3’-Deoxy-3’-(18F) Fluorothymidine Positron Emission Tomography/Computed Tomography in Non-small Cell Lung Cancer Treated With Stereotactic Body Radiation Therapy: A Pilot Study

Shirley Lewis, MD, FRCR,a,b Matthew Chan, MD, FRCPC,a,b,c Jessica Weiss, PhD,d Hamid Raziee, MD, FRCPC,a,b,e Brandon Driscoll, MASc,f Andrea Bezjak, MD, FRCPC,a,b Alexander Sun, MD, FRCPC,a,b Benjamin Lok, PhD,a,b Douglass Vines, MRT,a,b John Cho, PhD,a,b Jean-Pierre Bissonnette, PhD,a,b Srinivas Raman, MD, MASc, FRCPC,a,b Andrew Hope, MD, FRCPC,a,b,1 and Meredith Giuliani, MBBS, MEd, FRCPCa,b,*,1

aDepartment of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada; bRadiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada; cDepartment of Radiation Oncology, BC Cancer, Vancouver, British Columbia, Canada; dDepartment of Biostatistics, Princess Margaret Cancer Centre, Toronto, Ontario, Canada; eDepartment of Radiation Oncology, BC Cancer Kelowna, University of British Columbia, British Columbia, Canada; and fQuantitative Imaging for Personalized Cancer Medicine Program—Techna Institute, University Health Network, Toronto, Ontario, Canada

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Abstract

Purpose: The primary objective was to compare 3’-deoxy-3’-(18F) fluorothymidine (FLT) positron emission tomography (PET)/computed tomography (CT) uptake in 3 cohorts of stereotactic body radiation therapy (SBRT) patients: (1) pre-SBRT, (2) stable post-SBRT lung fibrosis, and (3) suspicious or proven local recurrence post-SBRT. The secondary objectives were to optimize FLT-PET imaging by comparing FLT uptake in respiratory-gated (4-dimensional) versus nongated (3-dimensional) FLT-PET scans.

Methods: Patients with early-stage non-small cell lung cancer planned or treated with SBRT at the institution with radiographic findings of fibrosis or recurrence were eligible for the study. All patients underwent imaging with FLT-PET/CT before SBRT in cohort 1 and at fibrosis or recurrence in cohort 2 and 3, respectively. The planned sample size was 20 patients in each cohort, with 60 patients total. FLT-PET standardized uptake value (SUV) variables including SUV_{max}, SUV_{mean}, SUV_{peak}, SUV_{50}, and SUV_{95} were compared...
Introduction

The use of stereotactic body radiation therapy (SBRT) in the curative treatment of early non-small cell lung cancer has increased.1-3 SBRT has demonstrated an impressive 3-year local control of 85% to 90%.3-5 However, surveillance following SBRT, including distinguishing between benign radiation therapy–related lung changes and tumor recurrence, has been a challenge for radiologists, radiation oncologists, and surgeons. The traditional follow-up method with computed tomography (CT) scans shows evolving radiation-induced radiographic lung changes that often resemble or obscure local recurrence, and the high-risk features on CT have not demonstrated accuracy.5-16 The uncertainty in detecting recurrence may lead to over- or under-investigation, posing the risks of missing a recurrence, unnecessary invasive procedures, and added health care system costs.

Studies exploring fluorodeoxy glucose (FDG) positron emission tomography (PET) and magnetic resonance imaging to supplement or assist CT scans in identifying a true recurrence have not yielded significant success.17-20 Pastis et al noted that FDG-PET 3 months after lung SBRT had a sensitivity of 50% and a specificity of 94%.21 The uncertainty about the results is due to increased FDG uptake by radiation-induced changes, leading to moderate post-SBRT FDG-PET hypermetabolic activity, which may persist 2 years after SBRT.22 Further study has failed to show a statistical correlation between FDG activity and quantitative malignant tumor cells, which has implications in assessing tumor response by FDG-PET, as it may not be reflective of a change in tumor burden.23

