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FLT-PET/CT in Non-Small Cell Lung Cancer treated with stereotactic body radiotherapy- A Pilot study.



Shirley Lewis MD FRCR , Matthew Chan MD FRCPC ,
Jessica Weiss PhD , Hamid Raziee MD FRCPC ,
Brandon Driscoll MASc , Andrea Bezjak MD FRCPC ,
Alexander Sun MD FRCPC , Benjamin Lok PhD ,
Douglass Vines MRT , John Cho PhD ,
Jean-Pierre Bissonnette PhD ,
Srinivas Raman MD, MASc, FRCPC , Andrew Hope MD FRCPC ,
Meredith Giuliani MBBS, MEd, FRCPC

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Title: FLT-PET/CT in Non-Small Cell Lung Cancer treated with stereotactic body radiotherapy- A Pilot study.

Shirley Lewis MD FRCR¹, Matthew Chan MD FRCPC^{1,2}, Jessica Weiss PhD³, Hamid Raziee MD FRCPC^{1,4}, Brandon Driscoll MSc⁵, Andrea Bezjak MD FRCPC¹, Alexander Sun MD FRCPC¹, Benjamin Lok PhD¹, Douglass Vines MRT¹, John Cho PhD¹, Jean-Pierre Bissonnette PhD¹, Srinivas Raman MD, MSc, FRCPC¹, Andrew Hope MD FRCPC¹, Meredith Giuliani MBBS, MEd, FRCPC¹.

1 Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada; Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada.

2 Department of Radiation Oncology, BC Cancer Vancouver, British Columbia, Canada.

3 Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, Ontario, Canada.

4 Department of Radiation Oncology, BC Cancer Kelowna, University of British Columbia, British Columbia, Canada.

5 Quantitative Imaging for Personalized Cancer Medicine Program—Techna Institute, University Health Network, Toronto, ON, Canada

*Drs Hope and Giuliani are co-Senior Authors

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Jessica Weiss. Email: jessica.weiss@uhnresearch.ca

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Corresponding Author:

Dr Meredith Giuliani

Associate Professor of Radiation Oncology

Radiation Medicine Program,

Princess Margaret Cancer Centre,

Toronto, Canada M5G1P7

Contact: Meredith.giuliani@rmp.uhn.ca

Phone number: 4169462000-3142

Abstract:

Purpose: The primary objective was to compare FLT-PET/CT uptake in three cohorts of stereotactic body radiotherapy (SBRT) patients: 1) pre-SBRT, 2) stable post-SBRT lung fibrosis, and 3) suspicious/proven local recurrence post-SBRT. The secondary objectives were to optimize FLT PET imaging by comparing FLT uptake in respiratory-gated (4D) versus non-gated (3D) FLT-PET scans.

Methods: Early-stage non-small cell lung cancer patients 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 prior to 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, 60 patients in total. FLT-PET SUV variables including SUV_{max} , SUV_{mean} , SUV_{peak} , SUV_{50} and SUV_{95} were compared between the three cohorts using Kruskal-Wallis test. The correlation of respiratory-gated and non-gated FLT-PET SUV variables was performed using spearman correlation coefficient.

Results: Forty-one patients were accrued in the study (20 in cohort 1, 16 in cohort 2 and 5 in cohort3) between 2015 and 2019. The majority were diagnosed with stage I lung cancer (86%) and the most common prescription was 48Gy in 4 fractions (59%). Respiratory-gated FLT-PET was performed in 35 patients. The FLT SUV variables were well correlated between respiratory-gated versus non-gated scans ($r=0.8-1.0$). The SUV_{peak} , SUV_{mean} , SUV_{max} were significantly lower in the fibrosis cohort compared to either recurrence or pretreatment cohorts. The SUV_{50} and SUV_{95} values in the recurrence cohort were statistically similar to the pretreatment cohort.

Conclusion: FLT-PET/CT may be helpful in differentiating SBRT related fibrosis from recurrence. Non-gated FLT-PET/CT with reporting of SUV_{max} and SUV₉₅ values is recommended.

Keywords: Lung cancer, stereotactic body radiotherapy (SBRT), SABR, FLT PET-CT, response, radiation lung injury, recurrence.

