

# Areas of High $^{18}\text{F}$ -FDG Uptake on Preradiotherapy PET/CT Identify Preferential Sites of Local Relapse After Chemoradiotherapy for Non–Small Cell Lung Cancer

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The high rates of failure in the radiotherapy target volume suggest that patients with stage II or III non–small cell lung cancer (NSCLC) should receive an increased total dose of radiotherapy. Areas of high  $^{18}\text{F}$ -FDG uptake on preradiotherapy  $^{18}\text{F}$ -FDG PET/CT have been reported to identify intratumor subvolumes at high risk of relapse after radiotherapy. We wanted to confirm these observations on a cohort of patients included in 3 sequential prospective studies. Our aim was to assess an appropriate threshold (percentage of maximum standardized uptake value [ $\text{SUV}_{\text{max}}$ ]) to delineate subvolumes on staging  $^{18}\text{F}$ -FDG PET/CT scans assuming that a smaller target volume would facilitate isotoxic radiotherapy dose escalation. **Methods:** Thirty-nine patients with inoperable stage II or III NSCLC, treated with chemoradiation or with radiotherapy alone, were extracted from 3 prospective studies (ClinicalTrials.gov identifiers NCT01261585, NCT01261598, and RECF0645). All patients underwent  $^{18}\text{F}$ -FDG PET/CT at initial staging, before radiotherapy, during radiotherapy, and during systematic follow-up in a single institution. All  $^{18}\text{F}$ -FDG PET/CT acquisitions were coregistered on the initial scan. Various subvolumes in the initial acquisition (30%, 40%, 50%, 60%, 70%, 80%, and 90%  $\text{SUV}_{\text{max}}$  thresholds) and in the 3 subsequent acquisitions (40% and 90%  $\text{SUV}_{\text{max}}$  thresholds) were pasted on the initial scan and compared. **Results:** Seventeen patients had a local relapse. The  $\text{SUV}_{\text{max}}$  measured during radiotherapy was significantly higher in locally relapsed tumors than in locally controlled tumors (mean, 6.8 vs. 4.6;  $P = 0.02$ ). The subvolumes delineated on initial PET/CT scans with 70%–90%  $\text{SUV}_{\text{max}}$  thresholds were in good agreement with the recurrent volume at a 40%  $\text{SUV}_{\text{max}}$  threshold (common volume/baseline volume, 0.60–0.80). The subvolumes delineated on initial PET/CT scans with 30%–60%  $\text{SUV}_{\text{max}}$  thresholds were in good to excellent agreement with the core volume of the relapse (90%  $\text{SUV}_{\text{max}}$  threshold) (common volume/recurrent volume and overlap fraction indices, 0.60–0.93). The agreement was moderate ( $>0.51$ ) when a 70%  $\text{SUV}_{\text{max}}$  threshold was used to delineate on initial PET/CT scans. **Conclusion:** High  $^{18}\text{F}$ -FDG uptake areas on pretreatment PET/CT scans identify tumor subvolumes at greater risk of relapse in patients with NSCLC treated by concomitant chemoradiation. We propose a 70%  $\text{SUV}_{\text{max}}$  threshold to delineate areas of high  $^{18}\text{F}$ -FDG uptake on initial PET/CT scans as the target volumes for potential radiotherapy dose escalation.

**Key Words:**  $^{18}\text{F}$ -FDG PET/CT; lung cancer; radiotherapy; target volume;  $^{18}\text{F}$ -FDG uptake; local relapse

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**T**he survival probability of patients with stage II or III non–small cell lung cancer (NSCLC) remains low after curative-intent chemoradiotherapy (1,2). Many relapses occur within the radiotherapy target volume, thereby suggesting an insufficient total dose of radiotherapy (3–5). Therefore, reduction of the target volume is expected to allow isotoxic dose escalation (6). Such an approach would benefit from recent improvements in stereotactic body radiotherapy with imaging-guided radiotherapy and intensity-modulated radiotherapy to improve the precision of radiotherapy delivery (6,7). A possible way to achieve this goal would be to take advantage of intratumor heterogeneity by specific targeting of treatment-resistant tumor subvolumes. The tumor subvolumes with high  $^{18}\text{F}$ -FDG uptake (standardized uptake value [ $\text{SUV}$ ]  $> 50\%$  of the maximum  $\text{SUV}$  [ $\text{SUV}_{\text{max}}$ ]) on preradiotherapy PET/CT have been reported to identify intratumor subvolumes that have a high risk of relapse after radiotherapy (8–11). The delivery of higher radiotherapy doses to these reduced target volumes was investigated in a randomized phase II study and seemed feasible (12). Our group has conducted 3 prospective studies (13–15) addressing the feasibility and role of  $^{18}\text{F}$ -FDG PET/CT during curative-intent chemoradiotherapy in 67 NSCLC patients. We selected 39 patients with a complete set of  $^{18}\text{F}$ -FDG PET/CT data who were analyzed in our institution (CHB, Rouen). Our aim was to investigate whether a higher ( $>50\%$ )  $\text{SUV}_{\text{max}}$  threshold on initial  $^{18}\text{F}$ -FDG PET/CT scans would still define tumor subvolumes at high risk for relapse, assuming that a smaller volume would facilitate radiotherapy dose escalation.