3'-Deoxy-3'-(18F) fluorothymidine (FLT)–PET is based on the integration of thymidine into DNA and may overcome the shortcomings of FDG-PET as it is more specific for the assessment of tumor proliferation suggestive of recurrence.24-27 The studies of FLT-PET in locally advanced or metastatic lung cancer show a correlation with tumor proliferation. Change in FLT uptake has demonstrated a correlation with decreased disease activity postradiation or chemoradiation, with a better response than FDG-PET.28-29 Compared with FDG, FLT has lower sensitivity but higher specificity for tumor detection, making it potentially attractive to monitor disease response/recurrence following SBRT.

To our knowledge, literature on post-SBRT surveillance with FLT-PET is limited.30,31 The present study explores the feasibility of FLT in assessing radiologic changes after SBRT to enable distinction of fibrosis from disease recurrence.

Methods and Materials

Study design

The institutional research ethics board approved this prospective single-arm feasibility study and was registered with clinicaltrials.gov (NCT02456246). The present 3-arm study aimed at testing FLT-PET in SBRT patients to differentiate tumor recurrence from radiation-induced lung fibrosis. The primary objective was to compare FLT uptake in 3 groups of patients: (1) pre-SBRT, (2) stable post-SBRT lung fibrosis, and (3) suspicious or proven local recurrence post-SBRT. The secondary objectives were to optimize FLT-PET imaging by comparing FLT uptake in respiratory-gated (4-dimensional [4D]) versus nongated (3-dimensional) FLT-PET scans.

Eligibility criteria

Patients with early-stage (T1-2N0M0 or T3N0M0 limited to the chest wall as per seventh edition of the American Joint Committee on Cancer staging manual) presumed or biopsy-proven non-small cell lung carcinoma, aged >18 years, and planned for SBRT at the institution or followed up after SBRT with radiographic findings of fibrosis or recurrence were eligible for the study.21 The exclusion criteria for the study were patients who were pregnant, unable to lie supine for 30 minutes, or on drug disulfiram. Patients who fulfilled the study criteria and provided written informed consent were assigned to 1 of 3 study cohorts. The 3 cohorts were...
patients who were treatment-naïve and planned for SBRT treatment according to established institutional practices (cohort 1); patients who have had SBRT and surveillance imaging with CT-demonstrated typical or stable lung fibrosis (cohort 2); and patients who have had SBRT and demonstrate imaging findings on CT scan suspicious for recurrence or have biopsy showing disease recurrence (cohort 3).

A consensus between at least 2 coinvestigators was essential before assignment to cohorts 2 and 3. The patients enrolled in cohort 1 could become eligible for cohort 2 or 3 following SBRT based on radiologic findings of fibrosis or recurrence. Patients who fit this demographic were screened for study and reconsented into cohort 2 or 3 and treated as a new case. All patients following inclusion into the study underwent imaging with FLT-PET/CT. The FLT-PET in cohort 1 was performed before SBRT.

**FLT-PET/CT protocol**

FLT injection and PET/CT imaging were performed using an integrated General Electric Discovery 610 PET-CT simulator (GE Health Care, Milwaukee, WI). FLT was administered by intravenous injection with a mean dose of 376 MBq ± 19 MBq. The respiratory-gated FLT-PET/CT scan commenced 60 ± 5 minutes after FLT injection. After voiding the bladder, the patients were positioned supine on the imaging couch with arms above their heads. A low-dose helical CT scan of the lungs (1-2 mSv) was performed for PET attenuation correction (AC), followed by respiratory-gated PET scan acquired for 20 minutes. The 2-field of view for the gated FLT-PET scan encompassed the primary tumor and adjacent lymph nodes (with a length of 25 cm). The respiratory-gated FLT-PET scan was followed by a 4D planning CT scan encompassing the thorax as per departmental clinical protocol. The adverse events related to FLT were recorded using Common Terminology Criteria for Adverse Events version 4.0.

