoregional control at 1 y for both methods (*22*). It is important to bear in mind that this trial also presents a toxicity analysis (*23*) and signals unexpectedly high rates of grade 5 toxicity for radiotherapy boosts exceeding 72 Gy, whether administered to the entire tumor or to a specific subvolume, but unlike PET-Plan, RTEP5, or RTEP7, radiotherapy was severely hypofractionated. In a single-arm phase II cohort, the Radiation Therapy Oncology Group had also demonstrated that it was possible to perform adaptive radiotherapy using PET scans during radiotherapy (*5*).

Regarding ^{18}F-FDG PET functional parameters, we found large decreases in SUV_{max} and MTV during radiochemotherapy, as previously shown (*12*), but in a larger cohort. Many functional parameters have been studied in terms of their prognostic value. Some

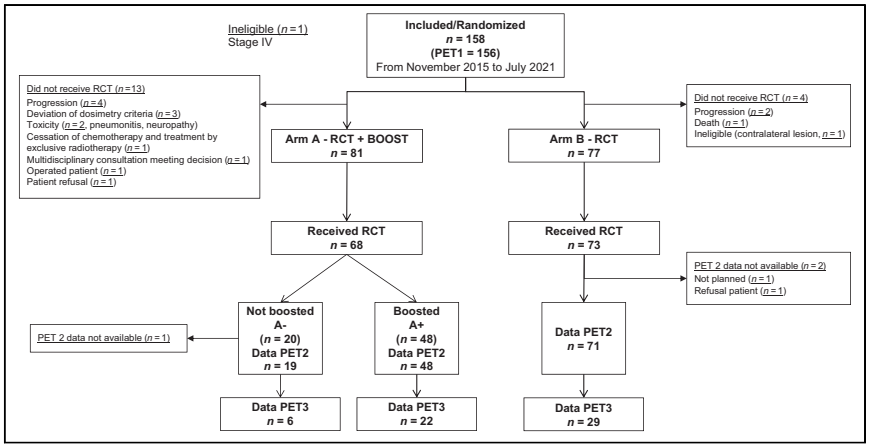

FIGURE 3. Flowchart. RCT = radiochemotherapy.

studies focused on TLG, such as that of Castello et al. (*24*), who showed that several metabolic parameters, including post-induction TLG, might differentiate responders from nonresponders after neoadjuvant chemotherapy in patients with stage III NSCLC. Katsui et al. (*25*) also suggested that the change in TLG calculated using PET/CT is a prognostic factor for patients with NSCLC treated via preoperative radiochemotherapy and surgery and may help physicians to determine treatment strategies. Vera et al. (*4*) and Ganem et al. (*16*) showed that TLG, the change in TLG, and the association of MTV and ΔSUV_{max} were more accurate

TABLE 2
PET1 Functional and Technical Parameters

Characteristic	Total patients (n = 156)	Group A (n = 80)	Group B (n = 76)	P
SUV_{max} (kBq/g)				
Mean ± SD	15.7 ± 7.9	16.17 ± 9.21	15.16 ± 6.26	0.42
Range	5.1–66.1	5.1–66.1	5.2–35.3	
SUV_{mean} (kBq/g)				
Mean ± SD	8.42 ± 3.24	8.41 ± 3.31	8.43 ± 3.19	0.97
Range	3.8–22.4	3.8–22.1	3.8–22.4	
SUV_{peak} (kBq/g)				
Mean ± SD	12.58 ± 6.53	12.93 ± 7.62	12.21 ± 5.18	0.49
Range	3.4–56.2	3.4–56.2	4.3–29.5	
SUL_{peak}				
Mean ± SD	9.67 ± 4.86	9.94 ± 5.47	9.39 ± 4.14	0.48
Range	2.7–36.1	2.7–36.1	3.3–24.2	
Tumor MTV (cm^3)				
Mean ± SD	43.6 ± 63.0	43.0 ± 56.8	44.2 ± 69.3	0.90
Range	0.0–338.0	0.0–306.0	0.0–338.0	
Total MTV (cm^3)				
Mean ± SD	56.2 ± 57.8	53.4 ± 46.9	57.3 ± 66.1	0.54
Range	0.4–338.0	0.4–215.0	0.9–338.0	
TLG SUV (g/mL × cm^3)				
Mean ± SD	501.2 ± 590.0	486.4 ± 546.0	528.1 ± 654.3	0.75
Range	1.7–3,252.0	1.7–2,270.0	5.0–3,252.0	
TLG SUL (g/mL × cm^3)				
Mean ± SD	388.4 ± 451.6	377.6 ± 416.3	409.8 ± 506.3	0.76
Range	1.4–2,360.0	1.4–1,930.0	4.0–2,360.0	
Glycemia level (mmol/L)				
Mean ± SD	5.92 ± 1.36	5.78 ± 1.40	6.05 ± 1.31	0.24
Range	4.0–15.1	4.0–15.1	4.4–12.1	
Injected activity (MBq)				
Mean ± SD	243 ± 73	243.6 ± 73.5	241.8 ± 73.8	0.88
Range	79.3–440.0	79.3–440.0	85.0–416.0	
MBq/kg				
Mean ± SD	3.37 ± 0.71	3.33 ± 0.75	3.42 ± 0.76	0.48
Range	1.0–5.9	1.0–5.2	1.7–5.9	

