Utility of ^{18}F-FDG PET/CT in metabolic response assessment after CyberKnife radiosurgery for early stage non-small cell lung cancer

Ngoc Ha Le[1*], Hong Son Mai[1], Van Nguyen Le[2], Quang Bieu Bui[2]

[1]*Department of Nuclear Medicine*
[2]*Radiosurgery and Radiation Oncology Department*
108 Military Central Hospital

Received 16 December 2016; accepted 27 February 2017

Abstract:

Objective: **To assess metabolic tumor response using ^{18}F-FDG PET/CT scan in early stage non-small cell lung cancer (NSCLC) treated by CyberKnife radiosurgery.** ***Materials and Methods*****: 30 patients were diagnosed proven by biopsy and inoperable stage I NSCLC, and were enrolled into this study. ^{18}F-FDG PET/CT was performed prior to the program, and at three months following the radiosurgery treatment. The tumor maximum standardized uptake value (SUVmax) was recorded for each time point and the PERCIST criteria was applied to assess tumor response.** ***Results:*** **30 patients with NSCLC, stage me after CyberKnife radiosurgery was followed-up after 12 months. The 1-year Kaplan-Meier local control estimate was 96.7%, the cut-off of SUVmax was 10, and revealed the local tumor control to have a statistically significant difference. Mean tumor SUVmax before treatment was 10.5±3.25 (range, 5.0 to 20). During early follow-up the mean SUVmax in the tumor remained high due to peritumoral radiation-induced pneumonitis visible on CT imaging. After radiosurgery for six months, ^{18}F-FDG PET/CT images showed that 21 of 30 patients (70%) had a partial metabolic response, 8 of 30 patients (26.7%) had stabilized diseases, and one patient (0.3%) had disease progression. Meanwhile, CT could not reveal the progressed patient.** ***Conclusions:*** **Local control following CyberKnife radiosurgery for stage I NSCLC is acceptable. Transient increases in tumor SUVmax are likely related to radiation-induced pneumonitis. The value of ^{18}F-FDG PET/CT imaging for early metabolic tumor response after stereotactic body radiation therapy (SBRT) could be higher than anatomic response on CT.**

Keywords: ***CyberKnife radiosurgery, non-small cell lung cancer, SBRT, ^{18}F-FDG PET/CT.***

Classification number: *3.2*

Introduction

Stereotactic Body Radiation Therapy (SBRT) is a proven treatment option for inoperable stage I NSCLC [1]. Several techniques have been employed to treat these potentially mobile tumors. Treatments require accurate, safe, and swift delivery of extremely high doses of radiation. As anticipated, SBRT has improved local control and overall survival rates relative to historical controls. Up to now, the enhanced accuracy and flexibility of the CyberKnife method facilitated the safe delivery of dose distributions designing to eradicate both gross tumor and known microscopic disease radiating. Focal radiation-induced pneumonitis and fibrosis may be seen as a side effect of treatment, hampering the assessment of the tumor response using CT and ^{18}F-FDG PET imaging [2]. However, approximately 10% of these patients developed local recurrences after high-doses of SBRT. Tumor hypoxia also plays an important role in radio-resistance. In recent studies, reductions of the diameters of CT suggestive hypoxic conditions within a tumor have been shown to correlate with local recurrence [3]. However, metabolic response was found in a few studies, having a significant impact on the biological behaviors of malignant tissue including NSCLC [4]. Metabolic response may have higher sensitivity in diagnostic and assessment treatment response. The relationship between pre-treatment and post-treatment glucose metabolism measurements has not yet been fully elucidated in NSCLC. In Vietnam, to our best knowledge, there has not been any articles related to this topic published. Following the reasons mentioned above, the aim of this study was to investigate the utility of ^{18}F-FDG PET/CT in the assessment of treatment responses and the prognostic impacts of SUVmax on local control (LC) in patients with SBRT- treated NSCLC.

