^{18}F-FLT PET/CT Adds Value to ^{18}F-FDG PET/CT for Diagnosing Relapse After Definitive Radiotherapy in Patients with Lung Cancer: Results of a Prospective Clinical Trial

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Diagnosing relapse after radiotherapy for lung cancer is challenging. The specificity of both CT and ^{18}F-FDG PET/CT is low because of radiation-induced changes. 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) PET has previously demonstrated higher specificity for malignancy than ^{18}F-FDG PET. We investigated the value of ^{18}F-FLT PET/CT for diagnosing relapse in irradiated lung cancer. **Methods:** Patients suspected of relapse of lung cancer after definitive radiotherapy (conventional fractionated radiotherapy [cRT] or stereotactic body radiotherapy [SBRT]) were included. Sensitivity and specificity were analyzed both within the irradiated high-dose volume (HDV) and on a patient basis. Marginal differences and interobserver agreement were assessed. **Results:** Sixty-three patients who had received radiotherapy in 70 HDVs (34 cRT; 36 SBRT) were included. The specificity of ^{18}F-FLT PET/CT was higher than that of ^{18}F-FDG PET/CT (HDV, 96% [95% CI, 87–100] vs. 71% [95% CI, 57–83] [P = 0.0039]; patient-based, 90% [95% CI, 73–98] vs. 55% [95% CI, 36–74] [P = 0.0020]). The difference in specificity between ^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT was higher after cRT than after SBRT. The sensitivity of ^{18}F-FLT PET/CT was lower than that of ^{18}F-FDG PET/CT (HDV, 69% [95% CI, 41–89] vs. 94% [95% CI, 70–100] [P = 0.1250]; patient-based, 70% [95% CI, 51–84] vs. 94% [95% CI, 80–99] [P = 0.0078]). Adding ^{18}F-FLT PET/CT when ^{18}F-FDG PET/CT was positive or inconclusive improved the diagnostic value compared with ^{18}F-FDG PET/CT alone. In cRT HDVs, the probability of malignancy increased from 67% for ^{18}F-FDG PET/CT alone to 100% when both tracers were positive. **Conclusion:** ^{18}F-FLT PET/CT adds diagnostic value to ^{18}F-FDG PET/CT in patients with suspected relapse. The diagnostic impact of ^{18}F-FLT PET/CT was highest after cRT. We suggest adding ^{18}F-FLT PET/CT when ^{18}F-FDG PET/CT is inconclusive or positive within the previously irradiated volume to improve diagnostic value in patients for whom histologic confirmation is not easily obtained.

Key Words: lung cancer; radiotherapy; relapse; ^{18}F-FDG PET/CT; ^{18}F-FLT PET/CT

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Disease control after definitive radiotherapy is initially high, but 15%–40% of the patients will eventually experience locoregional failure (*1–5*). Many patients experience radiation-induced pneumonitis (3%–35%) or fibrosis (30%–50%) after radiotherapy (*3,6*), and distinguishing local recurrence from radiation-induced lung injuries is challenging. Active surveillance with CT is recommended (*7*), but changes on CT after radiotherapy may mimic recurrence (*8*). ^{18}F-FDG PET/CT is recommended if relapse is suspected (*9*). Posttreatment inflammation may, however, cause high ^{18}F-FDG uptake, thus reducing the specificity of ^{18}F-FDG PET (*10*).

3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) is a marker of proliferation (*11*). ^{18}F-FLT PET has a higher specificity than ^{18}F-FDG PET and performed better in differential diagnosis of inflammatory lesions in the lung (*12*). The potential of ^{18}F-FLT PET to differentiate malignancy from radiation-induced changes is less well described (*13–15*).

One small study showed correct diagnosis of disease progression with ^{18}F-FLT PET/CT in 7 of 8 patients after stereotactic body radiotherapy (SBRT) for lung cancer (*14*). To our knowledge, no publications have addressed the diagnostic value of ^{18}F-FLT PET after conventional fractionated radiotherapy (cRT) in patients with lung cancer.

In the current study, we hypothesized that ^{18}F-FLT PET/CT could better diagnose relapse after radiotherapy for lung cancer.

MATERIALS AND METHODS

Patients

Patients were prospectively included if meeting the following criteria: histologically confirmed non–small cell or small cell lung cancer, treatment with definitive radiotherapy within the last 24 mo, and current suspicion of relapse warranting an ^{18}F-FDG PET/CT examination. The causes of relapse suspicion are specified in Table 1. Patients were analyzed according to treatment regime: cRT (i.e., normo- and hyperfractionated radiotherapy) or SBRT.