TABLE 3
PET2 Functional and Technical Parameters and Variation in Functional Parameters

Characteristic	Total patients (n = 138)	Group A (n = 67)	Group B (n = 71)	P
SUV_{max} (kBq/g)				
Mean ± SD	6.93 ± 4.35	6.96 ± 4.70	6.91 ± 4.03	0.94
Range	1.7–30.4	1.7–30.4	2.3–19.2	
SUV_{mean} (kBq/g)				
Mean ± SD	5.03 ± 1.96	4.99 ± 1.97	5.06 ± 1.96	0.85
Range	1.5–12.8	1.5–12.8	1.7–10.5	
SUV_{peak} (kBq/g)				
Mean ± SD	5.25 ± 3.21	5.33 ± 3.67	5.18 ± 2.73	0.78
Range	1.3–24.8	1.3–24.8	2.0–12.6	
SUL_{peak}				
Mean ± SD	4.07 ± 2.57	4.16 ± 2.93	3.98 ± 2.20	0.70
Range	0.6–20.4	1.1–20.4	0.6–9.9	
Tumor MTV (cm^3)				
Mean ± SD	5.96 ± 12.7	6.19 ± 13.9	5.73 ± 11.5	0.83
Range	0.0–90.5	0.0–90.5	0.0–56.2	
Total MTV (cm^3)				
Mean ± SD	10.3 ± 18.4	11.0 ± 21.9	9.7 ± 14.0	0.68
Range	0.0–159.0	0.0–159.0	0.0–56.2	
TLG SUV (g/mL × cm^3)				
Mean ± SD	59.8 ± 152.1	71.0 ± 200.4	49.0 ± 83.4	0.41
Range	0.0–1,510.0	0.0–1,510.0	0.0–517.0	
TLG SUL (g/mL × cm^3)				
Mean ± SD	42.8 ± 80.5	45.9 ± 94.6	39.8 ± 64.7	0.66
Range	0.0–582.0	0.0–582.0	0.0–382.0	
Glycemia level (mmol/L)				
Mean ± SD	6.03 ± 1.46	6.01 ± 1.40	6.06 ± 1.53	0.83
Range	3.9–13.6	4.1–13.6	3.9–13.6	
Injected activity (MBq)				
Mean ± SD	255.2 ± 70.9	258,3 ± 67.6	252.0 ± 74.2	0.61
Range	109.6–433.0	131.0–433.0	109.6–403.0	
MBq/kg				
Mean ± SD	3.52 ± 0.65	3.50 ± 0.62	3.53 ± 0.68	0.76
Range	1.9–5.1	2.0–5.1	1.9–5.1	
ΔSUV_{max}*				
Mean ± SD	−52.1 ± 27.8	−52.4 ± 24.2	−51.8 ± 31.0	0.91
Range	−88.9–135	−88.9–36.5	−85.6–135	
ΔMTV†				
Mean ± SD	−61.7 ± 138	−44.9 ± 190	−78.6 ± 40.2	0.18
Range	−100–1,170	−100–1,170	−100–178	

*ΔSUV_{max} = [(SUV_{max} PET2 − SUV_{max} PET1)/SUV_{max} PET1] × 100.
†ΔMTV = [(MTV PET2 − MTV PET1)/MTV PET1] × 100.

than clinical, pathologic, or pretherapeutic imaging data. The present study confirmed that the ΔSUV_{max} is an independent predictor of OS.