[*]*Corresponding author: Email: lengocha108@yahoo.com*

Materials and methods

This study was approved by the hospital institutional review board. 30 patients were consecutively treated on a single institution prospective protocol with inoperable biopsy proven clinical stage I NSCLC, and were evaluated. Inoperability was defined as a post-operative predicted forced expiratory volume in one second (FEV1) of less than 40%, heart disease, diabetes, and patients refusal of operation. The performance status is rather good with ECOG 0-2. The patients in stage II, III, IV, FEV1 < 1,000 ml/minute, ECOG 3-4 were excluded. Patients were treated according to protocol using at the CyberKnife Radiosurgery Center, located at 108 Military Central Hospital. Briefly, fine-cut (1-mm) treatment planning CTs were obtained over 7-10 days after a CT-guided percutaneous biopsy and fiducial placement. Gross tumor volumes (GTV) were contoured utilizing lung windows. The GTV margin was expanded by 5 mm to establish the planning treatment volume (PTV). A treatment plan was generated using the CyberKnife non-isocentric, inverse-planning algorithm with tissue-density heterogeneity corrections for lungs. The radiation dose ranged from 42-60 Gy in three fractions, and was prescribed to an isodose line that covered at least 95% of the PTV and resulted in the 30-Gy isodose contour extending a minimum of 1 cm from the GTV.

^{18}F-FDG PET/CT imaging was performed two weeks prior to CyberKnife radiosurgery and at three months following the radiation treatment. CT was used for attenuation correction of the PET emission image data. Quantitative values of tumor metabolic activity were expressed as tumor SUVmax, defined as the maximum standardized uptake value within the tumor. Values were obtained using three-dimensional regions of interest placed on lung lesions, which were anatomically defined by combined review of the PET and CT images. Local tumor recurrence was defined as unequivocal progression on serial ^{18}F-FDG PET/CT imaging. Biopsy was required to confirm recurrence if needed. Clinical follow-up was consecutively at 6 and 12 months afterward. For patient preparation, the serum glucose levels were checked to exclude hyperglycemia. Afterwards, the patients were allowed to rest in the waiting room before an intravenous injection of 2.5 MBq/kg body weight (±10%) of ^{18}F-FDG PET and low-dose CT scans from cranial top to the mid-thigh were performed 60 min after the ^{18}F-FDG injection was given, as is standard procedure. In general, ^{18}F-FDG PET/CT was read independently by one of two nuclear medicine physicians with thorough knowledge about the patient's clinical history; then, the other physician reviewed all lesion-related findings and impressions. Disagreements were resolved by consensus. A positive lesion on ^{18}F-FDG PET/CT imaging was defined as a focal ^{18}F-FDG uptake with relatively higher activity than that of the surrounding normal tissue or when the SUVmax of the lesion was revealed to be more than 2.5. Treatment response criteria based on RECIST 1.1 and PERCIST as prescribed on articles published previously [5].

Data was analyzed and graphs were prepared with the SPSS 18.0 statistical package. The follow-up duration was defined as the time from the date of completion of treatment to the last date of recurrence or at the end of study (12 months). Actuarial local control was calculated from the conclusion of treatment using the Kaplan-Meier method. The T-test and Mann-Whitney Tests were used for mean and median comparison. The confidence intervals (95%) were determined.

Results

Table 1. Clinical characteristics of NSCLC patients.

Clinical characteristics	Number (n = 30)	Percentage (%)
Mean age±SD	66.3±10.74	
Age < 60	7	23.3
Age ≥ 60	23	76.7
Gender		
Male	24	80.0
Female	6	20.0
Histopathology		
Adenocarcinoma	16	53.3
Squamous cell	7	23.3
Large cell	4	13.3
Others	3	10.0
T-Stage		
T1a	2	6.7
T1b	6	20
T2a	22	73.3

The total patients in this study were 30 objects, followed-up over 12 months (Table 1). The median age and SD were 66.3±10.74 (range, 55-80). The group of age were divided in to two subgroups under 60 (23.3%) and over 60 (76.7%). The percentage of male patients was four-fold higher than that of

female patients. Among histopathologic types of non-small cell lung cancer in this study, adenocarcinoma occurred in more than half of cases. According to T-stage, T2a was seen more frequently with 73.3%. This figure is much higher than those of T1a and T1b.