**Image analysis**

The CT and FLT-PET images were coregistered, and the PET images were corrected for decay. The PET data were converted to standardized uptake values (SUVs). Both helical CT and phase-matched 4D CT were used for AC for respiratory-gated FLT-PET images. The volumes of interest for the primary tumor/fibrosis/recurrence were contoured manually using the coregistered CT images on the helical and the maximum inhale and exhale 4D-CT images. The intensity of FLT uptake was determined using the metrics $SUV_{\text{max}}$, $SUV_{\text{peak}}$, $SUV_{\text{mean}}$, $SUV_{50}$, and $SUV_{95}$ and determined as follows:

- $SUV_{\text{max}}$: voxel with the maximum uptake
- $SUV_{\text{peak}}$: 1.0-cm diameter spherical volume of interest, centered on the maximum voxel
- $SUV_{\text{mean}}$: mean of values within the volumes of interest
- $SUV_{50}$: 50th percentile value of SUV distribution
- $SUV_{95}$: 95th percentile value of SUV distribution

**Treatment protocol**

Patients received standard treatment with SBRT according to the institutional treatment policies. The standard fractionation used was 48 Gy in 4 fractions (12 Gy per fraction alternate days), 54 Gy in 3 fractions (18 Gy per fraction alternate days) for peripheral tumors, and 60 Gy in 8 fractions (7.5 Gy per fraction daily) for central tumors. The results from the FLT-PET/CT did not alter the SBRT treatment planning. Routine follow-up following SBRT, including management of acute and late side effects, was performed as per institutional policy for all cohorts. Patients were followed up every 3 months in the first year, every 6 months in the second year, and yearly thereafter.

**Statistical analysis**

We aimed to accrue 20 patients in each cohort, 60 patients in total, with a planned accrual rate of 3 patients per month over a total duration of 2 years. Descriptive statistics were used to describe the variables using proportions, means with standard deviations, and medians with range where appropriate. The SUV variables were compared between the 3 cohorts using the Kruskal-Wallis test. The motion of tumor was compared using Wilcoxon rank sum test. The correlation of nongated and respiratory gated FLT scans were performed using Spearman correlation coefficient. The $SUV_{\text{max}}$ of FLT-PET and FDG-PET in cohort 1 were compared using the paired Wilcoxon test. Statistical significance was set at $P < .05$.

**Results**

From January 2015 to April 2021, 41 patients were recruited to the study. There were 20 patients in cohort 1, 16 patients in cohort 2, and 5 patients in cohort 3. Due to poor accrual in cohorts 2 and 3, the study was closed after 5 years. The reasons were low recurrence rates in patients treated with SBRT and poor accrual during the COVID-19 pandemic.
Baseline characteristics

The median age of the entire cohort was 77 years (range, 46-89). Men constituted 61% of the cohort. Table 1 summarizes the baseline characteristics. Thirty patients (73%) were treatment-naïve, 8 patients had previous surgery (lobectomy or wedge resection), and 3 patients had prior SBRT for stage I lung cancer. Most patients received a diagnosis of stage I lung cancer (80.5%), and adenocarcinoma was the most common histology. Ten patients were treated without a tissue diagnosis. The most common dose fractionation was 48 Gy in 4 fractions (83%). Two patients in the fibrosis cohort received SBRT to new primary lesions; 1 received 48Gy in 4 fractions and another 60 Gy in 8 fractions.

FLT-PET variables

A nongated FLT-PET was performed for all patients, and a respiratory-gated FLT-PET was done in 35 patients due to equipment nonavailability. The median dose of FLT isotope administered was 379 MBq (range, 280-403), and no toxicity was reported with its administration. The average follow-up for cohorts 1, 2, and 3 were 3.3 years, 4.6 years, and 3.0 years, respectively. The median time to FLT-PET in cohort 2 was 1.5 years (range, 0.5-7.3 years), and in cohort 3, it was 1.3 years (range, 0.9-2.7 years).