Moreover, in this work, 3 methods were evaluated for response to treatment (EORTC, PERCIST, and VA). We compared PET1 (n = 156) with PET3 (n = 57), as PET2 (n = 138) is not routinely performed in clinical practice. These 3 methods were not significantly different between groups A and B and gave similar results (Cohen $\kappa \geq 0.85$). We have shown that the EORTC, PERCIST, and VA results obtained by physicians are highly correlated. Accordingly, we conclude that the visual evaluation of ^{18}F-FDG PET by trained nuclear physicians is as effective as objective methods for detecting NSCLC changes.

We found only 1 study on the visual evaluation of treatment response on ^{18}F-FDG PET. Fledelius et al. (*26*) showed that PERCIST 1.0 was readily implementable and highly comparable to visual evaluation of response using early ^{18}F-FDG PET scanning for locally advanced NSCLC patients. Indeed, the present study revealed that the parameters ΔSUV_{max} and SUV_{max} of PET2 are significantly associated with OS and PFS, respectively. This could

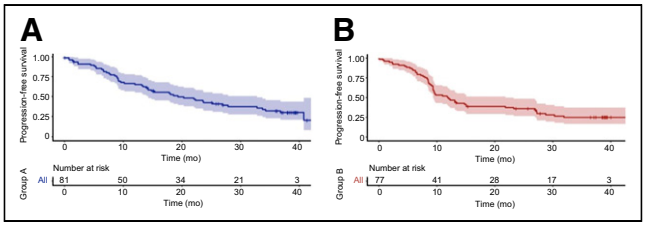

FIGURE 4. PFS for groups A and B.

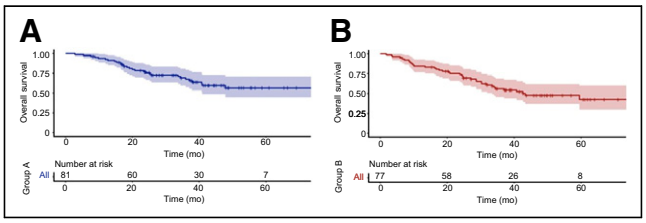

FIGURE 5. OS for groups A and B.

be explained by the fact that these patients are good responders to radiochemotherapy treatment. The use of ^{18}F-FDG PET scans during radiation therapy makes it possible to identify patients with the lowest chance of disease recurrence and death.

Our study is a prospective, randomized, multicenter, open-label, randomized, controlled phase II/III study. This study was designed to test the safety and feasibility of a boost based on ^{18}F-FDG PET but was not designed to show a difference in PFS or OS, and this new paradigm of increasing the dose on the basis of functional ^{18}F-FDG PET requires confirmation in phase III clinical trials.

CONCLUSION

In this new study, we confirm that it is possible to increase the radiotherapy dose in NSCLC using ^{18}F-FDG PET/CT data. Indeed, a 42-Gy ^{18}F-FDG PET scan performed during radiotherapy identified metabolic parameters that are prognostic for PFS according to the SUV_{max} of PET2 and OS according to the ΔSUV_{max}.

TABLE 4
Univariate and Multivariate Analyses of PFS

	Univariate analysis (n = 158)				Multivariate analysis (n = 138)		
Parameter	n	HR	95% CI	P	HR	95% CI	P
Radiotherapy method							
IMRT	116	1	—	0.20			
3D-CRT	27	0.70	0.41–1.21				
Age	158	1.00	0.985–1.031	0.51			
Sex							
Female	47	1	—	0.25			
Male	111	1.29	0.83–2.00				
Performance status							
0	95	1	—	0.53			
1	63	1.13	0.77–1.67				
Histology							
SCC	60	1	—	0.82			
Non-SCC	98	1.05	0.71–1.55				
Stage							
IIIA	84	1	—	0.065			
IIIB	72	1.44	0.98–2.11				
ΔSUV_{max}* (decrease of 10 units)	138	0.93	0.87–0.99	**0.048**	1.02	[0.93–1.12]	0.67
SUV_{max} PET2 (kBq/g)	138	1.08	1.03–1.13	**0.002**	1.09	[1.02–1.17]	**0.007**
SUV_{max} PET1 (kBq/g)	156	1.01	0.98–1.03	0.38			
$\Delta MTV^{\dagger}$ (decrease of 10 units)	138	0.99	0.97–1.01	0.42			
MTV PET1 (cm^3)	156	1.0	0.99–1.01	0.98			
MTV PET2 (cm^3)	138	1.01	0.99–1.03	0.23			
Treatment arms							
Group B	77	1	—	0.11			
Group A	81	0.82	0.56–1.20				
Durvalumab							
No	82	1	—	**0.0001**	1	—	**0.008**
Yes	76	0.50	0.34–0.74		0.57	0.38–0.86	

