HOSPITAL CHRONICLES 2016, 11(1): 29–34

REVIEW

The Role of Fluorodeoxyglucose Standardized Uptake Value in Diagnosis, Staging and Restaging of Non-Small Cell Lung Cancer

Maria Boudali, MD,[1] Evangelia Skoura, MD, PhD,[1,2]
Ioannis E. Datseris, MD, PhD,[1] Konstantinos N. Syrigos, MD, PhD[3]

[1]*Nuclear Medicine Department, Evagelismos General Hospital, Athens, Greece*
[2]*Insitute of Nuclear Medicine, University College London Hospitals (UCLH), London, United Kingdom*
[3]*Oncology Unit GPP at University of Athens, School of Medicine, Athens, Greece*

KEY WORDS: *[18F]fluorodeoxyglucose; positron emission tomography; lung cancer; standardized uptake value; non-small lung cancer*

Abbreviations
BAC = bronchioloalveolar carcinoma
FDG = [18F]Fluorodeoxyglucose
MRI = magnetic resonance imaging
NSCLC = non-small cell lung cancer
PET/CT = positron emission tomography / computed tomography
SUV = standardized uptake value
TNM = tumor-node-metastasis (staging system)
WHO = World Health Organization

Correspondence to:
Maria Boudali, Nuclear Medicine Department, Evagelismos General Hospital, Ipsilantou 45-47, Athens 106 76, Greece; Tel: +30-213-2045741; E-mail: marympou1@gmail.com

Manuscript received June 12, 2015; revised manuscript received January 7, 2016; Accepted January 8, 2016

ABSTRACT

Molecular imaging with [18F]-fluorodeoxyglucose positron emission tomography / computed tomography ([18F]FDG-PET/CT) has become part of the standard of care in oncology patients. In oncology, the quantification for the analysis of PET data is an important tool for tumor diagnosis, staging, determination of prognosis and assessment of response to treatment. In clinical practice, standardized uptake value (SUV), a semi-quantitative parameter, is the most widely used parameter for the analysis of tracer uptake in PET imaging. The purpose of this review is to evaluate the role of the SUV in diagnosis, staging and restaging of the lung cancer, and also to establish the differences in [18F]FDG uptake across different histopathological subtypes of non-small lung cancer (NSCLC). Furthermore another purpose of the study is to gather and compare the SUVmax cut-off values, in differentiating benign from malignant lesions, in assessing the response to treatment and finally to identify the optimal threshold.

INTRODUCTION

The combination of functional metabolic and anatomical data has been available since 2001, when the combined positron emission tomography / computed tomography (PET/CT) scanner was introduced. This technology has had a significant impact on many medical disciplines, including cardiology and neurology but undoubtedly the greatest impact has been in the field of oncological imaging. In clinical practice, visual inspection of PET/CT images is the main tool for image interpretation and for staging or restaging. Ultimately, PET using [18F]fluorodeoxyglucose (FDG) was developed as a quantitative tool and its quantitative characteristics are increasingly being recognized as providing an objective, more accurate, and less observer-dependent measure for prognosis and response monitoring purposes than visual inspection alone. The most commonly used measure of [18F]FDG uptake is the *standard uptake value* (SUV). Other synonymous terms for SUV, in the literature, are DUR (dose uptake ratio) or SUR (standard uptake ratio).[1] The definition of SUV is tissue uptake (μCi/mL)

Disclosure: The authors declare that they have no conflict of interest

divided by whole body administered activity, normalized for body weight (mCi/Kg).[1]

$$\text{SUV} = \text{tissue uptake } (\mu\text{Ci/mL}) / \text{administered activity } (\text{mCi/Kg})$$

The standardized uptake value although it is regarded as unitless, it has the dimensions of density (g/mL) but most of the body has density close to 1.0, so the units are usually ignored.[2] Although SUV is a simple, straight forward concept, there are significant problems with it. Table 1 lists the most important sources of error concerning SUV, which we have to avoid.[2]