Table 2 shows the FLT-PET variables across the cohorts. Using the nongated FLT-PET information, $SUV_{peak}$, $SUV_{mean}$, and $SUV_{max}$ were significantly lower in the fibrosis cohort than in the recurrence and pretreatment cohorts. The $SUV_{50}$ and $SUV_{95}$ values in the recurrence cohort were similar to the pretreatment cohort and significantly different from the fibrosis cohort (Fig. 1).

The average superior-inferior tumor motion was 0.48 cm (standard deviation, 0.5; range, 0.01-2.8 cm) for the whole cohort and was similar between pretreatment and fibrosis/recurrence cohort (0.45 vs 0.52 cm, $P = .36$). The average anteroposterior and lateral motion for entire cohort was 0.1 cm each. The FLT-PET variables were correlated between respiratory gated (helical and phase matched) versus nongated scans, and there was good correlation in the SUV variables ($r = 0.8-1.0$), as shown in Figs. 2 and 3.

In the pretreatment cohort, all patients had baseline FDG-PET/CT as part of the diagnostic staging. The mean $SUV_{max}$ of FLT was lower than FDG-PET/CT (3.4 vs 8, $P = .003$). None of the patients in cohort 2 underwent biopsy. In cohort 3, recurrences were based on radiologic findings in most. FDG-PET/CT was performed in 3 patients at recurrence. Biopsy was attempted in 2 patients; 1 was negative, and the other confirmed adenocarcinoma (Fig. E1). Based on the prior study by Hiniker et al, we assessed the ratio of $SUV_{max}$ of the tumor to the mediastinal blood pool in

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Table 1 Baseline characteristics

| Characteristic                  | Cohort 1, n (n = 20) | Cohort 2, n (n = 16) | Cohort 3, n (n = 5) | Total, n (%)(n = 41) |
|--------------------------------|----------------------|----------------------|---------------------|----------------------|
| Tumor location                 |                      |                      |                     |                      |
| Right upper lobe               | 5                    | 2                    | 3                   | 10 (24)              |
| Right middle lobe              | 1                    | 2                    | 1                   | 4 (10)               |
| Right lower lobe               | 2                    | 6                    | 0                   | 8 (20)               |
| Left upper lobe                | 7                    | 5                    | 1                   | 13 (32)              |
| Left lower lobe                | 5                    | 1                    | 0                   | 6 (15)               |
| AJCC TNM stage                 |                      |                      |                     |                      |
| T1N0M0                         | 16                   | 14                   | 3                   | 33 (80.5)            |
| T2N0M0                         | 4                    | 1                    | 2                   | 7 (17)               |
| T3N0M0                         | 0                    | 1                    | 0                   | 1 (2.5)              |
| Histology                      |                      |                      |                     |                      |
| Squamous carcinoma             | 3                    | 0                    | 1                   | 4 (10)               |
| Adenocarcinoma                 | 13                   | 10                   | 4                   | 27 (66)              |
| Biopsy not done                | 4                    | 6                    | 0                   | 10 (24)              |
| SBRT schedule                  |                      |                      |                     |                      |
| 48 Gy in 4 fractions           | 17                   | 13                   | 4                   | 34 (83)              |
| 60 Gy in 8 fractions           | 3                    | 3                    | 1                   | 7 (17)               |

Abbreviations: AJCC = American Joint Committee on Cancer; TNM = tumor node metastases.
the recurrence cohort (Table 3).

In 4 of the 5 patients, the SUVmax and ratio of SUVmax of the tumor to the mediastinal blood pool was >2.