## MATERIALS AND METHODS

### Patient Population

Data were extracted from 3 prospective studies (RTEP1, RTEP2, and RTEP4) registered on ClinicalTrials.gov (identifiers NCT01261585, NCT01261598, and RECF0645, respectively) and approved by the institutional review board for human studies (13–15). Sixty-seven patients

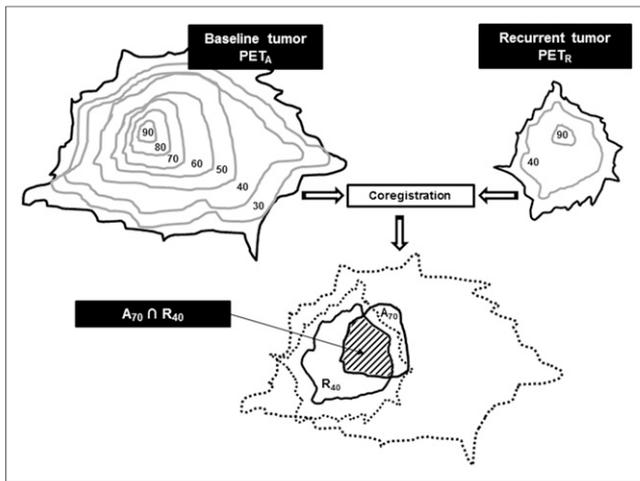
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**FIGURE 1.** Estimation of typical overlapping of  $A_{70}$  and  $R_{40}$  subvolumes after coregistration and reports. Numbers indicate  $SUV_{max}$  thresholds as percentages.

with inoperable stage II or III NSCLC had been treated with chemoradiotherapy or with radiotherapy alone. The included patients were those who underwent  $^{18}\text{F}$ -FDG PET/CT at initial staging, before radiotherapy, during radiotherapy (42 Gy), and during systematic follow-up (3 mo and 1 y) in a single center (CHB, Rouen). Thirty-nine patients with complete clinical and imaging data available were selected for the present study. All patients gave written informed consent before inclusion.

#### $^{18}\text{F}$ -FDG PET/CT Imaging

The  $^{18}\text{F}$ -FDG PET/CT data were acquired on a Biograph Sensation 16 Hi-Rez device (Siemens Medical Solutions). The patients were required to fast for at least 6 h before imaging to ensure that the serum glucose and endogenous serum insulin levels were low at the time of  $^{18}\text{F}$ -FDG administration. A 5 MBq/kg dose of  $^{18}\text{F}$ -FDG was injected after 20 min of rest. Sixty minutes later ( $\pm 10$  min), the acquisition began with noninjected CT in the cephalocaudal direction. The images were acquired with the patients' arms positioned over the head while they were breathing freely. The PET data were then acquired in the caudocephalad direction using a whole-body protocol (3 min per bed position). The acquisition time was adapted as a function of the injected activity (regarding the standard 5 MBq/kg) and the delay between the injection and acquisition (standardized to 60 min) to obtain a normalized counting rate for all patients. Six to 8 bed positions per patient were acquired, and the axial field of view for 1 bed position was 162 mm with a bed overlap of 25% (plane spacing, 2 mm). The PET images were reconstructed using Fourier rebinning and attenuation-weighted ordered-subset expectation maximization with clinical software. The images were corrected for random coincidences, scatter, and attenuation using the CT scan data. The  $^{18}\text{F}$ -FDG PET images were smoothed with a gaussian filter (full width at half maximum, 5 mm).

For each patient, the first  $^{18}\text{F}$ -FDG PET/CT scan ( $PET_A$ ) was obtained at initial staging, followed by a second  $^{18}\text{F}$ -FDG PET/CT scan before radiotherapy if induction chemotherapy was administered ( $PET_B$ ). A third  $^{18}\text{F}$ -FDG PET/CT scan ( $PET_C$ ) was obtained during the fifth week of radiotherapy, at an approximate dose of 40–45 Gy. A fourth  $^{18}\text{F}$ -FDG PET/CT scan was acquired during systematic follow-up (3 mo and 1 y) or if there was a suspected relapse ( $PET_R$ ).

#### $^{18}\text{F}$ -FDG PET/CT Analysis

The 156 PET/CT scans acquired for the 39 selected patients were analyzed in consensus by two senior physicians (a nuclear medicine

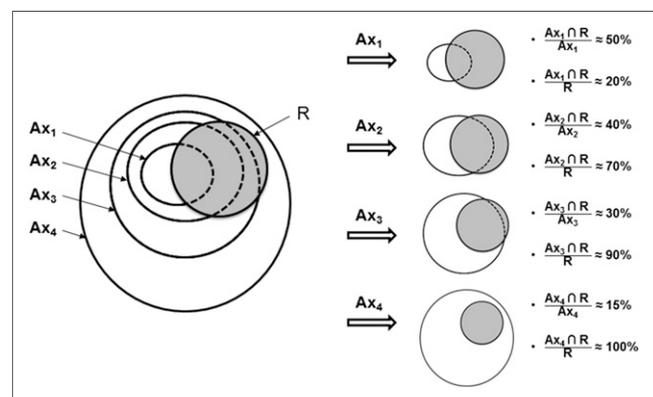
specialist and a radiation oncology specialist) in a single center (Henri Becquerel Center, Rouen) on a Planet Onco workstation (Planet Onco, version 2.0; DOSISoft).

The  $SUV_{max}$  and metabolic tumor volume data were collected. The metabolic tumor volume was defined with a threshold at 40% of tumor  $SUV_{max}$  since this value is widely used to delineate volumes with significant  $^{18}\text{F}$ -FDG uptake (16,17). For each patient, all PET/CT acquisitions were coregistered on the initial CT scan, focusing on the tumor, with a rigid registration method (block-matching rigid registration method (18)). The physicians were allowed to manually adjust the registration to avoid obvious misregistration (pleural effusion, pulmonary retraction, radiation-induced pneumonitis, tumor volume decrease, respiration motion, or change in patient position). The  $PET_A$  scan was systematically used as a reference. In total, 117 coregistrations were performed.