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Patients were recruited from Copenhagen University Hospital, Rigshospitalet, Bispebjerg University Hospital, and Herlev University Hospital in Denmark from January 2015 to January 2019. The study protocol was approved by the local Ethics Committee (approval H-4-2014-060) and by institutional review boards. All patients gave written informed consent. The study was registered at clinicaltrials.gov (identifier NCT029995889).

Imaging

^{18}F-FDG PET/CT was conducted as a routine clinical investigation at the referring hospital according to local procedures. Details are available in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). Patients fasted at least 4 h before receiving an injection of ^{18}F-FDG (200 MBq or 4 MBq/kg, according to institutional protocol) and rested 60 min between injection and scan. Images were reconstructed following vendor recommendations or international clinical guidelines for ^{18}F-FDG PET imaging.

^{18}F-FLT PET/low-dose CT was performed at Rigshospitalet on a Siemens Biograph TruePoint TrueV 40 or 64 PET/CT scanner. ^{18}F-FLT (5 MBq/kg; maximum, 350 MBq) was injected 60 ± 10 min before PET/CT without restrictions regarding fasting or resting. Static regional imaging was obtained from the skull base to the iliac bone. ^{18}F-FLT PET images were reconstructed using ordered-subset expectation maximization with point-spread-function modeling, 3 iterations,

TABLE 1
Patient Characteristics

Characteristic	All patients (n = 63)	cRT patients (n = 34)*	SBRT patients (n = 30)*
Age at ^{18}F-FLT PET/CT (y)	70 (55–86)	68 (58–86)	75 (55–86)
Sex			
Male	36 (57%)	18 (53%)	19 (63%)
Female	27 (43%)	16 (47%)	11 (37%)
Histology			
Adenocarcinoma	30 (47.6%)	15 (44.1%)	15 (50%)
Squamous cell carcinoma	25 (39.7%)	13 (38.2%)	13 (43.3%)
NSCLC not otherwise specified	4 (6.3%)	2 (5.9%)	2 (6.7%)
SCLC	2 (3.2%)	2 (5.9%)	0
Mixed NSCLC/SCLC	2 (3.2%)	2 (5.9%)	0
Stage at diagnosis			
Ia	13 (20.6%)	0	13 (43.3%)
Ib	6 (9.5%)	1 (2.9%)	5 (16.7%)
IIa	2 (3.2%)	0	2 (6.7%)
IIb	5 (7.9%)	1 (2.9%)	4 (13.3%)
IIIa	15 (23.8%)	14 (41.2%)	2 (6.7%)
IIIb	16 (25.4%)	15 (44.1%)*	1 (3.3%)*
IV	6 (9.5%)	3 (8.8%)	3 (10.0%)
Radiotherapy			
Normofractionated, 60 Gy (24–33 F)	30 (47.6%)	31 (91.2%)	
Hyperfractionated, 45–60 Gy (30–40 F)	3 (4.8%)	3 (8.8%)	
SBRT			
50 Gy (5 F)	2 (3.2%)		2 (6.7%)
45–72 Gy (3 F)	28 (44.4%)		28 (93.3%)
Chemotherapy	35 (55.6%)	32 (94.1%)	3 (10%)
Cause of relapse suspicion			
Symptoms	1 (1.6%)	1 (2.9%)	0
CT (surveillance)	53 (84.1%)	30 (88.2%)	24 (80%)
CT and symptoms	2 (3.2%)	2 (5.9%)	0
^{18}F-FDG PET/CT (surveillance)	6 (9.5%)	0	6 (20%)
^{18}F-FDG PET/CT and symptoms	1 (1.6%)	1 (2.9%)	0
Days between radiotherapy end and ^{18}F-FLT PET/CT	237 (34–729)	277 (34–626)	236 (108–729)
Days between ^{18}F-FDG and ^{18}F-FLT PET/CT	6 (1–30)	6 (1–22)	6 (1–30)

*One patient was included in both subgroups.
NSCLC = non–small cell lung cancer; SCLC = small-cell lung cancer; F = fractions.
Qualitative data are numbers and percentages; continuous data are medians and ranges.