**Discussion**

Surveillance and detection of recurrence in patients treated with SBRT for lung cancer is challenging due to fibrosis on CT scans. Various strategies including CT based radiomic signatures, apparent diffusion coefficient maps from magnetic resonance imaging, and PET have been tried to differentiate fibrosis from recurrence. FDG-PET measures glucose metabolism and is the most common PET tracer used across malignancies to evaluate recurrence. Due to nonspecific uptake in inflammatory tissue, its use in posttreatment settings led to equivocal findings and the evaluation of other PET tracers. FLT-PET has emerged promising as it is specific for tumor proliferation and shows minimal uptake in inflammatory tissues. The present study evaluated FLT-PET in a cohort of patients with lung cancer treated with SBRT. It showed that FLT-PET SUVmax values were lower in the fibrosis cohort, and FLT-PET may help differentiate fibrosis from recurrence.

FLT-PET is explored for assessment of response following conventionally fractionated radiation therapy in lung cancer. Everitt et al compared the response following radical chemoradiation in patients with lung cancer between FDG and FLT-PET. They found median SUVmax values were lower with FLT than FDG posttherapy. Studies evaluating FLT-PET/CT after SBRT to lung assessing fibrosis or recurrence are scarce. Christensen et al investigated FDG and FLT-PET/CT in 61 patients suspected of relapse following definitive radiation therapy for lung cancer. Twenty-eight patients (45%) received SBRT alone, and the FLT and FDG SUVmax values were higher in those who relapsed. A pilot study by Hiniker et al evaluated FLT-PET in 10 patients treated with SBRT/hyperfractionated radiation therapy to the lung with equivocal FDG-PET for assessment of recurrence. FLT-PET accurately differentiated inflammatory changes from recurrence in 7 of 8 patients (87.5%). The FLT parameters of high SUVmax and the ratio of SUVmax of the lesion to SUVmax of the mediastinal pool >2 were indicative of recurrence. In the present study, 4 of 5 patients in the recurrence cohort had SUVmax >2 and ratio of the lesion to mediastinal SUVmax >2.

The role of FLT-PET in the diagnosis of lung cancer has been studied, and it shows high specificity but low sensitivity compared with FDG-PET, making it attractive to differentiate malignant from benign lung nodules. The uptake of FLT is low compared with FDG at diagnosis. The baseline FLT SUVmax may carry a prognostic

| Variable | Cohort 1 (n = 20) | Cohort 2 (n = 16) | Cohort 3 (n = 5) | P value |
|----------|------------------|------------------|------------------|---------|
| SUVpeak |                  |                  |                  |         |
| Mean (SD) | 3 (1.5)      | 1.8 (0.7)      | 3.4 (1.9)     | .015     |
| Median (range) | 2.5 (0.9-6.1) | 1.7 (0.8-3.9) | 2.8 (1-6)   |         |
| SUVmean |                  |                  |                  |         |
| Mean (SD) | 1.9 (0.8)      | 1.1 (0.2)      | 1.7 (0.5)     | .0011    |
| Median (range) | 1.7 (0.7-3.4) | 1.1 (0.7-1.5) | 1.6 (1.1-2.3) |         |
| SUVmax |                  |                  |                  |         |
| Mean (SD) | 3.5 (1.7)      | 2.1 (0.7)      | 4.2 (2.2)     | .0093    |
| Median (range) | 3 (1.1-7)    | 2 (0.8-4.1)   | 3.7 (1.7-7.6) |         |
| SUV50    |                  |                  |                  |         |
| Mean (SD) | 1.8 (0.7)      | 1.1 (0.2)      | 1.6 (0.4)     | .0017    |
| Median (range) | 1.6 (0.7-3.4) | 1.1 (0.7-1.5) | 1.4 (1.1-2.3) |         |
| SUV95    |                  |                  |                  |         |
| Mean (SD) | 3 (1.3)       | 1.6 (0.4)      | 2.7 (0.9)     | .0019    |
| Median (range) | 2.8 (1-5.8)  | 1.6 (0.8-2.8) | 2.8 (1.4-3.8) |         |
| Tumor volume (cc) |       |                  |                  |         |
| Mean (SD) | 14.3 (27)     | 38.8 (33.3)    | 95.3 (119.6)  | .015     |
| Median (range) | 6.7 (1-124.5) | 29.8 (6.4-138.3) | 54.8 (11.2-301) |         |