Title: FLT PET-CT in Non-Small Cell Lung Cancer treated with stereotactic body radiotherapy- A Pilot study.

Introduction

The use of stereotactic body radiotherapy (SBRT) in the curative treatment of early non-small cell lung cancer (NSCLC) has increased^{1,2}. SBRT has demonstrated an impressive three-year local control of 85 to 90%³⁻⁵. However, surveillance following SBRT, including distinguishing between benign radiotherapy 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 which often resemble or obscure local recurrence and the high-risk features on CT have not demonstrated accuracy⁶⁻¹⁶. 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 fluoro-deoxy glucose (FDG) positron emission tomography (PET) and magnetic resonance imaging (MRI) to supplement or assist CT scans in identifying a true recurrence have not yielded significant success¹⁷⁻²⁰. 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 two years after SBRT²². 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 burden²³.

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 would be more specific for the assessment of tumor proliferation suggestive of recurrence²⁴⁻²⁷. 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 post-radiation or chemoradiation, with a better response than FDG-PET^{28,29}. Compared to FDG, FLT has lower sensitivity but higher specificity for tumour 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 radiological changes after SBRT to enable distinction of fibrosis from disease recurrence.

Material and methods

Study design

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

Eligibility criteria

Early-stage (T1-2N0M0 or T3N0M0 limited to the chest wall as per 7th edition American Joint Committee on Cancer staging manual) presumed or biopsy-proven non-small cell lung carcinoma, aged more than 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 study³². 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 one of three study cohorts. The three cohorts were:

1. Cohort 1: Patients who were treatment naïve and planned for SBRT treatment according to established institutional practices.
2. Cohort 2: Patients who have had SBRT and surveillance imaging with CT demonstrate typical or stable lung fibrosis.
3. Cohort 3: Patients who have had SBRT and demonstrate imaging findings on CT scan suspicious for recurrence or have biopsy showing disease recurrence.

A consensus among at least two co-investigators was essential before assignment to Cohorts 2 and 3. The patients enrolled in cohort one could become eligible for cohort two or three following SBRT based on radiological findings of fibrosis or recurrence. Patients who fit this demographic were screened for study and reconsented into cohort 2 or 3, treated as a new case. All patients following inclusion into the study underwent imaging with FLT-PET CT. The FLT-PET in cohort one was performed before SBRT.

FLT PET-CT protocol

FLT injection and PET/CT imaging were performed using an integrated General Electric (GE) Discovery 610 PET-CT simulator (GE Healthcare, Milwaukee, USA). FLT was administered by intravenous injection

with a mean dose of $376 \text{ MBq} \pm 19 \text{ MBq}$. The respiratory-gated FLT-PET/CT scan commenced $60 \text{ min} \pm 5 \text{ min}$ 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 ($1\text{-}2 \text{ mSv}$) 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 CTCAE Version 4.0.

Image analysis

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

- a) SUV_{max} : voxel with the maximum uptake.
- b) SUV_{peak} : 1.0-cm diameter spherical volume of interest, centred on the maximum voxel.
- c) SUV_{mean} : mean of values within the VOI.
- d) SUV_{50} : 50th percentile value of SUV distribution.
- e) 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 48Gy in four fractions (12 Gy per fraction alternate days), 54Gy in three fractions (18 Gy per fraction alternate days) for peripheral tumours, and 60 Gy in eight 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 three months in the first year, six-monthly 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 three 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 three cohorts using the Kruskal-Wallis test. The motion of tumor was compared using Wilcoxon Rank Sum test. The correlation of non-gated and respiratory gated FLT scans were performed using Spearman correlation coefficient. The SUV_{max} of FLT-PET and FDG -PET in cohort 1 were compared using the paired Wilcoxon-test. Statistical significance was set at $p < 0.05$.

Results

From January 2015 to April 2021, 41 patients were accrued to the study. There were 20 patients in cohort 1, 16 patients in cohort two, and five in cohort 3. Due to poor accrual in cohorts 2 and 3, the study was closed after five 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). Males constituted 61% of the cohort. Table 1 summarizes the baseline characteristics. Thirty patients (73%) were treatment naïve, eight patients had previous surgery (lobectomy or wedge resection) and three had prior SBRT for stage I lung cancer. Most were diagnosed with stage I lung cancer (80.5%), and adenocarcinoma was the most common histology. Ten patients were treated without a tissue diagnosis. 48Gy in four fractions was the most common dose fractionation (83%). Two patients in the fibrosis cohort received SBRT to new primary lesions; one received 48Gy in four fractions and another 60 Gy in eight fractions.

