Potential clinical utility of dual time point FDG-PET for distinguishing benign from malignant lesions: implications for oncological imaging

Posible utilidad clínica del estudio FDG-PET en dos tiempos para distinguir las lesiones benignas de las malignas: implicaciones para la imagen oncológica

S. Sanz-Viedma, D.A. Torigian, M. Parsons, S. Basu and A. Alavi*

Division of Nuclear Medicine, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA.

Introduction

The utility of 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) is widely recognized for the management of patients with cancer encompassing several aspects including diagnosis, staging, and monitoring therapeutic intervention. However, FDG not only accumulates within malignant tumor sites but also in the inflammatory lesions. As a result, the clinical utility of FDG-PET is also being investigated for detection, characterization, and monitoring of patients with infectious and non-infectious inflammatory processes in several centres across the world.

Functional imaging, in certain settings, has superior diagnostic performance characteristics compared with those of structural imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). For example, FDG-PET has been shown to be highly sensitive in the detection of chronic osteomyelitis, infection of implanted prostheses, the source of fever of unknown origin, vasculitis, inflammatory bowel disease, and atherosclerosis. However, non-specific accumulation of FDG in benign processes such as inflammation and infection can make it difficult at times to distinguish malignant neoplastic lesions from the benign ones. Fortunately, dual time point and delayed FDG-PET imaging allows for distinction between these two distinct pathological categories, as the pattern and rate of FDG uptake over time vary considerably between malignant and benign processes. Hence, dual time point FDG-PET has gained considerable interest in the recent literature as an important diagnostic approach to improve the overall sensitivity, specificity, and accuracy of FDG-PET.

Standardized uptake value

Standardized uptake value (SUV) is the most commonly used semi-quantitative parameter in routine practice for assessing the degree of FDG accumulation within normal tissues and abnormal lesions. It is calculated by dividing the radiotracer activity in the region of interest (ROI) drawn around a structure of interest (MBq/ml) by the injected dose (MBq), the latter of which is then divided by the body weight (g). Many factors are known to affect SUV: patient size, plasma glucose levels, dose extravasation, technical factors, and partial volume effects.

Correction of SUV based on patient body weight (SUV<sub>wt</sub>) can lead to an overestimation of SUV in heavy patients with higher fat content and underestimation in lighter patients. For this reason, it has been proposed that SUV based on lean body mass (SUV<sub>lbm</sub>) or SUV based on body surface area (SUV<sub>bsa</sub>) be used instead. In addition, in patients with plasma glucose levels above 250 mg/dl, SUV measurements are substantially underestimated. Hyperinsulinemia leads to increased glycolysis in the adipose tissues and muscles which results in low FDG uptake in other tissues. Dose extravasation often leads to an underestimation of SUV. Technical factors such as image reconstruction parameters and attenuation correction methods can also affect SUV measurements. For example, maximum SUV increases with the number of iterations of correction. Artifacts due to patient motion and misregistration can also affect SUV. Partial volume effects are a major contributor to the inaccuracy of SUV, leading to underestimation of the actual values. This problem can be avoided by using the lesion size as measured on CT to correctly define the exact volume of the lesion of interest and therefore specifically measure the FDG uptake in that volume.

SUV measurement has been used as a quantitative method for distinguishing between malignant and benign lesions (fig. 1). However, it is clear that there is quite often substantial overlap between SUVs from active inflammatory processes (both of infectious and non-infectious origin) with those of malignant lesions. Therefore, a threshold value for SUV alone cannot be generally employed to differentiate between malignancy and benignity. Furthermore, there is a certain degree of variability between FDG uptake and the histopathology of the tumor, which means that tumors can have a wide range of SUVs partly related to the tumor biology. For example, in one report in the literature, squamous cell carcinoma of the lung was noted to have an average SUV of 13.4, whereas adenocarcinoma and large cell carcinoma of the lung were reported to have significantly lower average SUV levels of 7.1 and 5.9, respectively.