We defined 507 volumes of interest: 7 on  $PET_A$  and 2 each on  $PET_B$ ,  $PET_C$ , and  $PET_R$ . On  $PET_A$ , the baseline subvolumes were delineated using a relative threshold method (30%, 40%, 50%, 60%, 70%, 80%, and 90% of primary tumor  $SUV_{max}$ , with the corresponding volumes being referred to as  $A_{30}$ ,  $A_{40}$ ,  $A_{50}$ ,  $A_{60}$ ,  $A_{70}$ ,  $A_{80}$ , and  $A_{90}$ , respectively). On  $PET_B$ , 40% and 90% of  $SUV_{max}$  were used as thresholds to delineate the  $B_{40}$  and  $B_{90}$  subvolumes, respectively. The same process was applied to  $PET_C$  ( $C_{40}$  and  $C_{90}$ ) and  $PET_R$  ( $R_{40}$  and  $R_{90}$ ). Each subvolume of  $PET_A$  was then reported on  $PET_B$ ,  $PET_C$ , and  $PET_R$ , and each subvolume of  $PET_B$ ,  $PET_C$ , and  $PET_R$  was reported on  $PET_A$ , to quantify their respective overlaps as shown in Figure 1.

#### Overlap Quantification

Our objective was to find the highest threshold (as a percentage of  $SUV_{max}$ ) delineating the smallest subvolume on baseline PET yielding the highest overlap index compared with the relapse volume ( $PET_R$ ) and compared with the metabolically active residual-disease volumes during the therapeutic sequence ( $PET_B$  and  $PET_C$ ). We investigated all potential overlaps between the above-defined volumes of interest: baseline tumor ( $A_{30}$ – $A_{90}$ ) versus postinduction chemotherapy tumor subvolumes ( $B_{40}$  and  $B_{90}$ ), per-radiotherapy subvolumes ( $C_{40}$  and  $C_{90}$ ), and relapse subvolumes ( $R_{40}$  and  $R_{90}$ ). The following 5 indices were used: the Dice index ( $2 \times \frac{V_1 \cap V_2}{V_1 + V_2}$ ), the Jaccard index ( $\frac{V_1 \cap V_2}{V_1 \cup V_2}$ ), the overlap fraction ( $\frac{V_1 \cap V_2}{\min(V_1, V_2)}$ ), the common volume divided by the initial volume ( $\frac{V_1 \cap V_2}{V_1}$ ), and the common volume divided by the compared volume ( $\frac{V_1 \cap V_2}{V_2}$ ).



**FIGURE 2.** Study flow for scenario of  $PET_A$  and  $PET_R$  subvolume comparisons. Shown are indices of common volume ( $A \cap R$ ), with A referring to staging  $^{18}\text{F}$ -FDG PET/CT and R to  $^{18}\text{F}$ -FDG PET/CT at recurrence.

**TABLE 1**  
Patient Demographics and Characteristics

Characteristic	Details	Total	CR	LR	DR
Mean age (y)		58 (39–77)	59 (39–77)	58 (46–74)	59 (40–76)
Sex	Male	31 (79)	7 (64)	15 (88)	9 (81)
	Female	8 (21)	4 (36)	2 (12)	2 (18)
Histology	SCC	21 (54)	2 (18)	14 (82)	5 (45)
	ADC	10 (26)	5 (45)	1 (6)	4 (36)
	LCUC	8 (20)	4 (36)	2 (12)	2 (18)
TNM stage	Ila	3 (8)	1 (9)	11 (6)	1 (9)
	Ilb	2 (5)	1 (9)	1 (6)	0
	IIla	15 (38)	4 (36)	8 (47)	3 (27)
	IIlb	19 (49)	5 (45)	7 (41)	7 (64)
Location of tumor	RSL	19 (39)	5 (45)	6 (35)	8 (73)
	RML	3 (8)	1 (9)	2 (12)	0
	RIL	3 (8)	2 (18)	1 (6)	0
	LSL	11 (28)	3 (27)	6 (35)	2 (18)
	LIL	4 (10)	0	3 (18)	1 (9)
Induction chemotherapy	Yes	33 (85)	9 (81)	13 (76)	10 (91)
	No	6 (15)	2 (18)	4 (24)	1 (9)
Dose (Gy)	At PET <sub>C</sub>	44 (40–52)	45 (42–50)	45 (40–52)	43 (40–46)
	Total	67 (60–70)	66 (60–70)	67 (60–70)	68 (66–70)
Time of follow-up (mo)		30 (6–76)	46 (18–76)	22 (6–60)	27 (11–51)
RT duration (d)		48 (39–66)	47 (41–53)	48 (39–66)	48 (45–52)
SUV <sub>max</sub>	PET <sub>A</sub>	11.0 (3.7–22.1)	11.7 (5.5–18.1)	11.7 (3.7–22.1)	10.9 (5.1–16.6)
	PET <sub>B</sub>	8.4 (1.2–20.8)	7.5 (1.2–15.2)	9.1 (2.5–18.9)	8.4 (2.8–20.8)
	PET <sub>C</sub>	5.6 (0.8–13.1)	4 (0.8–5.9)	6.8 (2.3–11.9)	5.2 (1.1–3.15)
MTV (cm <sup>3</sup> )	PET <sub>A</sub> (A <sub>40</sub> )	54.0 (2.4–176.3)	44.8 (6.6–125.8)	63.8 (10.6–176.3)	47.0 (2.4–103.2)
	PET <sub>B</sub> (B <sub>40</sub> )	26.2 (1.7–86.6)	18.2 (0.7–31.2)	32.4 (9.2–86.6)	24.8 (1.5–73.4)
	PET <sub>C</sub> (C <sub>40</sub> )	30.9 (0.8–77.8)	28.6 (0.8–77.6)	34 (4.2–76.2)	5.2 (2.9–57.8)

SCC = squamous cell carcinoma; ADC = adenocarcinoma; LCUC = large cell undifferentiated carcinoma; RSL = right superior lobe; RML = right median lobe; RIL = right inferior lobe; LSL = left superior lobe; LIL = left inferior lobe; RT = radiotherapy; MTV = metabolic tumor volume.