LUNG CANCER DIAGNOSIS

Lung cancer imaging using PET with the glucose analogue [^{18}F]FDG is based on the enhanced glucose metabolism of cancer cells. [^{18}F]FDG undergoes the same uptake as glucose but is metabolically trapped and accumulated in the cytoplasm of cancer cells after phosphorylation by hexokinase. The pattern of [^{18}F]FDG distribution in the body detected on PET/CT allows differentiation between normal and malignant tissues. In questionable cases of pulmonary nodules, the prolonged observation of the metabolic activity and the SUV value in delayed imaging, meaning at 90 minutes post injection or more, has been proven to aid in the differential diagnosis. Hilar or mediastinal lymph nodes with [^{18}F]FDG uptake higher than the surrounding tissue, as determined by qualitative analysis and SUVmax value more than 2 (as determined by quantitative analysis), were considered positive findings. Also, the assessment of the SUVmax in PET/CT findings has the potential to differentiate an adenocarcinoma in situ and minimally invasive adenocarcinoma from invasive adenocarcinomas. A study from 2009, when the term bronchioloalveolar carcinoma (BAC) was still used, showed that the SUVmax can differentiate the adenocarcinoma with BAC from other subtypes of non-small cell lung cancer (NSCLC).[3] A nodule with a mixed pattern with partly solid and ground glass opacity was significantly more frequent CT feature of an adenocarcinoma with BAC (50%) compared to the other subtypes (1.8%) ($p<0.0001$).[3] Maximum SUV of adenocarcinoma with BAC was significantly lower than that of other subtypes of NSCLC ($p<0.0001$). Sensitivity, specificity, positive predictive value, and negative predictive value of CT for differentiating adenocarcinoma with BAC from other subtypes was 50%, 98.2%, 80%, and 93%, respectively.[3] Sensitivity, specificity, positive predictive value, and negative predictive value of combination of two modalities, [^{18}F]FDG-PET and CT, was 81.3%, 85.3%, 44.8%, and 96.9,%, respectively.[3] Furthermore, in surgically managed lung cancer patients, SUVmax is a predictor of overall survival after resection. The addition of SUVmax to pathologic tumor size identifies a subgroup of patients at high risk for death as a result of recurrent disease after resection.[4]

STAGING

The tumor-node-metastasis (TNM) staging system is considered the most important tool to estimate prognosis and to date is the most important guide in treatment decisions. However, the TNM staging system provides an incomplete biologic profile of NSCLC, thus, it is far from perfect as a prognostic indicator. Quantitative measures of biologic aggressiveness, like [^{18}F]FDG uptake, could be better indicators

TABLE 1. The most important sources of error in the SUV measurement

Biological Factor	**Effect**
Blood glucose level	Increased blood glucose level = lower SUV value
Uptake period	Increased time interval between injection and start of PET study= higher SUV
Patient motion/breathing	Imaging artefacts in case of mismatch in position between CT and PET scan and resolution loss due to respiratory motion (possible lower SUV)
Patient comfort Inflammation	Patient stress and uncomfortable waiting conditions increase uptake of FDG in muscle and/or brown fat and may effect SUV quantification Inflammatory processes near or at the tumor site may result in a false positive increase of SUV
Error	**Effect**
Incorrect synchronization of clocks of PET camera and dose dispensing system Use of injection time rather than dose dispensing time (or use of incorrect amount of dose)	Incorrect decay correction resulting in incorrect SUV Incorrect time interval used for decay correction of the administered dose results in incorrect SUV.

CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography; SUV = standardized uptake value

for survival and risk of recurrence, and thus for selection of patients for adjuvant treatment. For prognostic stratification, the SUVmax can be calculated using a single whole-body [^{18}F] FDG-PET scan that is routinely performed in patients with NSCLC as part of their pre-therapeutic staging procedure in most of the countries worldwide, as well as in Greece. A great advantage of measurement of [^{18}F]FDG uptake is that this can be done before any treatment has been performed. The prognostic value of [^{18}F]FDG-PET at diagnosis has been evaluated in several studies. These studies have shown that the pre-therapeutic [^{18}F]FDG-PET not only improved patient staging, but also provided prognostic information (Table 2).[5-15] All studies showed that patients with low [^{18}F]FDG uptake values in their primary tumor have a significant longer overall- and progression-free survival than patients with high [^{18}F]FDG uptake. Higashi et al[16] and Sasaki et al[17] found that [^{18}F]FDG uptake in the primary tumor was a better prognostic variable than pathologic TNM system staging in predicting recurrence of patients with NSCLC. Sasaki et al observed that patients with high SUVs of their regional lymph nodes and low SUVs in their primary tumors did not experience any local or distant recurrence.[17] Therefore, it is at least speculated that the SUVs for the regional lymph nodes do not agree with and are not stronger prognostic factors than the SUVs for the primary tumor.