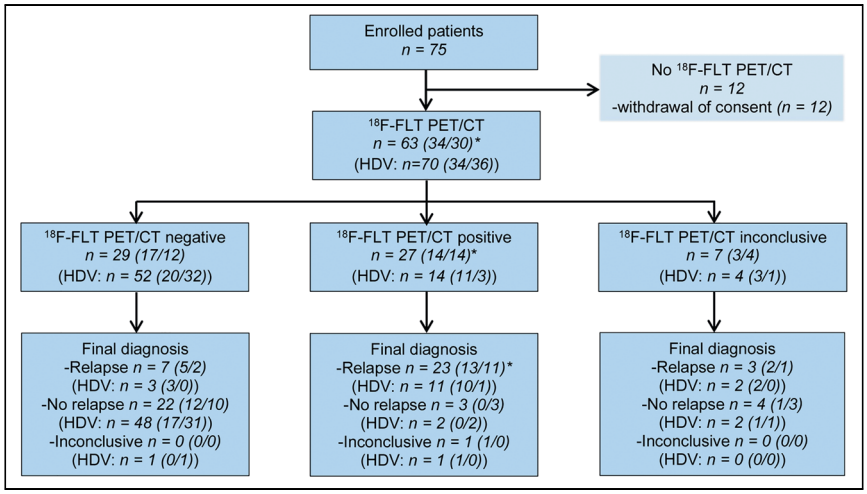

FIGURE 1. Patient flow in study. Numbers in parentheses refer to subgroups (cRT/SBRT). *One patient was included in both subgroups.

21 subsets, and a gaussian postreconstruction filter of 2 mm in full width at half maximum.

Image Analysis

All images were analyzed on a Mirada Medical Ltd. XD 3.6 workstation.

The PET/CT images were interpreted retrospectively as project readings, independently of subsequent management of the patients. The interpreters were unaware of the clinical data and previous PET results but not of previous CT results. Project readings were performed qualitatively and jointly by an experienced nuclear medicine physician and a radiologist. The ^{18}F-FLT PET/CT images were double-read by 2 observer-teams. Interpretation of ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT images from the same patient by the same observer-team was separated by a minimum of 3 mo.

Up to 3 lesions in each PET/CT scan were evaluated for malignancy using a 5-point scale: definitely benign, probably benign, inconclusive, probably malignant, and definitely malignant (patient-based analysis). From the previous radiotherapy plan, the high-dose volume (HDV) was defined within the 50% isodose curve, and PET-evaluated lesions within the HDV were identified (HDV-based analysis). If an HDV lesion was not matched with a PET-evaluated lesion, the HDV lesion was classified as definitely benign.

SUV_{max} from ^{18}F-FDG PET and ^{18}F-FLT PET was measured in the evaluated lesions and in the HDV.

Endpoint and Reference Standard

The endpoint was relapse status (relapse or no relapse) within 6 mo after ^{18}F-FLT PET/CT. Confirmation by histology was encouraged in the protocol. However, if histology was not clinically feasible, a compound reference standard was applied. Use of this standard was assigned by an experienced clinical oncologist and was based on a review of patient records, including histology, imaging, invasive procedures, and conference decisions. The clinical oncologist did not know the name or age of the patient, the dates of the exams, or the names of involved physicians.

Statistics

The study size was determined from a power calculation based on previous studies suggesting different results from ^{18}F-FDG PET and ^{18}F-FLT PET in at least 20% of lung cancer patients (16–18). With a power of 80% and a 2-sided α-level of 0.05 for significance, there needed to be at least 29 patients in each group. Taking the possibility of dropouts into account, each group was appointed up to 35 patients.

The diagnostic values of ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT were analyzed within the HDV and on a patient basis as a whole-body analysis. For the HDV-based analysis, all HDVs from each patient were included. For the patient-based analysis, the worst grading on the 5-point scale in each patient was selected. Sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were calculated. Inconclusive PET results were included in the analysis one time as a positive result and one time as a negative result, and the 2 scenarios were analyzed separately. Patients or HDVs with an inconclusive reference standard were excluded from the diagnostic analysis. Marginal differences in sensitivity and specificity between ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT were calculated by McNemar tests for all 4 combinations of handling inconclusive ^{18}F-FDG PET and ^{18}F-FDG PET results. Interobserver agreement was calculated with κ-statistics for positive versus negative or inconclusive ^{18}F-FLT PET/CT results.

A model combining ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT was suggested, and the diagnostic value of combined ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT was calculated.

Statistical analyses were performed in SPSS, version 25. With MedCalc (version 19.2; MedCalc Software Ltd.), 95% CIs for diagnostic value and marginal differences were determined.

RESULTS

Patients

In total, 75 patients were enrolled. However, 12 patients withdrew consent; thus, 63 patients were evaluable (Fig. 1). Two patients participated twice in the study; the second time was due to a newly suspected relapse. One patient received both cRT and SBRT and was included in both subgroups. This patient was treated initially with cRT and later with SBRT because of a new malignant lesion. Accordingly, 34 patients had been treated with cRT and 30 patients with SBRT. In accordance with the indications for the radiotherapy regimes, the stage at the time of diagnosis was higher for the cRT group than for the SBRT group. Patient characteristics are presented in Table 1.

In total, 70 HDVs (34 cRT HDVs; 36 SBRT HDVs) from the 63 patients were included in the analysis. Two patients were treated with radiotherapy twice; the second time was due to local relapse. Four patients received SBRT in 2 (n = 3) or 3 (n = 1) SBRT HDVs at initial diagnosis because of several lung lesions. In each patient, cRT HDV was coherent; thus, 1 cRT HDV was included per cRT patient.