Data in parentheses are percentages or ranges.

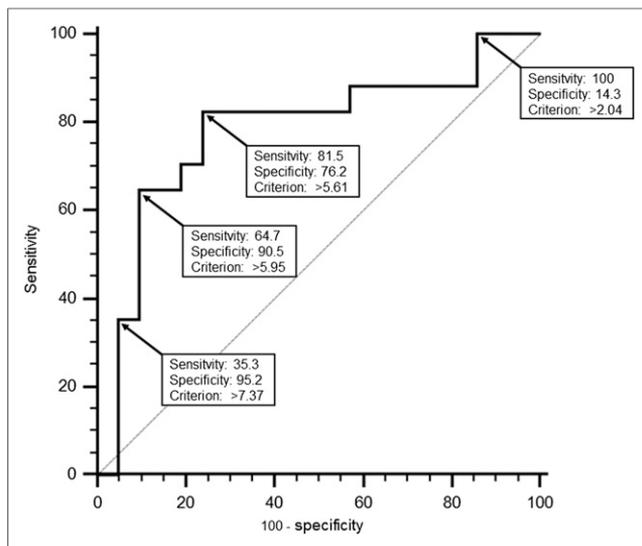
The Dice, Jaccard, and overlap fraction indices are widely used to compare delineated volumes obtained with different methods or by multiple investigators (19). Their values vary between 0 (if the volumes are completely disjointed) and 1 (if the volumes match perfectly in size,

shape, and location). They can be misleading when the sizes of the delineated volumes differ. The  $A_x \cap R_{40} / A_x$  was used to estimate the larger subvolume with high chances of containing the recurrent tumor volume ( $R_{40}$ ), aiming to limit the irradiation of areas with a low risk of recurrence.

**TABLE 2**  
Subvolumes Delineated with Various SUV<sub>max</sub> Thresholds

Stage	Volume 30 (cm <sup>3</sup> )	Volume 40 (cm <sup>3</sup> )	Volume 50 (cm <sup>3</sup> )	Volume 60 (cm <sup>3</sup> )	Volume 70 (cm <sup>3</sup> )	Volume 80 (cm <sup>3</sup> )	Volume 90 (cm <sup>3</sup> )	SUV <sub>max</sub>
A	76.2 (60.4)	53.7 (45.6)	37.0 (33.7)	22.6 (21.6)	11.8 (11.8)	4.5 (5.5)	0.92 (1.3)	11.4 (4.4)
B		26.2 (21.6)					0.45 (0.45)	8.4 (4.2)
C		30.9 (21.9)					0.44 (0.79)	5.6 (2.8)
R		60.0 (65.1)					0.50 (0.4)	6.0 (2.6)

Numeric indices refer to threshold for delineation. Data are mean followed by SD within parentheses.



**FIGURE 3.** Receiver-operating-characteristic curve analysis of  $SUV_{max}$  as predictor of LR.

The  $A_x \cap R_{90}/R_{90}$  index was used to estimate the smaller subvolume on  $PET_A$  containing the highest uptake area in the recurrent tumor ( $R_{90}$ ), to avoid omitting areas at high risk of recurrence from the target volume.

A schematic example of the interpretation of overlap indices is shown in Figure 2.

### Statistics

To classify the quality of overlap, we chose the criteria used for the Cohen  $\kappa$  test when assessing the agreement between investigators: 0–0.2, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, very good agreement (15).

The mean and SD were used for descriptive statistics. The association between  $^{18}F$ -FDG PET/CT and clinical parameters was tested using repeated-measures ANOVA and the  $\chi^2$  test. A  $P$  value of less than 0.05 was considered statistically significant (bilateral test). All analyses were performed using MedCalc Statistical Software, version 12.7.2 (MedCalc Software bvba).

## RESULTS

### Patient Characteristics

Of the 67 patients included in the RTEP studies, 39 (RTEP1, 9/10; RTEP2, 23/52; RTEP4, 4/5) were eligible for the present study (Table 1). The noneligible patients were those for whom the full set of sequential  $^{18}F$ -FDG PET/CT scans was not available (patients who were treated in another center or scans with technical problems).

The mean follow-up of the total studied population was  $30 \pm 19$  mo. Eleven patients remained in complete metabolic response (CR). Seventeen patients had a local relapse (LR) with or without nodal or metastatic disease. We considered metabolically persistent residual disease and local recurrence to be equal. Eleven patients had a distant dissemination (nodal or metastatic) without local residual disease (DR). Ipsilateral (outside the initial radiotherapy target volume) or contralateral lung recurrence was considered metastasis. Metastasis occurred in 16 patients.

A manual adjustment of the coregistered images was required in 10 patients. No significant differences were observed when the

overlap indices were compared with those obtained in 7 patients without manual adjustment. All patients were pooled for further analyses. The volume measurements in LR patients are summarized in Table 2. The mean initial tumor metabolic volume ( $A_{40}$ ) was  $54 \text{ cm}^3$  (range, 2.4–176  $\text{cm}^3$ ; SD, 46  $\text{cm}^3$ ), and the mean  $A_{70}$  subvolume was  $12 \text{ cm}^3$  (range, 0.6–51  $\text{cm}^3$ ; SD, 12  $\text{cm}^3$ ).

### Univariate Analysis

When LR ( $n = 17$ ), DR ( $n = 11$ ), and CR ( $n = 11$ ) patients were compared, there were no significant differences in age; sex; TNM stage; tumor location; induction chemotherapy; radiotherapy dose and duration; tumor metabolic volume at  $PET_A$ , at  $PET_B$ , and  $PET_C$  (threshold = 40%  $SUV_{max}$ ); or  $SUV_{max}$  at  $PET_A$  and  $PET_B$ . None of these parameters was significantly different in the 16 metastatic patients.