*ΔSUV_{max} = [(SUV_{max} PET2 − SUV_{max} PET1)/SUV_{max} PET1] × 100.
†ΔMTV = [(MTV PET2 − MTV PET1)/MTV PET1] × 100.
HR = hazard ratio; IMRT = intensity-modulated radiation therapy; 3D-CRT = 3-dimensional conformal radiation therapy; SCC = squamous cell carcinoma. Continuous data are ranges.

TABLE 5
Univariate and Multivariate Analysis of OS

Parameter	Univariate analysis (n = 158)				Multivariate analysis (n = 138)		
	n	HR	95% CI	P	HR	95% CI	P
Radiotherapy method							
IMRT	116	1	—				
3D-CRT	27	0.95	0.50–1.83				
Age	158	1.001	0.973–1.029	0.97			
Sex							
Female	47	1	—	0.72			
Male	111	1.29	0.83–2.00				
Performance status							
0	95	1	—	0.55			
1	63	1.16	0.71–1.90				
Histology							
SCC	60	1	—	0.52			
Non-SCC	98	0.85	0.52–1.39				
Stage							
IIIA	84	1	—	0.24			
IIIB	72	1.34	0.82–2.19				
ΔSUV_{max}* (decrease of 10 units)	138	0.91	0.84–0.99	**0.027**	0.86	0.77–0.96	**0.005**
SUV_{max} PET1 (kBq/g)	156	0.97	0.94–1.01	0.13			
SUV_{max} PET2 (kBq/g)	138	0.99	0.94–1.06	0.98	0.93	0.85–1.02	0.12
$\Delta MTV^{\dagger}$ (decrease of 10 units)	138	0.98	0.97–1.00	0.12			
MTV PET1 (cm^3)	156	1.0	0.99–1.01	0.58			
MTV PET2 (cm^3)	138	1.0	0.98–1.02	0.94			
Treatment arms							
Group A	77	1	—	0.26			
Group B	81	0.82	0.43–1.26				
Durvalumab							
No	82	1	—	0.08	0.79	0.46–1.35	0.39
Yes	76	0.64	0.39–1.06				

*ΔSUV_{max} = [(SUV_{max} PET2 − SUV_{max} PET1)/SUV_{max} PET1] × 100.
†ΔMTV = [(MTV PET2 − MTV PET1)/MTV PET1] × 100.
HR = hazard ratio; IMRT = intensity-modulated radiation therapy; 3D-CRT = 3-dimensional conformal radiation therapy; SCC = squamous cell carcinoma. Continuous data are ranges.

KEY POINTS

QUESTION: Is there prognostic value of using the ^{18}F-FDG PET parameter variation between baseline (PET1) and 42 Gy (PET2) of radiochemotherapy at 6 mo and 1 y of evaluation in patients with stage III inoperable NSCLC?

PERTINENT FINDINGS: This study confirms that it is possible to increase the radiotherapy dose in NSCLC using ^{18}F-FDG PET/CT data. Indeed, a 42-Gy ^{18}F-FDG PET scan performed during radiotherapy identified metabolic parameters that are prognostic for PFS according to the SUV_{max} of PET2 and OS according to the ΔSUV_{max}. PET is therefore an indispensable examination for considering adaptive radiotherapy or personalizing maintenance treatments (duration and type of immunotherapy or targeted therapies).

IMPLICATIONS FOR PATIENT CARE: Adaptative radiotherapy based on ^{18}F-FDG PET is feasible without toxicity, allowing a boost of radiotherapy in patients with stage III inoperable NSCLC.

DISCLOSURE

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