Abbreviations: FLT-PET = 3'-deoxy-3'-(18F) fluorothymidine positron emission tomography; SD = standard deviation; SUV = standardized uptake value.
value. Saga et al showed that in 20 patients with lung cancer treated with carbon ion radiation therapy, patients who developed recurrence or died during follow-up had high pretreatment FLT uptake and those with FLT SUVmax < 3.7 had better progression-free survival. In the present study, the SUVmax values were lower with FLT than FDG PET in the pretreatment cohort. No local recurrences were identified, and the prognosis was not assessed in this cohort.

The FLT-PET parameters have varied among the studies, with use of SUVmax, SUVmean, or SUVpeak to assess the response or for prognosis. Hiniker et al used SUVmax and ratio of SUVmax to the mediastinal pool, whereas Christensen evaluated various parameters such as SUVmax, SUVpeak, and planning target volume 80% and 50%. In the present study, we used SUVmax, SUVmean, SUVpeak, SUV50, and SUV95, and all were lower in fibrosis than the recurrence cohort. The disparity in PET variables and values reported across studies for PET could be due to inconsistencies in procedures (eg, isotope injection and imaging time, fasting duration, different scanners, blood glucose concentration).

### Table 3  FLT and FDG parameters in recurrence cohort

| Patient | SUVmax FDG | SUVmax FLT | Ratio of SUVmax lesion FLT and SUVmax mediastinal pool FLT |
|---------|------------|------------|----------------------------------------------------------|
| 1       | 15.6       | 3.7        | 3.3                                                      |
| 2       | 7.3        | 3.2        | 3.2                                                      |
| 3       | 10.6       | 4.7        | 4.2                                                      |
| 4       | NA         | 7.6        | 6.6                                                      |
| 5       | NA         | 1.6        | 1.9                                                      |

*Abbreviations: FDG = fluoro-deoxy glucose; FLT = 3'-deoxy-3'-(18F) fluorothymidine; NA = not available; SUV = standardized uptake value.*
a need for standardization of reporting of SUV values across institutions and adherence to guidelines.43-45

PET images are affected by partial volume effects, which are intensified in lung due to respiratory movement.46 This effect is significant for FLT-PET, where the signal-to-background ratio is lower compared with that of FDG-PET. In a study comparing 4D and nongated FDG-PET, 4D PET defined moving tumors better and reduced blurring.47 We did not find any statistically significant difference in our FLT-PET SUV variables between nongated and 4D gated FLT-PET, both phase-matched and helical-gated. This finding could be due to low average tumor motion of this cohort and absence of selection of moving tumor (>1 cm). Comparing 4D with nongated could be more helpful in tumors with greater respiratory motion and will be evaluated in the future. Driscoll et al found motion blur to be significant for SUV_{mean}, SUV_{max}, and SUV_{peak} for motion >1 cm and 4D PET reconstructions significantly reduced the blur.48 The use of phase matched AC for respiratory gated PET significantly improved precision over helical CT for hypoxia PET imaging.

The study’s strengths are that this is one of few studies evaluating FLT-PET in a homogenous cohort of patients treated with SBRT in early lung cancer. We have explored various FLT parameters and assessed the effect of breathing. The limitations of the study are the small sample size in the recurrence cohort. The absence of longitudinal information across the cohorts led to inability to compare pre- and post-SBRT FLT parameters. We did not attempt to generate threshold values for FLT-PET SUV parameters due to low patient numbers. Larger multi-institutional validation studies are needed.
to ascertain the utility of FLT-PET to confirm the findings of the present study.

**Conclusion**

FLT-PET may be helpful in differentiating SBRT related fibrosis from recurrence. A nongated FLT-PET with reporting of $SUV_{\text{max}}$ and $SUV_{95}$ values is recommended.

**Supplementary materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101037.

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