The frequency of LR was higher for squamous cell carcinoma (14/21, 66%) than for adenocarcinoma (1/10, 10%) or undifferentiated carcinoma (2/8, 25%) ( $P = 0.03$ ).

The  $SUV_{max}$  measured on  $PET_C$  was significantly higher in relapsing tumors than in locally controlled tumors (mean, 6.8 vs. 4.6;  $P = 0.02$ ). The area under the receiver-operating-characteristic curve was 0.78 (95% confidence interval, 0.62–0.90) (Fig. 3). An  $SUV_{max}$  of more than 5.6 (i.e., the mean of  $SUV_{max}$  observed in the locally relapsed and controlled groups) yielded a sensitivity of 82% (95% confidence interval, 57%–96%) and a specificity of 76% (95% confidence interval, 53%–92%) to predict LR.

### Overlap Comparisons

We obtained 6,650 indices corresponding to 1,330 potential overlaps of 507 volumes of interest on the 156 PET/CT scans. Overlap comparisons of  $PET_A$  subvolumes with  $PET_B$  and  $PET_C$  subvolumes were performed for all 39 included patients. Overlap comparisons between  $PET_A$  and  $PET_R$  subvolumes were performed only for the 17 LR patients. An example is shown in Figure 4. The mean overlap indices are reported in Figure 5 (Details are provided in Supplemental Fig. 1; supplemental materials are available at <http://jnm.snmjournals.org>).

### $A_x$ Versus $B_{40}$ , $C_{40}$ , and $R_{40}$ Comparisons

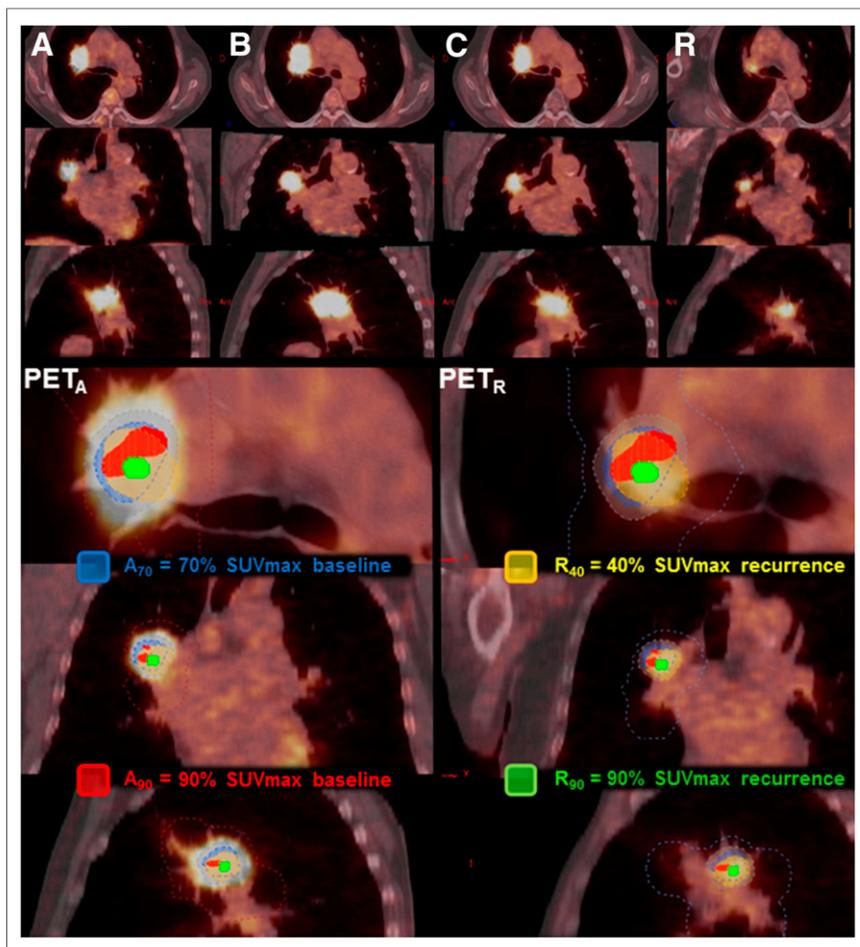
We first tried to identify an  $SUV_{max}$  threshold on  $PET_A$  scans that would consistently delineate a volume that included the areas with significant  $^{18}F$ -FDG uptake (40%  $SUV_{max}$ ) on subsequent PET scans (panels A, C, and E in Fig. 5).

The overlap fractions between the  $PET_A$  scans and the  $PET_B$ ,  $PET_C$ , and  $PET_R$  scans showed good agreement (between 0.60 and 0.80) for all initial  $SUV_{max}$  thresholds (except  $A_{80} \cap C_{40}$  and  $A_{90} \cap C_{40}$ , which were slightly below 0.60). The  $A_x \cap R_{40}/A_x$  indices between  $PET_A$  scans and  $PET_R$  scans at the time of recurrence showed good agreement (values between 0.60 and 0.80) for  $A_x$   $SUV_{max}$  thresholds between 70% and 90%. The  $A_x \cap R_{40}/R_{40}$  index was good only for the 30%  $SUV_{max}$  threshold. The Dice and Jaccard indices showed poor to moderate agreement. The low variations between panels A, C, and E indicate that the position of the subvolumes was similar during the therapeutic sequence.

### $A_x$ Versus $B_{90}$ , $C_{90}$ , and $R_{90}$ Comparisons

We then investigated whether the areas with high  $^{18}F$ -FDG uptake (with a 90%  $SUV_{max}$  threshold) on subsequent PET scans could be identified on the  $PET_A$  scans (panels B, D, and F in Fig. 5).