Basis for differential FDG accumulation in cells

The accumulation of FDG within cells is dependant upon two main factors: the number of membrane transporters and the ratio of hexokinase to glucose-6-phosphatase. Both malignant and inflammatory cells have high concentrations of membrane transporters. The brain and the heart have the highest levels of hexokinase and lower levels of.
of glucose-6-phosphatase, and generally accumulate FDG. Malignant cells have substantially enhanced glucose transporters (GLUT) on their surface. Malignant cells also express high levels of hexokinase and low levels of glucose-6-phosphatase, which lead to an accumulation of FDG in these cells. As FDG accumulates, the contrast between lesions and the normal surrounding tissue increases. This leads to their prominent visualization of lesions on FDG-PET imaging.

In contrast, inflammatory cells have higher levels of glucose-6-phosphatase than malignant cells, and therefore a lower ratio of hexokinase to glucose-6-phosphatase. Consequently, FDG-6-phosphate is rapidly dephosphorylated and cleared from the cell, leading to decreasing concentration of this metabolic product in these cells over time. It should also be noted that different types of malignant cells accumulate variable amounts of FDG. One explanation for this is the varying amount of glucose-6-phosphatase present in these cells. The most actively proliferating tumors tend to have the lowest levels of glucose-6-phosphatase. Therefore, it is these types of tumor cells that will be most readily detected initially and by dual time point FDG-PET imaging.

**In vitro and in vivo animal studies**

*In vitro* studies performed by the researchers at the University of Pennsylvania School of Medicine have shown that mononuclear cells have a different time course of FDG uptake from that of most other cells tested. These results support the idea that imaging at two time points with FDG-PET may be useful for optimal distinction between malignant and benign processes. Zhuang et al investigated the differences between the amount of FDG uptake in malignant and inflammatory cells. They measured FDG uptake in different tumor cell lines including human malignant mesothelioma, rat malignant mesothelioma, mouse malignant melanoma, mouse mesothelioma, human myeloma, and human ovarian cancer. All tumor cells demonstrated increased FDG uptake over time although the degree of change varied between tumor cell lines. The ovarian cancer cell lines had the lowest average change in SUV (10% ± 26%) while human malignant mesothelioma cell lines had the highest change in SUV between the two time points (198% ± 48%). In contrast, the FDG uptake in mononuclear cells from 7 of 8 different donors decreased over time with an average decrease of 13% (fig. 2).

**Clinical applications**

Quantitative dual time point imaging with FDG-PET has recently been found to be more accurate than single time point imaging for the discrimination between benign and malignancy lesions in a variety of clinical settings. This has been of great importance in anatomic regions where inflammatory lesions are commonly noted.

**Head and neck**

The head and neck is an anatomic location where there is generally an appreciable amount of physiological FDG uptake by the normal structures. Also, not infrequently, episodes of infection result in inflammatory lesions at these sites. Another quite frequently encountered phenomenon is radiation induced inflammation that causes “metabolic flare” and hence leads to false positive FDG-PET in these patients. Therefore, differentiation among inflammatory sites, neoplastic lesions, and physiological tissue uptake poses a challenge on FDG-PET scans. Investigators at the University of Pennsylvania were the first to present dual time point imaging as a means to address this issue. They described the utility of dual time point imaging in the head and neck region in 21 patients (18 patients with a history of head and neck cancer and 3 patients with suspected osteomyelitis). The mean time interval between the scans was 28 minutes (range, 13-49 minutes). They showed that an average increase for the malignant lesions in SUV (12%) from the first time point to the second time point of FDG-PET allowed for differentiation between non-specific FDG uptake in normal and inflammatory tissues from FDG uptake in malignant tumors. The preliminary encouraging results led to further investigation in other organs and sites where such lesions are encountered frequently.

**Solitary lung nodule**

The important role of FDG-PET in the evaluation of solitary pulmonary nodule has been highly emphasized in the literature. In this setting, FDG-PET has high sensitivity but relatively low specificity for a malignant underlying cause of a solitary pulmonary nodule. The most frequent reasons for a false positive result on FDG-PET include pathologies such as pulmonary granuloma, hematoma, round pneumonia, rounded atelectasis, and arteriovenous malformation.