Table 2. Characteristics of NSCLC tumors on ^{18}F-FDG PET/CT imaging.

Characteristics of tumors		Number (%)	SUVmean±SD	p
Location of tumor	Right lung	21 (70)	10.2±3.5	> 0.05
	Left lung	9 (30)	9.5±3.46	
	Peripheral	20 (67)	9.6±2.67	> 0.05
	Central	10 (33)	11.2±5.7	
Longest diameter of tumor	Mean±SD	3.71±0.95	-	
	<20 mm	25 (75)	7.5±3.52	> 0.05
	>20 mm	5 (25)	11.6±4.31	
Histopathology	Adenocarcinoma	16 (53.4)	15.7±4.32	p = 0.022
	Squamous cell	7 (23.3)	10.4±3.67	
	Others	7 (23.3)	7.68±4.33	

The primary tumor was observed to be 70% on the right and 67% at the peripheral lung, the percentage was even higher than that on the left and the central lung (Table 2). The mean of the longest diameter of the tumor was 3.7±0.95, and the diameter under 20 mm was seen more frequently than those larger than 20 mm. Among all of histopathology types, adenocarcinoma (AD) was the most popular with 53.4%, squamous cell (SCC) and others was 23.3% for each of the types. There were no significant difference in the SUVmean±SD between positions of the tumor and diameters of the tumor (p>0.05). However, the significant difference between the histopathologic types was noted (p=0.02).

After three months of SBRT, almost SUVmax had been going down. However, there were several cases in which SUVmax had transient elevations (Fig. 1). Mean±SD of SUVmax before treatment was decreased from 10.5±3.25 to 5.3±4.1 after treatment of three months (p <0.05).

Assessing by RECIST criteria on CT (anatomic criteria), statistics shows 18 of 30 patients had partial response, 12 of 30 patients had disease stability, and disease progression was not seen in any patient. Regarding the PERCIST criteria (metabolic criteria), the number of partial responses was 21 of 30 higher than those of RECIST, and the number of stable diseases had decreased (Fig. 2). Moreover, ^{18}F-FDG PET/CT scan revealed

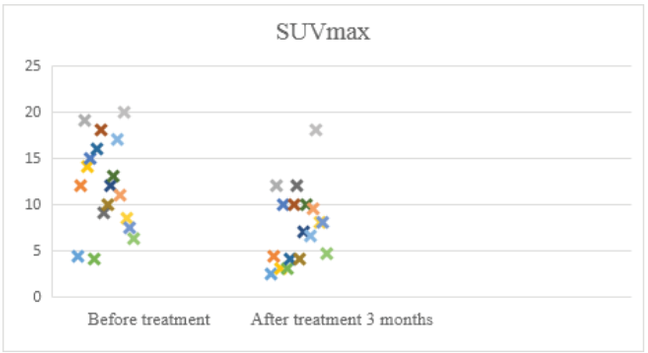

Fig. 1. The change of SUVmax in primary NSCLC tumors before and after radiosurgery.