In previously published studies, univariate analyses have been performed to determine a cut-off point for the SUV in the primary tumor to discriminate between a more or less favorable prognosis. It has been assessed that the cut-off of SUV value ranges widely from 5 to 20. Sasaki et al and Hisaghi et al reported that the patient group with SUV cutoff value of 5 had better prognosis.[16-17] On the other edge, Dhital et al have proposed a significantly higher SUV cutoff value of 20.[18] Jeong et al,[19] as well as Vansteenkiste et al,[20] found a cut-off of 7, Downey et al[21] a cutoff of 9, and Ahuja et al[22] a cutoff of ≈10.

RESTAGING AND RESPONSE TO TREATMENT

The conventional approach to determine if a tumor is responding to chemotherapy or radiotherapy is the size measurement using computed tomography (CT) or magnetic resonance imaging (MRI) and see if the tumor is being decreased or increased in size over time. It has been proven that the metabolic changes precede changes in the tumor size.[23] Quantitative measures of FDG uptake have started to be used as a way to access response to therapy.[24-25] It is likely that SUV will become an important measure of response to therapy that will be combined with other parameters such as circulating tumor markers and size measured with CT or MRI. The major questions in using [^{18}F]FDG-PET to assess response to therapy are when to image and what decrease of SUV value is considered indicative of response. General guidelines are to wait 3-4 weeks after chemotherapy, 1 month after surgery and 3-4 months after radiotherapy.[26]

Several studies have indicated a possible role for PET in assessment of response during or after radiotherapy[25], or induction chemotherapy,[26-27] or a combination thereof.[28-32] In one of these studies, patients with a higher [^{18}F]FDG uptake on their baseline PET showed a better response to treatment. The recurrence rate was higher in lesions that revealed higher [^{18}F]FDG uptake at baseline, as well as after treatment. Also a more prominent decrease in the [^{18}F]FDG uptake was noted in patients with a response on CT measurement, compared with those with no change on CT. In the pilot study of Vansteenkiste et al,[27] who studied 15 patients before and after induction chemotherapy, a reduction in [^{18}F]FDG uptake of at least 50% in the primary tumor or mediastinal clearance proved to be a better predictor of long-term survival compared with the standard WHO criteria used for response assessment on CT. [33-34] Another study that evaluated response monitoring of induction chemotherapy showed that [^{18}F] FDG-PET identified prognostically different strata in patients considered responsive according to CT.[26] In this prospective multicenter study, [^{18}F]FDG-PET was performed before, after 1 and 3 cycles of induction chemotherapy. [26] This was the only study that evaluated [^{18}F]FDG-PET at an earlier and perhaps clinically more relevant stage of treatment. The accuracy of a dynamic [^{18}F]FDG-PET scan in the prediction of pathological tumor response was 83% to 96%.[26] The SUVmax in the mediastinal lymph nodes after completion of radio-chemotherapy predicted the histopathologic lymph node status after radio-chemotherapy with a sensitivity and specificity of 73% and 89%.[35] Significantly more patients with a larger percentage decrease in SUVmax in the primary tumor during induction therapy stayed free from extra cerebral recurrence compared with patients with a lesser response (83% vs 46% at 16 months). [35] All studies showed that [^{18}F]FDG-PET is a significant predictor of therapy outcome and provides results of great prognostic significance.

CONCLUSION

Quantitation of [^{18}F]FDG uptake using SUVmax is a simple and robust measure of the degree of uptake and thus the metabolic rate of a tumor. It is useful for assessing the probability that a mass is malignant or that a known tumor is responding to therapy. The key role of SUVmax in many parameters of [^{18}F]FDG-PET imaging allows us to have the ability to face the challenges not only in diagnosis but also in staging and restaging. It is a valuable tool that should be used on a regular basis to assist in the interpretation of [^{18}F] FDG PET studies.