Good to excellent overlap fractions (0.60–0.93) were obtained for the volumes delineated on  $PET_A$  with  $SUV_{max}$  thresholds between 30% and 60%. Similarly, high values for the  $A_x \cap R_{90}/R_{90}$



**FIGURE 4.** Example of 74-y-old man with right superior lobe squamous cell carcinoma T3N0M0. Shown are staging PET<sub>A</sub> (A), PET<sub>B</sub> (B), PET<sub>C</sub> (C), and PET<sub>R</sub> (R). Numeric indices refer to threshold for delineation. A<sub>70</sub> and A<sub>90</sub> subvolumes were reported on PET<sub>R</sub>, and R<sub>40</sub> and R<sub>90</sub> subvolumes on PET<sub>A</sub>.  $A_{70} \cap R_{90} / R_{90}$  index was calculated at 0.69, meaning that two thirds of R<sub>40</sub> was included in A<sub>70</sub>.  $A_{70} \cap R_{90} / R_{90}$  index was calculated at 1.00, meaning that R<sub>90</sub> was totally included in A<sub>70</sub>.

index were obtained with the same thresholds on PET<sub>A</sub>. The 70% baseline SUV<sub>max</sub> threshold showed moderate agreement (overlap fractions and  $A_x \cap R_{90} / R_{90} > 0.51$ ) when compared with PET<sub>B</sub>, PET<sub>C</sub>, and PET<sub>R</sub>. The Dice, Jaccard, and  $A_x \cap R_{90} / A_x$  indices were very low (mostly  $< 0.10$ ) irrespective of the thresholds used on PET<sub>A</sub>. The low variations between panels B, D, and F indicate that the position of the subvolumes was similar during the therapeutic sequence.

## DISCUSSION

NSCLC is known to have high and heterogeneous <sup>18</sup>F-FDG uptake. A selective increase in radiotherapy dose to the most radioresistant areas within the tumor is tempting, as a way to improve local control rates without excessive toxicity. Along with others (8–11), we have shown in 39 patients (17 relapses) included in 3 prospective trials that intratumor subvolumes with high <sup>18</sup>F-FDG uptake (SUV  $> 70\%$  SUV<sub>max</sub>) can easily be delineated on staging PET scans to indicate areas at increased risk of relapse. This is of interest because the RTOG 0617 randomized trial (20) reported no benefit from an increased radiotherapy dose targeted

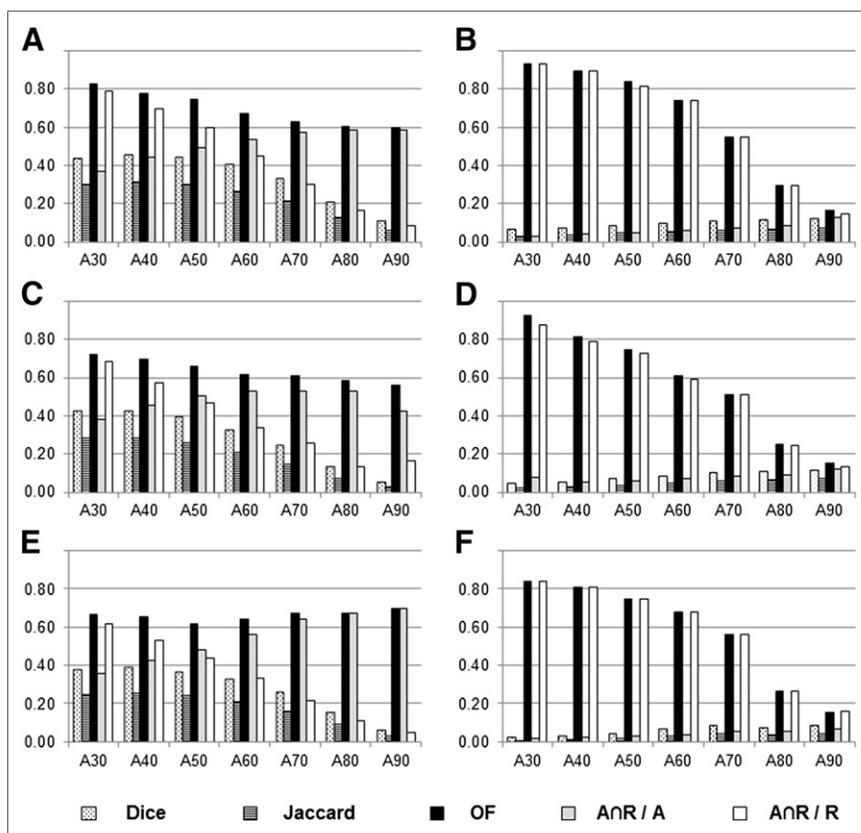
on initial tumor volume on PET scans (SUV  $> 40\%$  SUV<sub>max</sub>). An alternative approach could be to delineate smaller target volumes, based on <sup>18</sup>F-FDG uptake (e.g.,  $> 70\%$  SUV<sub>max</sub>), that could receive total doses much higher than the conventional range (60–74 Gy). Very high precision in radiotherapy delivery is therefore required to avoid excessive irradiation of the normal tissues surrounding the target volume (6,7, 21). In addition, doses larger than 2 Gy per fraction can be delivered to shorten the overall radiotherapy duration, counterbalancing tumor cell proliferation and increasing the probability of cure. A prospective feasibility study of stereotaxic body radiotherapy after conventional therapy, increasing the total dose to residual disease above 100 Gy, showed no increase in acute toxicity compared with what was expected after conventional chemoradiotherapy (21).