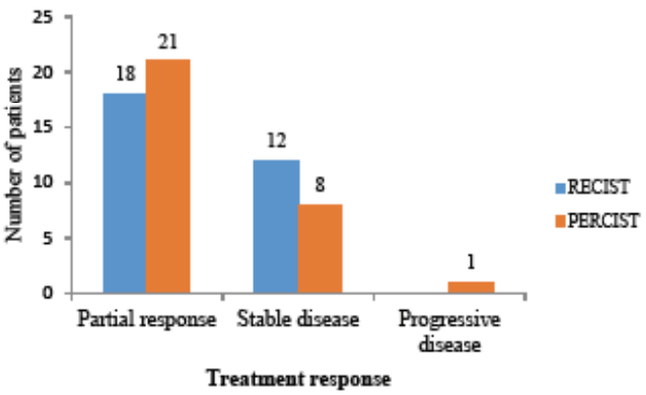

Fig. 2. Comparison of metabolic and anatomic treatment response assessment.

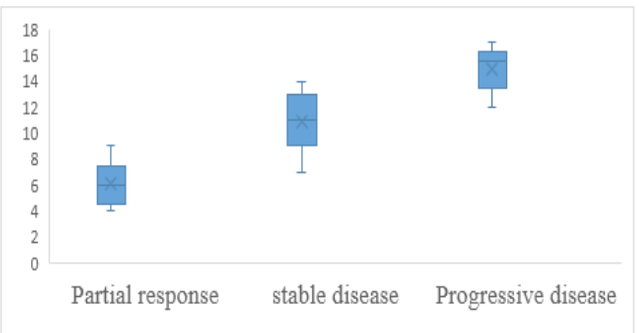

Fig. 3. The relation between the SUVmax and levels of treatment response.

one patient with distant metastases and recurrence after treatment for three months.

The SUVmax mean measured on the primary tumor of partial response, stabling diseased and progressing diseased patients, was 6.1±2.1, 10.3±3.21 and 15.2±2.42 respectively. The SUVmax of the primary tumor in progressing diseased patients tended to be greater than that of the primary tumor in partial response patients (p<0.05) (Fig. 3).

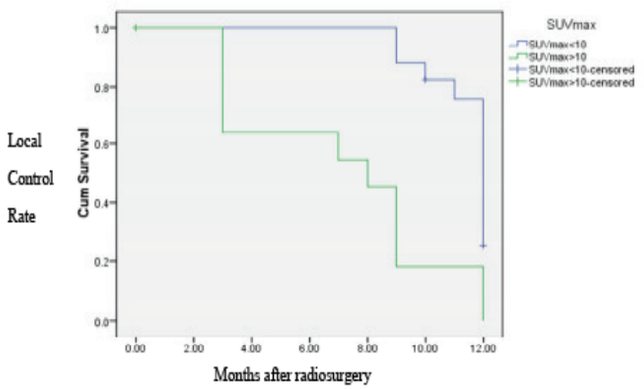

Fig. 4. Kapplan - Meier curves of local tumor control with a cut-off SUVmax at 10.

Following-up by CT after three months, six months, and 12 months after the SBRT, there were significant difference in local control estimations between patients with SUVmax under ten and above ten measured on primary tumor before treatment (Fig. 4).

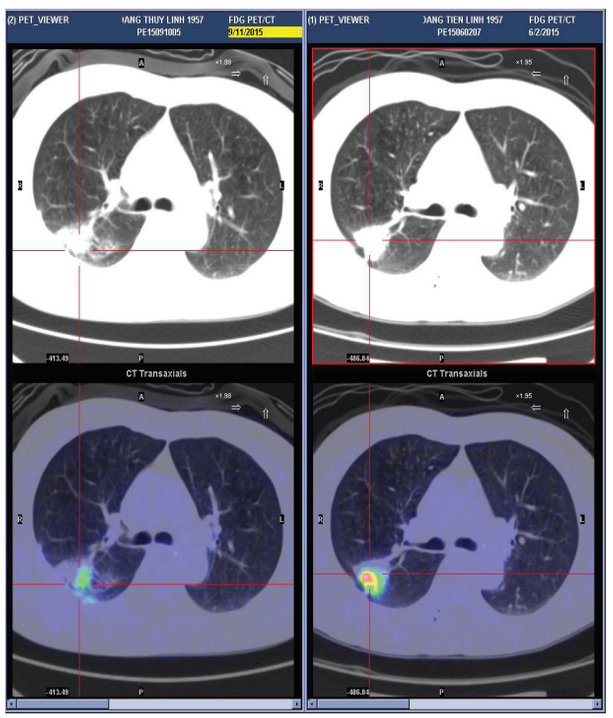

Fig. 5. NSCLC patient (78-years old, man with adenocarcinoma of lower right lobe of lung, T1aN0M0) was treated with CyberKnife radiosurgery with three fractions.