TABLE 2
Clinical Outcome and Basis for Confirmation

Outcome	Confirmation basis	All	cRT	SBRT
HDVs		70	34	36
Relapse		16	15	1
	Histology	4	4	0
	Subsequent progression	6	5	1
	^{18}F-FDG PET/CT only	6	6	0
No relapse		52	18	34
	No subsequent progression	44	15	29
	Negative biopsy (follow-up not applicable because of systematic treatment)	1	0	1
	^{18}F-FDG PET/CT only (follow-up not applicable because of systematic treatment)	7	3	4
Inconclusive		2*†	1*	1†
Patients		63	34‡	30‡
Relapse		33	20	14
	Histology	8	4	4
	Subsequent progression	11	5	7
	Disseminated disease	6	4	2
	^{18}F-FDG PET/CT only	8	7	1
No relapse		29	13	16
	No subsequent progression	29	13	16
Inconclusive		1†	1†	0

*Biopsies were performed twice; both were suggestive but not conclusive of malignancy. Two months after end of follow-up, relapse was diagnosed on basis of metastatic adenocarcinoma cells in exudate from pericardium.

†Clinical PET report described "progression of radiation-induced changes," and biopsy was suggested although not performed. Follow-up was not applicable, as patient received systemic treatment due to distant relapse.

‡One patient was included in both subgroups.

Diagnostic Value of ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT in Irradiated HDV

During the 6 mo of follow-up, relapse was diagnosed in 16 HDVs, as confirmed by biopsy or, in 10 of the 16 cases, by subsequent progression. Nonrelapse was confirmed by 6 mo of follow-up without progression or by negative biopsy in 45 of 52 HDVs; in the remaining HDVs, the confirmation level was low (Table 2).

^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT were positive in 14 and 29 HDVs, respectively. Sensitivity and negative predictive value were lower for ^{18}F-FLT PET/CT than for ^{18}F-FDG PET/CT, and the specificity and positive predictive value were higher for ^{18}F-FLT PET/CT than for ^{18}F-FDG PET/CT, both when considering inconclusive PET results positive and when considering inconclusive PET results negative. The results from all diagnostic analysis are presented in Table 3. A cross-tabulation of PET results relative to clinical outcome is available in Supplemental Table 2.

For simplification, this and the following subsection describe results from analyses considering inconclusive ^{18}F-FDG PET/CT results as positive and inconclusive ^{18}F-FLT PET/CT results as negative.

The specificity of ^{18}F-FLT PET/CT within the HDV was 25% (95% CI, 13%–37%) higher than the specificity of ^{18}F-FDG PET/CT ($P = 0.0039$); that is, ^{18}F-FDG PET/CT was false-positive in 25% more cases than ^{18}F-FLT/PET/CT. The difference in specificity was largest in the cRT HDVs (cRT HDV, 39% [95% CI, 16%–61%] [$P = 0.0156$]; SBRT HDV, 18% [95% CI, 5%–30%] [$P = 0.0313$]).

Though the sensitivity of ^{18}F-FDG PET/CT was higher than the sensitivity of ^{18}F-FLT PET/CT, the difference was not significant (all, 25% [95% CI, 4%–46%] [$P = 0.1250$]; cRT HDV, 27% [95% CI, 4%–49%] [$P = 0.1250$]; SBRT HDV, inconclusive because there was only one relapse). Cross-tabulations of ^{18}F-FLT PET results versus ^{18}F-FDG PET results and results from all McNemar analyses with variant handlings of inconclusive results are available in Supplemental Tables 3 and 4.

^{18}F-FLT SUV_{max} in relapsed HDVs was 1.8–9.7 (median, 2.4), compared with 0.4–4.5 (median, 2.2) in benign HDVs. ^{18}F-FDG SUV_{max} in relapsed HDVs was 4.0–20.5 (median, 12.8), compared with 0.7–17.5 (median, 4.1) in benign HDVs.

PET images illustrating the diagnostic strengths and weaknesses are shown in Figure 2.