TABLE 2. Studies evaluating the prognostic formation of [^{18}F]FDG uptake (SUVmax value) in patients with NSCLC

Reference	N of patients	Histology of carcinoma	Stage	Treatment	Survival	P value
5	155	Squamous 37% Adenocarcinoma 34% Large-cell 7% Undetermined 22%	I or II 45% III 35% IV 20%	Unspecified	Median survival (months) SUV >10 11.4 SUV ≤10 24.6	0.0049
6	125	Squamous 54% Adenocarcinoma 25% Large-cell 21%	I 37% II 15% IIIA 30% IIIB 18%	Resection 73% Nonsurgical 27%	2-y survival SUV >7 43% SUV ≤7 83%	0.001
7	38	Squamous 32% Adenocarcinoma 50% Large-cell 18%	I 19% II 13% IIIA 50% IIIB 3% IV 13%	Resection 76% Nonsurgical 24%	3-y survival SUV >8.72 40% SUV ≤8.72 70%	0.2256
8	77	Squamous 58% Adenocarcinoma 23% Large-cell 13% Other 5%	All stages IIIA	Not reported	Median survival SUV >20 6 SUV ≤20 33	0.001
9	57	Squamous 14% Adenocarcinoma 23% Large-cell 2% BAC 23% Adenosquamous 2%	I 81% IA 67% IB 14% II 2% III 17%	Resection 100%	5-y survival SUV >5 20% SUV ≤5 90% 5-y free survival SUV >5 17% SUV ≤5 88%	0.0002 <0.0001
10	73	Squamous 51% Adenocarcinoma 41% Large-cell 3% BAC 5%	I 44% II 23% IIIA 7% IIIB 19% IV 7%	Resection 92% Nonsurgical 8%	2-y survival SUV ≥7 56% SUV <7 96%	0.0011
11	100	Squamous 24% Adenocarcinoma 67% Large-cell 3% Adenosquamous 2% Carcinoid 4%	All T1-4,N0-2 M0	R0 resection 100%	2-y survival SUV >9 68% SUV <9 96%	<0.01
12	162	Squamous 43% Adeno or large-cell 46% Other 10%	I 40% II 16% IIIA 20% IIIB 24%	Resection 57% Radical radio 43%	2-y survival SUV >5 65% SUV ≤5 94%	0.02
13	315	Squamous 54% Adenocarcinoma 33% Other 13%	IA 19% IB 26% II 18% IIIA 23% IIIB 5% IV 9%	Resection 71% Nonsurgical 29%	Mean survival SUV ≥10 1.6 SUV <10 3.2	<0.0001
14	51	Squamous 33% Adenocarcinoma 25% Large-cell 20% Other 22%	I 41% II 22% III 37%	Radical radio 100%	2-y survival SUV ≥15 27% SUV <15 60%	<0.0001
15	137	Squamous 45% Adenocarcinoma 29% Large-cell 12% Other 14%	IIIA 43% IIIB 57%	Chemoradiation 100%	Median survival SUV >12 9 SUV <12 22	0.05