Table 3 is a comparison with previous works. Abramiyuk et al. (8) reported that the relapse volume defined with an automatic delineation method (ROVER; ABX Advanced Biochemical Compounds) was visually included in the initial volume defined with a 35% SUV<sub>max</sub> threshold. Aerts et al. (9,10) compared retrospectively and prospectively the overlap fractions of initial subvolumes defined with 34%, 40%, 50%, 60%, 70%, and 80% SUV<sub>max</sub> with relapse volumes defined with a fixed SUV threshold higher than 2.5% and 5%, aorta SUV, and relative threshold at 70%, 80%, and 90% SUV<sub>max</sub>. Aerts proposed the 50% SUV<sub>max</sub> threshold on initial PET scans as more suitable for the radiation-boosting target. More recently, Shusharina et al. (11), using a nonrigid coregistration method,

prospectively compared the overlap fractions of an initial subvolume defined with the 50% SUV<sub>max</sub> and a relapse subvolume defined with the 80% SUV<sub>max</sub> threshold and confirmed Aerts' results.

After Aerts' first study (22) comparing overlap fractions of subvolumes defined with 34%, 40%, 50%, 60%, 70%, and 80% SUV<sub>max</sub> at baseline (PET<sub>A</sub>), at the seventh day of radiotherapy (PET<sub>B</sub>), and at the 14th day of radiotherapy (PET<sub>C</sub>), our results confirmed that the topography of the high <sup>18</sup>F-FDG uptake subvolumes within the tumor remains stable during the course of radiotherapy, despite large variations in absolute volumes. On the basis of these results, we conclude that residual metabolically active and relapse areas within the tumor can be identified using initial <sup>18</sup>F-FDG PET/CT scans.

Our present work, by relying on 5 different overlap indices, constitutes an extensive investigation. The disappointing values of the Dice and Jaccard indices can be attributed to very different absolute volumes (a ratio of more than 10 between A<sub>70</sub> and R<sub>90</sub>): two volumes with a good superimposition but a large difference in size will yield low Dice and Jaccard indices. Given the low resolution of <sup>18</sup>F-FDG PET/CT images and the uncertainties in



**FIGURE 5.** Histogram of mean values of overlap indices for various  $SUV_{max}$  thresholds (numeric indices refer to threshold for delineation) to delineate subvolumes on PET<sub>A</sub> ( $A_x$ ), PET<sub>B</sub> (after induction chemotherapy,  $B_{40}$  and  $B_{90}$ , panels A and B), PET<sub>C</sub> ( $C_{40}$  and  $C_{90}$ , panels C and D), and PET<sub>R</sub> ( $R_{40}$  and  $R_{90}$ , panels E and F). Detailed data are presented in Supplemental Figure 1. OF = overlap fraction.

registration,  $A_{90}$  and  $R_{90}$  (same range of absolute volumes) were not likely to perfectly match.

We have investigated the ability of the  $A_x \cap R_{40}/A_x$  and  $A_x \cap R_{90}/R_{90}$  indices to better estimate the overlapping of potential target volumes for radiotherapy dose escalation with relapse volumes. We found that the baseline PET subvolume defined with the 70%  $SUV_{max}$  threshold is an acceptable choice for dose escalation to avoid missing the hot spot of recurrence (as shown by the  $A_x \cap R_{90}/R_{90}$  index) and limit the irradiation of areas at a low risk of relapse (as shown by the  $A_x \cap R_{40}/A_x$  index).

In our hands, these potential target volumes are 2–3 times smaller than those delineated by Aerts and Shusharina (mean, 12 cm<sup>3</sup>; range, 0.6–51 cm<sup>3</sup>; SD, 12 cm<sup>3</sup>) and would allow higher dose escalation with stereotactic body radiotherapy. In agreement with others (14,23), the  $SUV_{max}$  at baseline or on planning <sup>18</sup>F-FDG PET was not significantly different in CR, DR, and LR patients.

In accordance with Aerts and our previous study (9,14), we have confirmed the association between persistent <sup>18</sup>F-FDG uptake during radiotherapy and poor outcome. The  $SUV_{max}$  on PET<sub>C</sub> was significantly higher in locally relapsing patients than in patients with distant metastases or remission. We found that patients with an  $SUV_{max}$  of more than 5.6 or 5.9 during the fifth week of radiotherapy were at high risk of LR. As an attempt to reverse this poor prognosis, one could consider replanning stereotactic body radiotherapy with a higher total dose on PET/CT performed during the fifth week of radiotherapy, since most uptake and functional

volume reduction has already occurred (13) and sufficient time is left to adapt the radiotherapy plan.

The present approach relies on careful coregistration of the sequential <sup>18</sup>F-FDG PET/CT images (117 coregistrations performed). We restricted our study to patients who were seen in a single institution, with images acquired under similar conditions and analyzed by two experienced physicians. Most of the difficulties occurred with follow-up <sup>18</sup>F-FDG PET/CT because of posttreatment alterations in morphology. Manual adjustment was allowed in cases of obvious misregistration until a consensus was obtained. The differences in overlap indices did not reach statistical significance between LR patients for whom coregistration did not need manual adjustment ( $n = 7$ ) and LR patients who required manual adjustment ( $n = 10$ ). This difference could be improved by using deformable registration techniques. However, these are difficult to validate and the reproducibility is limited. Respiratory gating was not required in our prospective trials. Strictly speaking, respiratory gating could have improved the precision of our results. Despite potential blurring due to respiratory movement, the clarity of our present results is nevertheless reassuring.

Our results apply to only the primary tumor site. Lymph node <sup>18</sup>F-FDG uptake was not investigated since local recurrence is usually at the site of the primary tumor. In addition, it would be difficult to increase the radiotherapy dose in 2 or more intrathoracic target volumes.