TABLE 3
Diagnostic Value of ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT Within Irradiated HDV

HDV group	Tracer	Handling of inconclusive PET results	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
All (n = 68)	^{18}F-FDG	As positive	94 (70–100)	71 (57–83)	50 (39–61)	97 (85–100)	76 (65–86)
		As negative	94 (70–100)	75 (61–86)	54 (41–65)	98 (85–100)	79 (68–88)
	^{18}F-FLT	As positive	81 (54–96)	92 (81–98)	76 (55–90)	94 (85–98)	90 (80–96)
		As negative	69 (41–89)	96 (87–100)	85 (58–96)	91 (80–96)	90 (80–96)
cRT (n = 33)	^{18}F-FDG	As positive	93 (68–100)	61 (36–83)	67 (52–78)	92 (62–99)	76 (58–89)
		As negative	93 (68–100)	67 (41–87)	70 (54–82)	92 (64–99)	79 (61–91)
	^{18}F-FLT	As positive	80 (52–96)	94 (73–100)	92 (64–99)	85 (67–94)	88 (72–97)
		As negative	67 (38–88)	100 (81–100)	100	78 (64–88)	85 (68–95)
SBRT (n = 35)	^{18}F-FDG	As positive	100 (3–100)	76 (59–89)	11 (6–19)	100	77 (60–90)
		As negative	100 (3–100)	79 (62–91)	13 (7–22)	100	80 (63–92)
	^{18}F-FLT	As positive	100 (3–100)	91 (76–98)	25 (10–50)	100	91 (77–98)
		As negative	100 (3–100)	94 (80–99)	33 (12–68)	100	94 (81–99)

Inconclusive PET results were handled as positive or negative. Results are from masked PET evaluations. Data are percentages, with 95% CIs in parentheses.

Patient-Based Diagnostic Value of ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT

During follow-up, 33 patients (52%) were diagnosed with relapse. Figure 3 illustrates the location of the relapse. In 19 of the 33 patients, relapse was confirmed by biopsy or subsequent progression according to RECIST 1.1. Nonrelapse was confirmed by 6 mo of follow-up without progression according to RECIST 1.1 in all patients (Table 2).

^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT were positive in 27 and 43 patients, respectively. Cross-tabulations and diagnostic value are available in Supplemental Tables 2 and 5.

The specificity of ^{18}F-FLT PET/CT was 34% (95% CI, 17%–52%) higher than the specificity of ^{18}F-FDG PET/CT in all patients (90% [95% CI, 73%–98%] vs. 55% [95% CI, 36%–74%]; P = 0.0020). In cRT patients, ^{18}F-FLT PET/CT outperformed ^{18}F-FDG PET/CT, with a 54% (95% CI, 27%–81%) higher specificity (100% [95% CI, 75%–100%] vs. 46% [95% CI, 19%–75%]; P = 0.0156). The specificity was not significantly different in SBRT patients (19% [95% CI, −0.4%–38%]; P = 0.2500).

The sensitivity of ^{18}F-FDG PET/CT was 24% (95% CI, 10%–39%) higher than the sensitivity of ^{18}F-FLT PET/CT in all patients (94% [95% CI, 80–99] vs. 70% [95% CI, 51–84]; P = 0.0078). In the subgroups, the difference in sensitivity did not reach statistical significance (cRT patients, 25% [95% CI, −6%–44%] [P = 0.0625]; SBRT patients, 21% [95% CI, −0.1%–43%] [P = 0.2500]). Cross-tabulations and McNemar analyses with variant handlings of inconclusive PET results are available in Supplemental Tables 3 and 6.

^{18}F-FLT SUV_{max} in patients with pulmonary relapse was 0.9–9.7 (median, 3.7), compared with 0.8–4.5 (median, 2.5) in patients without pulmonary relapse. ^{18}F-FDG SUV_{max} in patients with pulmonary relapse was 1.2–20.5 (median, 8.6), compared with 1.9–17.5 (median, 4.6) in patients with out pulmonary relapse.

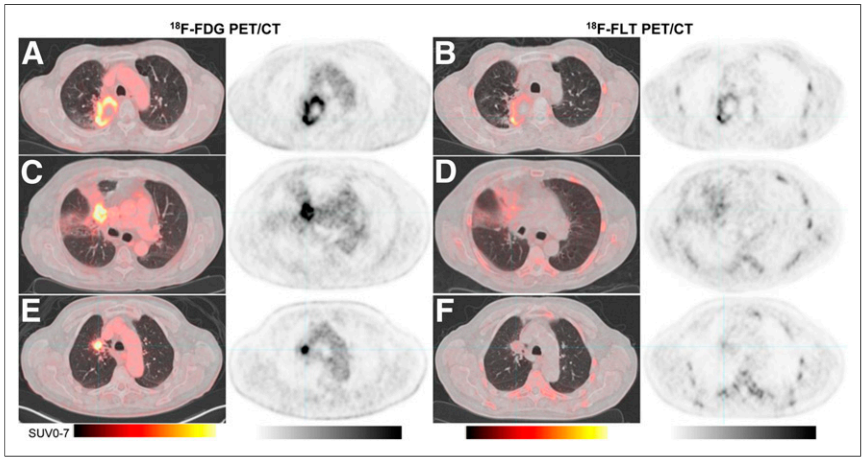

FIGURE 2. ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT in 3 representative patients with suspected relapse after cRT of lung cancer. (A and B) Relapse 19 mo after end of cRT detected by ^{18}F-FDG PET/CT (A) and ^{18}F-FLT PET/CT (B). (C and D) No relapse 4 mo after end of cRT; ^{18}F-FDG PET/CT was false-positive (C) and ^{18}F-FLT PET/CT true-negative (D). (E and F) Relapse 15 mo after end of cRT; ^{18}F-FDG PET/CT was true-positive (E) and ^{18}F-FLT PET/CT false-negative (F). Relapse was located in lung tissue as confirmed by biopsy, not in lymph node as it may appear on these images.