Early data reported by Zhuang et al revealed promising results in this setting. Soon thereafter, Matthies et al adopted the dual time point method for the evaluation of pulmonary nodules in a larger sample. Thirty-six patients with 38 known or suspected malignant pulmonary nodules underwent FDG-PET imaging of the thorax at two time points. The early imaging time point was performed at an...
average of 70 minutes after FDG injection (range, 56-110 minutes) and the delayed imaging time point was performed at an average of 123 minutes after the tracer injection (range, 100-163 minutes). The mean time interval between the scans was 56 minutes (range, 49-64 minutes). The SUV (mean ± SD) in the malignant tumors was 3.66 ± 1.95 on the first scan and 4.43 ± 2.43 on the second scan. The percent increase in SUV in the malignant lesions over time was 20.5 ± 8.1%. In contrast, the average SUVs in the benign lesions at the first and second scans were 1.14 ± 0.64 and 1.11 ± 0.70, respectively. The majority of the lesions in the latter group either had a stable level of FDG uptake or declined over time. The sensitivity, specificity, and accuracy were calculated for threshold dual time point changes in lesion SUV of 5%, 10%, and 15%. The sensitivity, specificity, and accuracy for dual time point PET imaging in this setting were 100%, 89% and 95%, respectively, when a threshold increase of 10% change in SUV was utilized. This is compared to a sensitivity of 80% and specificity of 94% when using early single time point imaging when a SUV of 2.5 is used as the threshold value to assess for benignity or malignancy15 (fig. 3).

In another study, Xiu et al showed that dual time point PET imaging is particularly useful in the assessment of lung nodules with mildly increased FDG uptake. A correct assessment of these nodules is difficult because not all lung nodules with mild uptake are benign. This is particularly true when partial volume correction has not been applied for accurate measurement of SUV. Forty-six patients who had dual time point PET scans for the evaluation of lung nodules were analyzed. Both initial and delayed images were compared by visual analysis and semi-quantitative analysis, and SUV of 2.5 for both scans was regarded as a threshold for separating malignant lesions from benign lesions. An increase of more than 10% in lesion SUV between the two scans was considered as suggestive of malignancy. Using this latter criterion, three false positives were found (two bronchoalveolar carcinomas and one well-differentiated adenocarcinoma). Also, four benign lesions (two sarcoidosis, one aspergillosis, and one tuberculosis) had a significantly increased retention index (more than 10%). In this study, the best results were generated by employing a threshold of increase in SUV of greater than 10% with a sensitivity of 81.3%, a specificity of 86.3%, and an accuracy of 84.8%16.

Basu et al evaluated the time course of FDG uptake in patients with non small cell lung carcinoma (NSCLC). Three patients underwent a series of whole body FDG-PET at several time points, beginning at 5 min and extending up to 8 h after the intravenous administration of FDG. Standardized uptake values (SUVmax) were calculated in the malignant lesions and all organs. Time activity curves (TACs) were generated utilizing these SUV values for each of these sites. The ratios of the SUVmax of the malignant lesions to those of normal organs (viz. lung and liver) at specific time points were also calculated and the TACs for these ratios were generated. The blood and plasma decay curves of (18)F activity over time were generated based on the counts obtained from blood sample analysis. The ratios of (18)F activity of blood to plasma were also calculated and the TACs of this ratio were generated. The SUVmax ratios of malignant lesions to those of normal lung and liver and their TACs demonstrate initial rise followed by a delayed plateau. The results from this preliminary study indicate that while the tumor sites show increased uptake of FDG during the course of 8 h, surrounding normal tissues demonstrate declining or stable values with time. This would indicate increasing contrast between the lesion and the background and, therefore, possibly improved sensitivity of the test17 (fig. 4).
Breast cancer

The role of FDG-PET imaging in the initial assessment of primary breast cancer is poorly defined at this time. However, the utility of FDG-PET for the staging of breast cancer as well as the detection of recurrent breast cancer has been described. The diagnostic capability in this setting is limited by the insensitivity of this technique in detecting small lesions (< 1 cm) and tumors with low grades of proliferation.