FLT PET variables

A non-gated FLT-PET was performed for all patients, while a respiratory-gated FLT-PET was done in 35 patients due to equipment non-availability. 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 cohort 1, 2 and 3 were 3.3 years, 4.6 years and 3 years respectively. The median time to FLT-PET in cohort 2 was 1.5 years (range 0.5-7.3 years), while in cohort 3 was 1.3 years (range 0.9-2.7 years).

Table 2 shows the FLT-PET variables across the cohorts. Using the non-gated 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 compared to the fibrosis cohort (Figure 1).

The average superior-inferior tumor motion was 0.48 cm (Standard deviation (SD): 0.5; range: 0.01-2.8cm) for the whole cohort and was similar between pretreatment and fibrosis/recurrence cohort (0.45 vs 0.52 cm, $p=0.36$). 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 non-gated scans, and there was good correlation in the SUV variables ($r=0.8-1$), as shown in figure 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=0.003). None of the patients in cohort 2 underwent biopsy. In cohort 3, recurrences were based on radiological findings in most. FDG-PET/CT was performed in 3 patients at recurrence. Biopsy was attempted in 2 patients; one was negative, and the other confirmed adenocarcinoma (Supplementary material, Figure 1). Based on the prior study by Hiniker et al., we assessed the ratio of SUV_{max} of the tumour to the mediastinal blood pool in the recurrence cohort (Table 3)³⁰. In four of the five patients, the SUV_{max} and ratio of SUV_{max} of the tumour to the mediastinal blood pool was greater than 2.

Discussion

Surveillance and detection of recurrence in patients treated with SBRT for lung cancer is challenging due to fibrosis on CT scans³³. Various strategies including CT based radiomic signatures, apparent diffusion coefficient maps from MRI, and PET have been tried to differentiate fibrosis from recurrence^{14,16}. FDG-PET measures glucose metabolism and is the most common PET tracer used across malignancies to evaluate recurrence. Due to non-specific uptake in inflammatory tissue, its use in post-treatment settings led to equivocal findings and the evaluation of other PET tracers^{22,34}. FLT-PET has emerged promising as it is specific for tumor proliferation and shows minimal uptake in inflammatory tissues^{35,36}. The present study evaluated FLT-PET in a cohort of lung cancer patients treated with SBRT. It showed that FLT-PET SUV_{max} 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 radiotherapy in lung cancer³⁷⁻³⁹. Everitt et al. compared the response following radical chemoradiation in lung cancer patients between FDG versus FLT-PET²⁸. They found median SUV_{max} values were lower with FLT than FDG post-therapy. 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 radiotherapy for lung cancer³¹. Twenty-eight patients (45%) received SBRT alone, and the FLT and FDG SUV_{max} values were higher in those who relapsed. A pilot study by Hiniker et al. evaluated FLT-PET in 10 patients treated with SBRT/hyperfractionated radiotherapy to the lung with equivocal FDG-PET for assessment of recurrence³⁰. FLT-PET accurately differentiated inflammatory changes from recurrence in 7 of 8 patients (87.5%). The FLT parameters – high SUV_{max} and the ratio of SUV_{max} of the lesion to SUV_{max} of the mediastinal pool more than two was indicative of recurrence. In the present study, four out of 5 patients in the recurrence cohort had SUV_{max} greater than two and ratio of the lesion to mediastinal SUV_{max} more than two.