Interobserver Agreement of ^{18}F-FLT PET/CT

Patient-based and HDV-based interobserver agreement was moderate (0.47 and 0.57, respectively). Interobserver agreement was highest in cRT patients

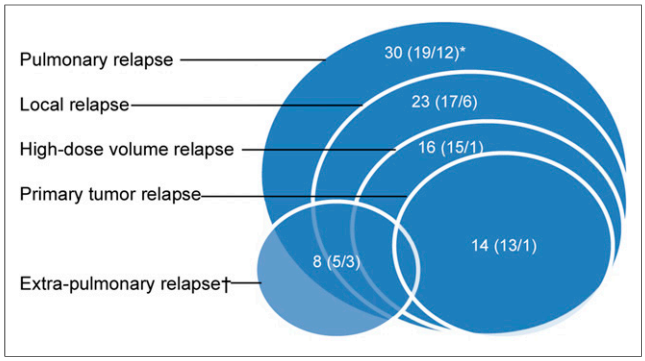

FIGURE 3. Location of relapse. In total, 33 patients had relapse; of these, 30 had pulmonary relapse. Numbers in parentheses refer to subgroups (cRT/SBRT). *One patient was included in both subgroups. †Three patients (1/2) had only extrapulmonary relapse.

(0.68) and cRT HDVs (0.70) and only moderate or poor in SBRT patients (0.45) and SBRT HDVs (−0.04).

Combined Diagnostic Value of ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT

To exploit the high negative predictive value of ^{18}F-FDG PET/CT and the high positive predictive value of ^{18}F-FLT PET/CT, we suggest adding ^{18}F-FLT PET/CT when the ^{18}F-FDG PET/CT results are positive or inconclusive. When ^{18}F-FDG PET/CT was negative, ^{18}F-FLT PET/CT provided no additional value, as all negative ^{18}F-FDG PET/CT results were accompanied by negative ^{18}F-FLT PET/CT results. The suggested diagnostic flow is illustrated in Figure 4.

Diagnostic accuracy was improved in the combined model when compared with a single positive or inconclusive ^{18}F-FDG PET/CT result (Table 4). The impact of adding ^{18}F-FLT PET/CT to positive or inconclusive ^{18}F-FDG PET/CT results was highest in cRT patients, raising the probability of malignancy from 72% after positive or inconclusive ^{18}F-FDG PET/CT results to 100% when ^{18}F-FLT PET/CT results were positive.

DISCUSSION

The main finding of this study was that ^{18}F-FLT PET/CT with a high specificity and positive predictive value adds value to ^{18}F-FDG PET/CT for the detection of relapse of lung cancer after radiotherapy. The sensitivity of ^{18}F-FLT PET/CT was, in most settings, not significantly different from that of ^{18}F-FDG PET/CT.

The superior specificity of ^{18}F-FLT PET/CT is consistent with results from pretreatment studies (*12*) and results after SBRT (*14*). In the small study of Hiniker et al., sensitivity (80% [4/5]) and specificity (100% [3/3]) were high, with only one false-negative ^{18}F-FLT PET/CT result after SBRT for lung cancer (*14*). Hiniker et al. included patients with suggestive ^{18}F-FDG PET/CT results, and the rate of local relapse was higher than in our study (5/8 vs. 1/35). With only one SBRT HDV relapse, our study did not have the statistical power to allow conclusions on sensitivity in this group. Similar results have also been demonstrated after concomitant chemoradiotherapy for esophageal cancer; ^{18}F-FLT PET/CT was superior to ^{18}F-FDG PET/CT in distinguishing malignant tissue from esophagitis (*13*).