In order to address this shortcoming, Kumar et al examined the utility of dual time point FDG-PET imaging for identification of malignant breast cancer lesions. They studied 54 breast cancer patients with a total of 57 specific breast lesions. Of the 57 lesions, 39 were invasive carcinoma and 18 were due to post-biopsy inflammation. The first scan imaged the whole body (from head to toe) and the second scan imaged the chest region alone. The average time interval between the first and second time points was 38 minutes. Of the 39 invasive cancers, 33 (85%) showed an increase in SUV and 6 (15%) showed either no change or a decrease in SUV over time. The average SUVs in the ROIs of these 39 malignant lesions at the first and second time points were 2.88 ± 3.04 and 3.38 ± 3.38 respectively. The percent change in SUV (mean ± SD) between the two time points was +12.6% ± 11.4% (p = 0.003). It is important to note that if a threshold SUV of 2.5 was used as a criterion for malignancy based on the SUV change over time, the sensitivity was 85% and the specificity was 94%.

Figure 4. Non-small cell lung cancer patient with serial imaging. Coronal fluorodeoxyglucose-positron emission tomography (FDG-PET) images at 1 h (A), 2 h (B) and 3 h (C) of a patient with carcinoma of the right lung. There is increasing FDG uptake over time (from 1 to 3 h) in the right lower lobe, right hilum (arrow) and right chest wall (arrow head). A small lesion in the lower back on the left side (curved arrow) of the patient which is faintly visualized in the initial images becomes clearly seen in the 2nd and 3rd hour.

Reproduced from Basu S, et al with permission from The Quarterly Journal of Nuclear Medicine and Molecular Imaging.
on single-time point imaging alone, only 38% of the lesions would have been considered malignant21.

Of the 18 inflammatory lesions, 3 (17%) showed an increase and 15 (83%) showed either no change or a decrease in SUV over time. The percent change in SUV was -10.2% ± 16.5%. Of the 57 normal contralateral breasts, 2 (3.5%) showed an increase in SUV over time and 55 (96.5%) showed either no change or a decrease in SUV. The percent change of SUVs from the first to the second time point was -15.8% ± 17% (p = 0.005). These results indicate a significant difference among malignant tumors, inflammatory lesions, and normal tissues with regard to the dynamics of FDG accumulation and retention over time21.

Mavi et al studied the relationship between FDG uptake and breast cancer histopathology, as well as that of the change in lesion SUV over time and breast cancer histopathology. They reported dual time point imaging data in 152 patients between the two time points following FDG-PET imaging. Patients were divided into two groups according to histopathology: invasive (≥ 4 mm) and non-invasive (< 4 mm). Visual assessment of FDG-PET images showed a sensitivity of 90.1% for invasive cancer > 10 mm in size, 82.7% for invasive breast cancer 4-10 mm in size, and 76.9% for non-invasive breast cancer. Average maximum SUVs at the two time points following FDG administration and percent change in maximum SUV over time were calculated. These were 3.9 ± 3.7, 4.3 ± 4.0, and 8.3 ± 11.5% for invasive cancer; 2.0 ± 0.6, 2.1 ± 0.6, and 3.4% ± 13.0% for non-invasive cancer; and 1.2 ± 0.3, 1.1 ± 0.2, and -10.0% ± 10.8% for the contralateral normal breast tissue, respectively. They concluded that FDG PET imaging at two time points improves the sensitivity and accuracy in detecting lesions in patients with breast cancer16. Also, FDG uptake and measured SUVs will change over time depending upon the histopathological type of primary breast cancer (fig. 5).

The same group also investigated the role of estrogen receptor (ER), progesterone receptor (PR), and C-erbB-2 receptor (C-erbB-2R) states in FDG uptake of primary breast cancer lesions. 213 breast cancer patients underwent FDG-PET prior to partial or complete mastectomy. Following surgery, standard immunohistochemistry was performed on a surgical specimen of the cancer lesion in order to identify the receptor state of the tumor cells. $\chi^2$ testing for ER and PR states demonstrated that if ER is positive then PR tends to be positive as well and vice versa (p < 0.01). The opposite relationship was found between ER and C-erbB-2R states. No relationship was detected between PR and C-erbB-2R states. ANOVA testing showed that ER state alone had an effect on FDG uptake ($p < 0.01$) but that PR state alone and C-erbB-2R state alone had no effect. These results suggest that FDG-PET may be able to provide valuable information about the relationship between the ER states of primary breast cancers and their metabolic disease activities22.