Before treatment (left), ^{18}F-FDG PET/CT showed a tumor with 25 x 28 mm in diameter, SUVmax: 15,8. After three months radiosurgery (right), SUVmax decreased to 3.0 although the diameters seem to be significantly unchanged.

Discussion

Several studies have published reports that documented deficiencies with CT tumor response assessment using the SBRT by the CyberKnife radiosurgery protocol for inoperable stage I NSCLC patients [2, 6]. CyberKnife radiosurgery delivered to lung tumors with adequate marginal damages to the peritumoral lung tissue, and often causes acute radiation pneumonitis. The lung injury has been shown to be repaired typically by inflammation in asymptomatic focal lung parenchyma fibrosis in the region corresponding to the high-dose radiation volume. Evidence of focal radiation induced pneumonitis and fibrosis was consistently observed within the target volumes of our patients during follow-up as well. ^{18}F-FDG PET/CT is the standard imaging staging for NSCLC at our hospital. It is both more sensitive and specific than conventional imaging for the detection of primary lung tumors, involved regional lymph nodes and distant metastases. Primary lung tumors with a SUVmax greater than 2.5 are considered malignant until proven otherwise. However, preliminary evidence suggested that like CT imaging, ^{18}F-FDG PET imaging is limited in assessing local tumor control following SBRT due to early elevations in tumor SUVmax, which are thought to be related to acute radiation induced pneumonitis. Therefore, prior to starting protocol therapy, the decision was made to routinely observe inoperable NSCLC patients with early transient elevations in tumor SUVmax following radiosurgery. Understanding this mechanism is very important to assess treatment response, in this study there were several cases when SUVmax increased after three months of SBRT. However, the CT imaging features of pneumonitis has been realized and the patients should be follow-up further. Pulmonary injury following radiation may commonly be seen in a metabolically active ^{18}F-FDG-avid lesion, rising transiently after treatment of SBRT up to two months. In our study, the cut-off SUVmax may be due to pneumonitis is 4.5. Most evidence supported a SUVmax of approximately 5.0 as a clinically useful threshold for the distinction between recurrence and fibrosis [7].

Recommendations for imaging follow-up after SBRT are generally based on retrospective evidence and expert opinion. The aim of follow-up actions serve three major goals including the detection of local recurrence and metastatic lesions occurred approximately of 2-10% per person-year [8, 9]. Tumor response assessment following definitive treatment is typically categorized according to Response Evaluation Criteria in