We demonstrated a higher difference in specificity between ^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT after cRT than after SBRT, because of a combination of lower specificity for ^{18}F-FDG PET/CT and higher specificity for ^{18}F-FLT PET/CT after cRT than after SBRT. Different patterns of injuries in the surrounding lung tissue from different radiotherapy regimes (*3,6*) may explain this difference. Toxicity is related to dose deposited in surrounding lung tissues; larger HDVs in cRT regimes cause larger volumes of lung tissue to be exposed. Smaller HDVs from SBRT regimes spare the surrounding lung tissue to a higher extent. A higher prevalence of radiation-induced changes may explain the lower specificity of ^{18}F-FDG PET/CT after cRT. The lower specificity and positive predictive value of ^{18}F-FLT PET/CT in the SBRT HDVs than in the cRT HDVs might be caused by the very low prevalence of relapse in SBRT HDVs.

The difference in specificity between ^{18}F-FDG PET/CT and ^{18}F-FLT/CT was higher on a patient basis than within HDVs, as a result of the low specificity of ^{18}F-FDG PET/CT on a patient basis. ^{18}F-FDG PET and ^{18}F-FLT PET were evaluated in a masked manner to make comparable and unbiased evaluations. However, in the clinical setting, knowledge of previous treatment and possible inflammatory sites is essential for evaluation of ^{18}F-FDG PET/CT (*10*), and a masked reading might have a higher impact on ^{18}F-FDG PET/CT than on ^{18}F-FLT PET/CT. With several lesions evaluated in each patient in the patient-based analysis, the consequence of masking was more pronounced on a patient basis than in the HDV-based analysis. To quantify the consequence of masking, we compared the masked ^{18}F-FDG PET/CT results with results from the clinical ^{18}F-FDG PET/CT report. The specificity of ^{18}F-FDG PET/CT was 10% (95% CI, −12%–32%) higher in the clinical report than in the masked results, but the difference was not significant ($P = 0.549$). Masking did not affect sensitivity (94%; $P = 1$). Applying ^{18}F-FLT PET in a patient-based analysis is controversial, as ^{18}F-FLT PET has limited use for diagnosing distant metastases due to high background-uptake in the liver and bone (*19*), and false positive results in lymph nodes may be caused by proliferative B lymphocytes (*20*). Our project was not designed to investigate the diagnostic value of ^{18}F-FLT PET/CT on metastases; however, 8 patients were diagnosed with metastases in bones or liver. In 5 patients,

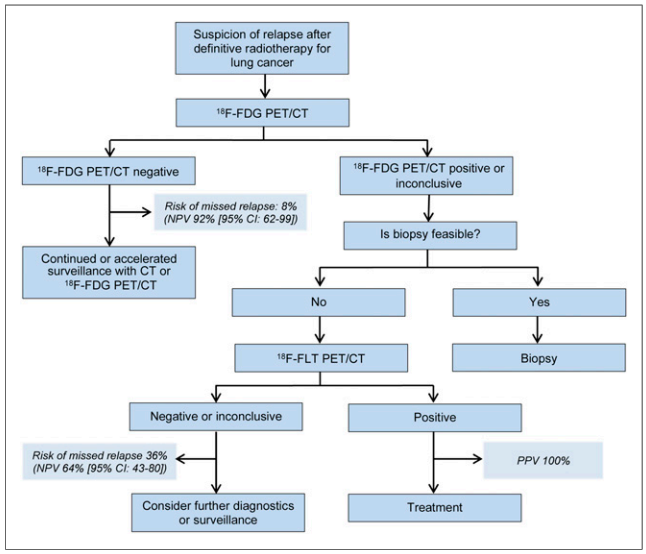

FIGURE 4. Suggested diagnostic flow for patients suspected for having relapse within irradiated HDV. Positive predictive value (PPV) and negative predictive value (NPV) are given for HDVs treated with cRT.

TABLE 4
Diagnostic Value of ^{18}F-FLT PET/CT After Positive ^{18}F-FDG PET/CT

Group	Pretest probability of malignancy*	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value	Negative predictive value	Accuracy
Patients								
All (n = 44)	70%	74% (55%–88%)	77% (46%–95%)	3.2 (1.2–8.9)	0.3 (0.2–0.7)	88% (74%–95%)	56% (39%–71%)	75% (60%–87%)
cRT (n = 25)	72%	72% (47%–90%)	100% (59%–100%)	NA	0.3 (0.1–0.6)	100%	58% (40%–75%)	80% (59%–93%)
SBRT (n = 20)	70%	79% (49%–95%)	50% (12%–88%)	1.6 (0.7–3.7)	0.4 (0.1–1.5)	79% (61%–90%)	50% (22%–78%)	70% (46%–88%)
HDVs								
All (n = 30)	50%	73% (45%–92%)	87% (60%–98%)	5.5 (1.5–20.7)	0.3 (0.1–0.7)	85% (59%–95%)	76% (58%–89%)	80% (61%–92%)
cRT (n = 21)	67%	71% (42%–92%)	100% (59%–100%)	NA	0.3 (0.1–0.7)	100%	64% (43%–80%)	81% (58%–95%)
SBRT (n = 9)	11%	100% (3%–100%)	75% (35%–97%)	4.0 (1.2–13.3)	0	33% (13%–62%)	100%	78% (40%–97%)

*Positive predictive value for positive or inconclusive ^{18}F-FDG PET/CT results.
NA = not applicable.
Data in parentheses are 95% CIs.