The subvolumes delineated on PET<sub>A</sub> were followed on PET<sub>B</sub>, PET<sub>C</sub>, and PET<sub>R</sub> subvolumes. We did not extensively investigate whether a similar approach could be applied to PET<sub>B</sub> or PET<sub>C</sub>. Our goal was to investigate the ability of a routine practice widely available—staging PET—to identify the intratumor site at high risk of relapse, whereas postchemotherapy preradiotherapy PET and per-radiotherapy PET are not accepted as part of clinical routine. As PET is increasingly used for radiotherapy planning, a recent prospective study showed that it is associated with higher overall survival rates in NSCLC patients (24); the ability of <sup>18</sup>F-FDG PET/CT performed after induction chemotherapy or during radiotherapy to identify the intratumor site at high of relapse has to be determined in future studies.

The small number of included patients is another limitation of our study. Our priority was to include carefully selected patients with complete clinical and imaging data available. Further confirmation requires prospective trials. Multivariate analysis was not performed since the population size was too small (lack of statistical power).

We did not use a specific tracer—such as <sup>18</sup>F-fluoromisonidazole—of hypoxia, a well-known factor of radioresistance. However, it has been reported that tumor hypoxia and <sup>18</sup>F-FDG uptake are related through the upregulation of glucose transporter 1 by

**TABLE 3**  
Literature Review

Authors	Patients (n)	LR (n)	Time of <sup>18</sup> F-DG PET/CT	Registration	Indices*	Defined and compared volumes†	Results
Aerts (*)	17	—	A: d0 B: Per-RT d7 C: Per-RT d14	Rigid ± manual	OF	A <sub>34-40-50-60-70-80</sub> B <sub>34-40-50-60-70-80</sub> C <sub>34-40-50-60-70-80</sub>	OF <sub>34-60</sub> > 0.70 OF <sub>70-80</sub> > 0.50
Abramyuk (8)	10	10	A: Pre-RT R: Post-RT m6-9	?	Visual	A <sub>35</sub> R automatic (ROVER)	R visually included in A <sub>35</sub> Threshold: 35% SUV <sub>max</sub>
Aerts (*)	55	22	A: Pre-RT R: Post-RT m3	Rigid ± manual	OF	A <sub>34-40-50-60-70</sub> R <sub>70-80-90</sub> R <sub>&gt;aorta</sub> ; R <sub>&gt;2.5</sub> ; R <sub>&gt;5</sub>	OF A <sub>50</sub> nR <sub>&gt;aorta</sub> = 0.70 OF A <sub>50</sub> nR <sub>80</sub> = 0.77 OF A <sub>50</sub> nR <sub>90</sub> = 0.84 Threshold: 50% SUV <sub>max</sub>
Aerts (*)	12	7	A: Pre-RT R: Post-RT m3	Rigid ± manual	OF	A <sub>34-40-50-60-70</sub> R <sub>70-80-90</sub> R <sub>&gt;aorta</sub>	OF A <sub>50</sub> nR <sub>&gt;aorta</sub> = 0.68 OF A <sub>50</sub> nR <sub>90</sub> = 0.74 Threshold: 50% SUV <sub>max</sub>
Shusharina (11)	61	17	A: Pre-RT R: Post-RT d10 R: Post-RT m3 R: Post-RT m6	Nonrigid Derived Transformation Matrix	OF	A <sub>50</sub> R <sub>80</sub>	OF A <sub>50</sub> nR <sub>d10</sub> = 0.80 OF A <sub>50</sub> nR <sub>m3</sub> = 0.63 OF A <sub>50</sub> nR <sub>m6</sub> = 0.38 Threshold: 50% SUV <sub>max</sub>
Present study	39	17	A: Pre-RT B: d0 C: Per-RT d21 R: Post-RT m3-12	Rigid ± manual	Dice Jaccard OF AnR/A AnR/R	A <sub>30-40-50-60-70-80-90</sub> B <sub>40</sub> and B <sub>90</sub> C <sub>40</sub> and C <sub>90</sub> R <sub>40</sub> and R <sub>90</sub>	A <sub>70</sub> nR <sub>40</sub> /A <sub>70</sub> = OF A <sub>70</sub> nR <sub>40</sub> = 0.67 A <sub>70</sub> nR <sub>90</sub> /R <sub>90</sub> = OF A <sub>70</sub> nR <sub>90</sub> = 0.56 A <sub>60</sub> nR <sub>90</sub> /R <sub>90</sub> = OF A <sub>60</sub> nR <sub>90</sub> = 0.68 Threshold: 70% SUV <sub>max</sub>

\*Overlap quantification.

†Numeric indices refer to threshold for delineation.

d = days after radiotherapy began; m = months after radiotherapy began; OF = overlap fraction; RT = radiotherapy.

Threshold refers to recommended threshold for hot-spot delineation.

hypoxia-inducible factor 1 (25,26). <sup>18</sup>F-FDG and <sup>18</sup>F-fluoromisonidazole certainly give different but complementary information, and they can display similar intratumor distribution patterns (27). Although <sup>18</sup>F-FDG is not a specific hypoxia tracer, it is widely used and widely available, and its accumulation reflects overall metabolic activity and tumor load. Accordingly, targeting tumor subvolumes with an increased metabolic burden might be beneficial in tumor eradication (28).

## CONCLUSION

Areas of high <sup>18</sup>F-FDG uptake on pretreatment PET/CT scans identify tumor subvolumes at greater risk of relapse in patients with NSCLC treated by concomitant chemoradiation. This result was obtained in 39 patients (17 relapses) included in a series of 3

prospective trials in a single institution. We provide further justification for clinical investigation of radiotherapy dose escalation in small target subvolumes delineated on initial <sup>18</sup>F-FDG PET/CT scans with a 70% SUV<sub>max</sub> threshold.

## DISCLOSURE

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## Areas of High $^{18}\text{F}$ -FDG Uptake on Preradiotherapy PET/CT Identify Preferential Sites of Local Relapse After Chemoradiotherapy for Non –Small Cell Lung Cancer

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