The role of FLT-PET in the diagnosis of lung cancer has been studied, and it shows high specificity, but low sensitivity compared to FDG-PET, making it attractive to differentiate malignant from benign lung nodules²⁶. The uptake of FLT is low compared to FDG at diagnosis⁴⁰. The baseline FLT SUV_{max} may carry a prognostic value. Saga et al. showed that in 20 lung cancer patients treated with carbon ion radiotherapy, patients who developed recurrence or died during follow up had high pretreatment FLT uptake and those with FLT SUV_{max} less than 3.7 had better progression-free survival⁴¹. In the present study, the SUV_{max} 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 SUV_{max}, SUV_{mean} or SUV_{peak} to assess the response or for prognosis³⁶. To evaluate recurrence, while Hiniker et al. used SUV_{max} and ratio of SUV_{max} to the mediastinal pool, Christensen evaluated various parameters like SUV_{max}, SUV_{peak}, PTV 80% and 50%^{30,31}. In the present study, we used SUV_{max}, SUV_{mean}, SUV_{peak}, 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 (isotope injection and imaging time,

fasting duration, different scanners, blood glucose concentration)⁴². There is a need for standardization of reporting of SUV values across institutions and adherence to guidelines⁴³⁻⁴⁵.

PET images are affected by partial volume effects which are intensified in lung due to respiratory movement⁴⁶. This effect is significant for FLT-PET, where the signal to background ratio is lower compared to FDG-PET. In a study comparing 4D and non-gated FDG-PET, 4D PET defined moving tumors better and reduced blurring⁴⁷. We did not find any statistically significant difference in our FLT-PET SUV variables between non-gated 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 non-gated 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 4DPET reconstructions significantly reduced the blur⁴⁸. 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 non-gated FLT-PET with reporting of SUV max and SUV 95 values is recommended.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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48. XXXXX

Figure legends:

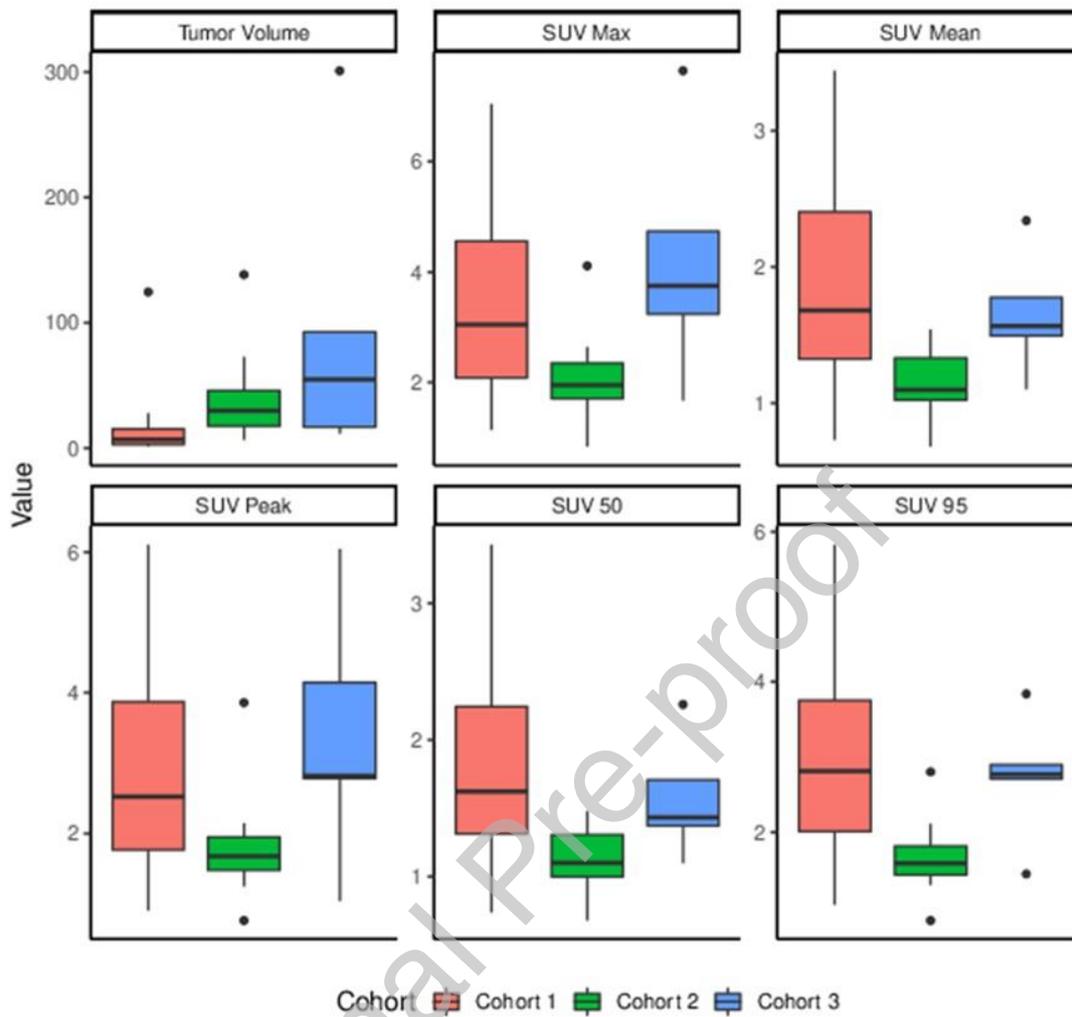


Figure 1: Box plot showing the non-gated FLT PET variables in the cohorts.

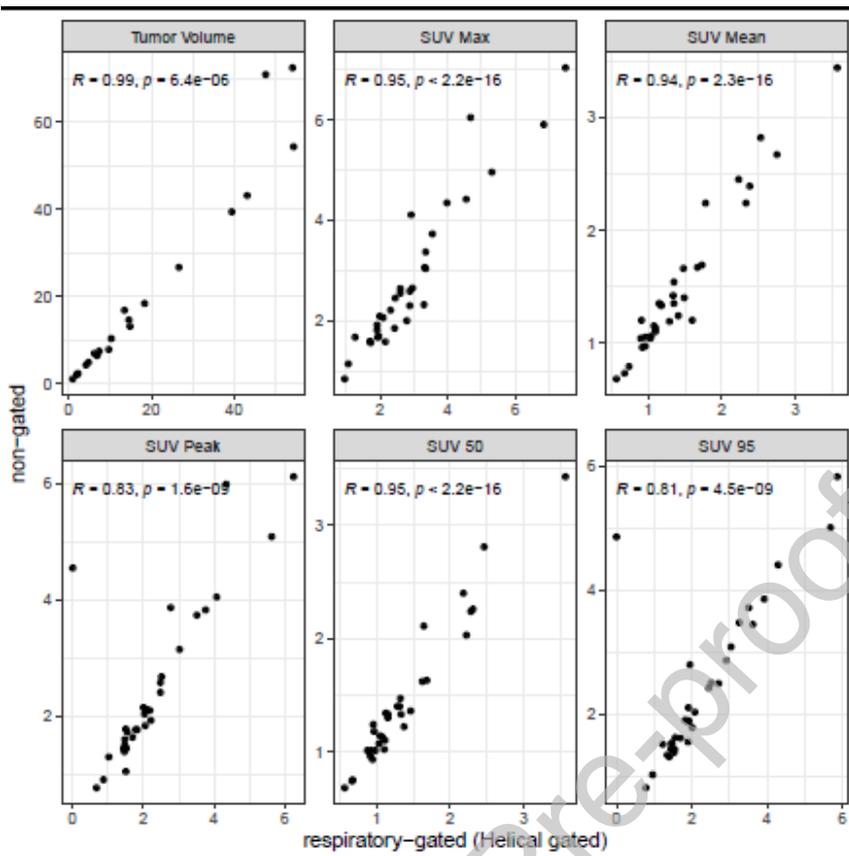


Figure 2: Scatter plots showing the correlation of SUV variables between non-gated FLT PET and respiratory gated (helical gated) scans.