^{18}F-FLT PET/CT missed bone or liver metastases, but because of other malignant lesions detected by ^{18}F-FLT PET/CT, only 3 patients had false-negative ^{18}F-FLT PET/CT results due to distant metastases. Accordingly, extrapulmonary metastases had no impact on specificity in this study but some impact on patient-based sensitivity.

There were some limitations to our study. Patients in whom recurrence was strongly suspected could be referred directly for biopsy or oncologic treatment and thus not included in this project. Masked reading of PET scans is a deviation from clinical guidelines (*10*) but was applied to make ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT evaluations comparable. Combining ^{18}F-FDG PET with diagnostic CT and combining ^{18}F-FLT PET with low-dose CT potentially gave ^{18}F-FDG PET/CT an advantage over ^{18}F-FLT PET/CT. Project readings were, however, not masked to CT, and previous diagnostic CT scans could therefore be accessed. Combining an added ^{18}F-FLT PET scan with low-dose CT seems sufficient and reduces excessive ionizing irradiation and cost. Neither ^{18}F-FDG nor ^{18}F-FLT PET/CT was done with respiratory gating. Lack of gating could potentially lead to misregistration between PET and CT and a potential underestimation of tracer uptake, especially in small nodules. Relapse status was in most cases confirmed by either histology or follow-up with subsequent progression or nonprogression. In some patients, the relapse diagnosis was based solely on ^{18}F-FDG PET/CT, as decided by a multidisciplinary conference, because of an obvious outcome on ^{18}F-FDG PET/CT or the patient's being unfit for invasive procedures. ^{18}F-FDG PET/CT is recommended as a second-step test for patients with suspected relapse after radiotherapy (*7*), and therefore we did not exclude patients without further confirmation than ^{18}F-FDG PET/CT. Thus, in these cases, the test result of ^{18}F-FDG PET/CT and the reference were not independent, potentially overestimating the sensitivity and specificity of ^{18}F-FDG PET/CT. When ^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT results agreed, a potential overestimate would concern the absolute values of sensitivity and specificity of ^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT but not their differences. However, when ^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT results did not agree, and the reference was based solely on ^{18}F-FDG PET/CT, ^{18}F-FLT PET/CT results would always be false. Only in 2 patients in whom relapse was based solely on the ^{18}F-FDG PET/CT did the ^{18}F-FLT PET/CT results not agree with the ^{18}F-FDG PET/CT results. Although ^{18}F-FDG PET/CT was favored when further confirmation of relapse status was not obtained, the specificity of ^{18}F-FLT PET/CT was significantly higher than that of ^{18}F-FDG PET/CT.

Early and precise diagnosis of lung cancer relapse are essential, as surgery or reirradiation with curative intent might be feasible (*1*). To improve diagnosis of relapse, we suggest adding ^{18}F-FLT PET/CT when ^{18}F-FDG PET/CT is positive or inconclusive within the HDV. We acknowledge that in many cases renewed biopsy is required because of the possibility of a pathologic transition, which potentially changes the treatment of choice. When biopsy is feasible and favored, ^{18}F-FLT PET/CT does not outperform invasive procedures; ^{18}F-FLT PET might have a place for guiding biopsies, but further investigations are needed. In the many patients in whom biopsy is not feasible because of poor lung condition or difficult location, ^{18}F-FLT PET/CT adds valuable diagnostic information.

CONCLUSION

^{18}F-FLT PET/CT has a higher specificity than ^{18}F-FDG PET/CT in patients who have been treated with radiotherapy, both within the HDV and on a patient basis. The diagnostic impact of ^{18}F-FLT

PET/CT was highest after cRT. We suggest adding ^{18}F-FLT PET/CT when the results of ^{18}F-FDG PET/CT are inconclusive or positive within the HDV in patients who are unfit for invasive procedures and when renewed histology is not essential for the further course.

DISCLOSURE

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KEY POINTS

QUESTION: Is ^{18}F-FLT PET valuable in diagnosing relapse of irradiated lung cancer?

PERTINENT FINDINGS: ^{18}F-FLT PET/CT had a higher specificity and positive predictive value than ^{18}F-FDG PET/CT on a patient basis and within the irradiated HDV.

IMPLICATIONS FOR PATIENT CARE: Adding ^{18}F-FLT PET to ^{18}F-FDG PET/CT when relapse is suspected in previously irradiated lung cancers improves diagnostic accuracy significantly.

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