Solid Tumors (RECIST) 1.1 as complete (disappearance of the target), partial (≥30% decrease), stable disease, or progression (≥20% increase) according to the diameter of the target tumor [10]. However, RECIST 1.1 has limitation, since the target lesion may actually represent lung fibrosis, and response may be misdiagnosis. ^{18}F-FDG PET scans are recommended in lung cancer diagnosis and re-staging, metabolic imaging currently has a limited clinical trial data in the evaluation of tumor response and detection of local recurrence. Nevertheless, metabolic criteria assessed by ^{18}F-FDG PET/CT may reveal the earlier treatment response than anatomic response. In our study, there was no complete metabolic response due to SUVmax transient elevation. Based on PET/CT imaging the number of patients of partial response was higher than that on CT imaging. The reasons could be understood that the biomarker imaging on PET is more sensitive than anatomic imaging. Although the diameters of primary lung tumors were unchanged significantly, the SUVmax was sharply decreased. Since, then the whole-body PET/CT is dominant of detection of distant metastases, this modality also revealed a progressive patient with suspicious recurrent on CT imaging. Generally, there is not any publications reported the status of tumor response but almost papers describe the rate of local control after SBRT. As can be seen on Kaplan Meier curve, the cutoff SUVmax in primary tumor is 10 in this study. The difference of local control between groups of SUVmax under 10 is significant higher than that of SUVmax upper 10. In contrast to other studies, this investigation is related to serial imaging and follow-up. Routine biopsy was not justified following radiosurgery and the risk associated with biopsy in this inoperable patient population. Therefore, confirmation of radiographic impressions was limited to a single biopsy in one patient following an increase in tumor SUVmax; biopsies were not taken to confirm the absence of the disease in cases in which tumor SUVmax remained low. Therefore, it is likely that the true local control rate in this study is less than our reported 95% rate. Furthermore, this difference in local control rates could be considerable in patients with low pre-treatment tumor SUVmax values. Shibamoto et al. presented that, a higher SUVmax according to pretreatment ^{18}F-FDG PET/CT in NSCLC was found to be a significant predictor of local recurrence after SBRT [7]. In our study, SUVmax mean in progressive disease was higher than that of stable disease and partial response patients.

Conclusions

Local control and treatment response following CyberKnife radiosurgery for stage I NSCLC is acceptable. However, transient SUVmax elevation in acute radiation induced pneumonitis may hinder early metabolic tumor response assessment. The value of ^{18}F-FDG PET/CT imaging for survival long term following lung SBRT should be deserved by further study.

ACKNOWLEDGMENTS

This study was supported by the Ministry of Science and Technology of Vietnam. We would like to thank all the staff at the Department of Nuclear Medicine for their assistance in data analysis.

REFERENCES

[1] J.A. Katzel, M.P. Fanucchi, Z. Li (2009), "Recent advances of novel targeted therapy in non-small cell lung cancer", *J Hematol Oncol.,* **2**, p.2.

[2] T. Takeda, et al. (2004), "Radiation injury after hypofractionated stereotactic radiotherapy for peripheral small lung tumors: serial changes on CT", AJR *Am J Roentgenol.,* **182(5)**, pp.1123-1128.

[3] M. Aoki, et al. (2016), "Prognostic impact of average iodine density assessed by dual-energy spectral imaging for predicting lung tumor recurrence after stereotactic body radiotherapy", *J Radiat Res.,* **57(4)**, pp.4-12.

[4] P. Baumann, et al. (2009), "Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy", *J Clin Oncol.,* **27(20)**, pp.3290-3296.

[5] Wahl, L. Richard, et al. (2009), "From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors", *Journal of nuclear medicine,* **50**, Suppl 1, pp.122S-150S.

[6] Nakajima, Naomi, et al. (2013), "Differentiation of tumor recurrence from radiation-induced pulmonary fibrosis after stereotactic ablative radiotherapy for lung cancer: characterization of ^{18}F-FDG PET/CT findings", *Annals of Nuclear Medicine,* **27(3)**, pp.261-270.

[7] Y. Shibamoto, et al. (2012), "Stereotactic body radiotherapy using a radiobiology-based regimen for stage I non-small cell lung cancer: a multicenter study", *Cancer.,* **118(8)**, pp.2078-2084.

[8] M. Dahele, et al. (2011), "Radiological changes after stereotactic radiotherapy for stage I lung cancer", *J Thorac Oncol.,* **6(7)**, pp.1221-1228.

[9] F. Lou, et al. (2013), "Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance", *J Thorac Cardiovasc Surg.,* **145(1)**, pp.75-81.

[10] E.A. Eisenhauer, et al. (2009), "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)", *Eur J Cancer,* **45(2)**, pp.228-247.