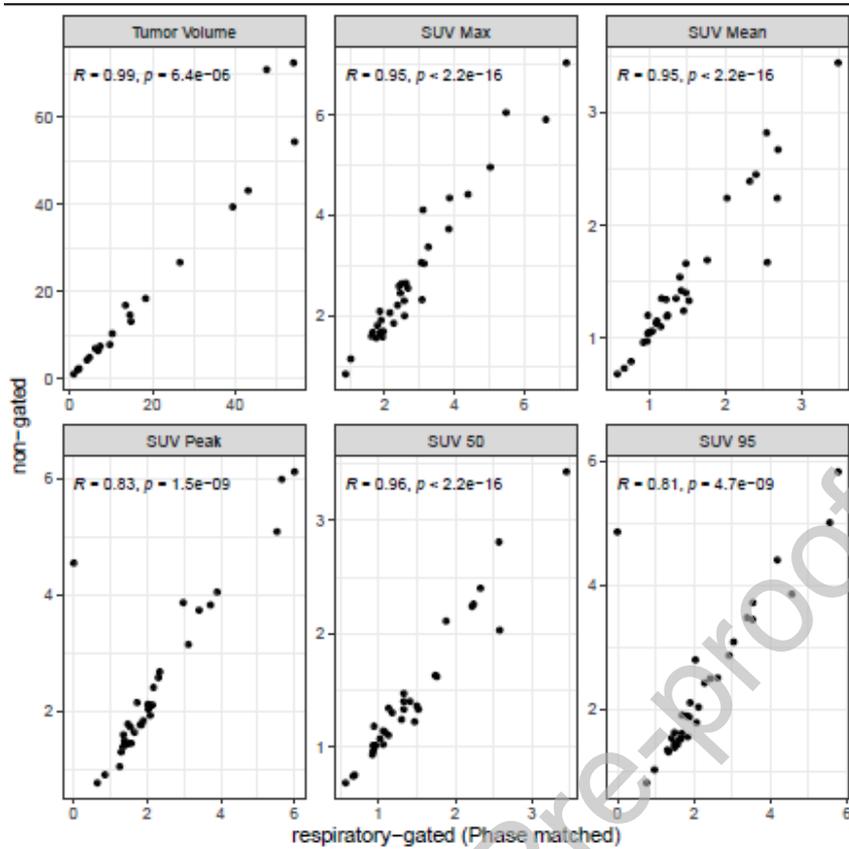


Figure 3: Scatter plots showing the correlation of SUV variables between non-gated FLT PET and respiratory gated (phase matched) scans.

Supplementary material:

Figure 1: A patient in cohort 3 with mass like lesion on follow-up computed tomography scan suspected for recurrence (A) and subsequently proven on biopsy. The lesion was metabolically active with SUV max of 7.3 on FDG PET (B) and SUV max of 3.2 on non-gated FLT PET (C).

Tables: Table 1: Baseline characteristics.

Characteristic	Cohort 1 (n=20)	Cohort 2 (n=16)	Cohort 3 (n=5)	Total (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				
48Gy in 4 fractions	17	13	4	34 (83%)
60Gy in 8 fractions	3	3	1	7 (17%)

*AJCC TNM: American Joint Committee on Cancer, tumor node metastases, # SBRT: stereotactic body radiotherapy

Table 2: FLT PET SUV variables across the cohorts.

Variable	Cohort 1 (n=20)	Cohort 2 (n=16)	Cohort 3 (n=5)	P value
SUV _{peak}				
Mean (SD)	3 (1.5)	1.8 (0.7)	3.4 (1.9)	0.015
Median (Range)	2.5 (0.9-6.1)	1.7 (0.8-3.9)	2.8 (1-6)	
SUV _{mean}				
Mean (SD)	1.9 (0.8)	1.1 (0.2)	1.7 (0.5)	0.0011
Median (Range)	1.7 (0.7-3.4)	1.1 (0.7-1.5)	1.6 (1.1-2.3)	
SUV _{max}				
Mean (SD)	3.5 (1.7)	2.1 (0.7)	4.2 (2.2)	0.0093
Median (Range)	3 (1.1-7)	2 (0.8-4.1)	3.7 (1.7-7.6)	
SUV ₅₀				
Mean (SD)	1.8 (0.7)	1.1 (0.2)	1.6 (0.4)	0.0017
Median (Range)	1.6 (0.7-3.4)	1.1 (0.7-1.5)	1.4 (1.1-2.3)	
SUV ₉₅				
Mean (SD)	3 (1.3)	1.6 (0.4)	2.7 (0.9)	0.0019
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)	0.015
Median(Range)	6.7 (1-124.5)	29.8 (6.4-138.3)	54.8 (11.2-301)	

Table 3: FLT and FDG parameters in recurrence cohort.

Patient	SUV max- FDG	SUV max- FLT	Ratio of SUV max lesion-FLT and SUV max 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

*NA- Not available

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