REFERENCES

1. Graham MM, Peterson LM, Hayward RM. Comparison of simplified quantitative analyses of FDG uptake. *Nucl Med Biol* 2000; 27:647-655.
2. Thie JA. Understanding the standardized uptake value, its methods and implications for usage. *J Nucl Med* 2004; 45:1431-1444.
3. Sun JS, Park KJ, Sheen SS, Yoon JK, Lee KB, Hwang SC. Clinical usefulness of the fluorodeoxyglucose (FDG)-PET maximal standardized uptake value (SUV) in combination with CT features for the differentiation of adenocarcinoma with a bronchioloalveolar carcinoma from other subtypes of non-small lung cancers. *Lung Cancer* 2009;66:205-210.
4. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. *J Clin Oncol* 2004;22:3255-3260.
5. Ahuja V, Coleman RE, Hemdon J, Patz EF, Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. *Cancer* 1998;83:918-924.
6. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. Prognostic importance of the standardized uptake value on F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. *J Clin Oncol* 1999;17:3201-3206.
7. Sugawara Y, Quint LE, Iannettoni MD, et al. Does the FDG uptake of primary non-small cell lung cancer predict prognosis? A work in progress. *Clin Positron Imaging*. 1999;2:111-118.
8. Dhital K, Saunders CA, Seed PT, O'Doherty MJ, Dussek J. [F]Fluorodeoxyglucose positron emission tomography and its prognostic value in lung cancer. *Eur J Cardiothorac Surg* 2000;18:425-428.
9. Hisaghi K, Ueda Y, Arisaka Y, et al. 18F-FDG uptake as a biologic prognostic factor for recurrence in patients with surgically resected non-small cell lung cancer. *J Nucl Med* 2002;43:39-45.
10. Jeong HJ, Min JJ, Park JM, et al. Determination of the prognostic value of [F]fluorodeoxyglucose uptake by using positron emission tomography in patients with non-small cell lung cancer. *Nucl Med Commun* 2002;23:865-870.
11. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer recection. *J Clin Oncol* 2004;22:3255-3260.
12. Sasaki R, Komaki R, Macapinlac H, et al. [18F]Fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. *J Clin Oncol* 2005;23:1136-1143.
13. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA. The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predict stage, recurrence, and survival. *J Thorac Cardiovasc Surg* 2005;130:151-159.
14. Borst GR, Belderbos JS, Boellaard R, et al. Standardized FDG uptake: a prognostic factor for inoperable non-small cell lung cancer. *Eur J Cancer* 2005;41:1533-1541.
15. Eschmann SM, Friedel G, Paulsen F, et al. Is standardized F-FDG uptake value an outcome predictor in patients with stage III non-small cell lung cancer? *Eur J Nucl Med Mol Imaging* 2006;33:263-269.
16. Van Rens MT, de la Riviere AB, Elbens HR, van den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I,II and IIIA. *Chest* 2000;117:374-379.
17. Sasaki R, Komaki R, Macapinlac H, et al. [18]Fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. *J Clin Oncol* 2005; 23:1136-1143.
18. Eschmann SM, Friedel G, Pauslen F, et al. Is standardized F-FDG uptake value an outcome predictor in patients with stage III non-small cell lung cancer? *Eur J Nucl Med Mol Imaging* 2006;33:263-269.
19. Jeong HJ, Min JJ, Park JM, et al. Determination of the prognostic value of [F]fluorodeoxyglucose uptake by using positron emission tomography in patients with non-small cell lung cancer. *Nucl Med Commun* 2002;23:865-870.
20. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. Prognostic importance of the standardized uptake value on F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. Leuven Lung Cancer Group. *J Clin Oncol* 1999;17:3201-3206.
21. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. *J Clin Oncol* 2004;22:3255-3260.
22. Ahuja V, Coleman RE, Herndon J, Patz EF Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. *Cancer* 1998;83:918-924.
23. Lowe VJ, Hoffman JM, DeLong DM, Patz EF, Coleman RE. Semiquantitative and visual analysis of FDG-PET images in pulmonary abdormalities. *J Nucl Med* 1994;35:1771-1776.
24. Graham MM. Is quantitation necessary for oncological PET studies? *Eur J Nucl Med Mol Imaging* 2002;29:135-138.
25. Ichiya Y, Kuwabara Y, Sasaki M, et al. A clinical evaluation of FDG-PET to assess the response in radiation therapy for bronchogenic carcinoma. *Ann Nucl Med* 1996;10:193-200.
26. Hoekstra CJ, Stroobants SG, Smit EF, et al. Prognostic relevance of response evaluation using [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. *J Clin Oncol* 2005;23:8362-8370.
27. Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Verbeken EK. Potential use of FDG-PET scan after induction chemotherapy in surgically staged IIIa-N2 non-small-cell lung cancer: a prospective pilot study. *The Leuven Lung Cancer Group. Ann Oncol* 1998;9:1193-1198.
28. Mac Manus MP, Hicks RJ, Matthews JP, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. *J Clin Oncol* 2003;21:1285-1292.
29. Choi NC, Fischman AJ, Niemierko A, et al. Dose-response relationship between probability of pathologic tumor control and glucose metabolic rate measured with FDG PET after preoperative chemoradiotherapy in locally advanced non-small-cell

lung cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1024-1035.
30. Mac Manus MP, Hicks RJ, Matthews JP, et al. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer* 2005;29:95-108.
31. Yamamoto Y, Nishiyama Y, Monden T, et al. Correlation of FDG-PET findings with histopathology in the assessment of response to induction chemoradiotherapy in non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2006;33:140-147.
32. Cerfolio RJ, Bryant AS, Winokur TS, Ohja B, Bartolucci AA. Repeat FDG-PET after neoadjuvant therapy is a predictor of pathologic response in patients with non-small cell lung cancer. *Ann Thorac Surg* 2004;78:1903-1909.
33. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-214.
34. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. *Invest New Drungs* 1992;10:239-253.
35. Pottgen C, Levegrun S, Theegarten D, et al. Value of 18F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in non-small-cell lung cancer for prediction of pathologic response and times to relapse after neoadjuvant chemoradiotherapy. *Clin Cancer Res* 2006;12:97-106.