Basu et al examined the characteristics of dual time point FDG-PET imaging in patients with triple negative breast carcinoma, and compared the results to the dual time point FDG-PET images of patients with ER+/PR+HER2- breast carcinomas. They found that patients with triple negative breast carcinoma had an average early time point maximum SUV of 7.27 ± 5.6, an average delayed time point maximum SUV of 8.29 ± 6.4, and a percentage change in average maximum SUV of 14.3% ± 15.8%. In the ER+/PR+/HER2- group, the average values for early time point maximum SUV, delayed time point maximum SUV, and percent change in maximum SUV over time were 2.68 ± 1.9, 2.84 ± 2.2, and 3.7% ± 13.0%, respectively. The average values for early time point maximum SUV, delayed time point maximum SUV, and percent change in maximum SUV over time were all significantly higher in the triple negative group, which is consistent with the aggressive nature of these tumors21.

Dual time point FDG-PET has also been used to look at the tumor activity in breast cancer patients with varying degrees of disease burden at diagnosis. Three groups were examined: Group I consisted of 64 patients with an initial diagnosis of primary and metastatic axillary lymphadenopathy. Group II included 18 patients with axillary nodal and distant metastases. Group III was comprised of 92 patients without any metastasis at lymph nodal or distant sites. In each patient, early and delayed time point maximum SUVs for each lesion (whether primary or metastatic) were measured, and the percent change in maximum SUV over time was also calculated for each lesion. The average values for early time point maximum SUV, delayed time point maximum SUV, and percent change in maximum SUV over time in Group I patients were as follows: primary lesion 4.8 ± 3.9, 5.3 ± 4.5, and 9.4% ± 12.8%, respectively, and axillary nodal lesions 3 ± 2.6, 3 ± 2.7, and 1.1% ± 21.3%, respectively. Similar measurements in Group II patients were as follows: primary lesion 7.7 ± 6.2, 8.9 ± 7.1, and 15.7% ± 10.8%, respectively, axillary nodal lesions 3.5 ± 3.1, 3.7 ± 3.1, and 6.3% ± 20.9%, respectively, and distant metastatic lesions 3.0 ± 1.4, 3.1 ± 1.2, and 8.5 ± 21.2%, respectively. Similar measurements in Group III patients were as follows: primary lesion 2.9 ± 2.7, 3.4 ± 2.4, and 4.5% ± 4.2%, respectively. The average percent changes in maximum SUV over time on dual time point FDG-PET were statistically different between the three groups of patients. Group I on average had the lowest maximum SUVs of primary lesions whereas Group II had the highest maximum SUVs of primary lesions. Furthermore, Group I on average had the smallest percent change in maximum SUV over time whereas Group III had the largest. These data demonstrate that more aggressive primary breast tumors, specifically those that are associated with metastatic disease, have a greater degree of metabolic disease activity in the primary
The usefulness of dual time point FDG-PET has been evaluated in other clinical settings as well. In the setting of cervical cancer, Shihi-Ya et al showed that the delayed FDG-PET improved the detection of para-aortic nodes (especially in the lower chains) whereas other modalities such as MRI showed false positive results due to inflammation, edema, or scar tissue associated with radiation or post-surgical changes. The sensitivity, specificity, and accuracy of FDG-PET were 100% when the ear-tissue associated with radiation or post-surgical changes. The sensitivity was improved when a maximum SUV of less than 2.9 was measured on the delayed scan, and a RI of -8% over time were used as the criteria to diagnose a benign gallbladder lesion. SUVs as well as tumor-to-liver uptake ratios were much higher on the delayed time point FDG-PET images, allowing for easier differentiation between malignant and benign lesions²⁶.

Nakamoto et al investigated the role of dual time point FDG-PET imaging in differentiating between malignant and benign pancreatic lesions. They reported that the use of a dual time point PET scan 2 hours after FDG injection provided a higher sensitivity, specificity, and accuracy compared to those for single-time point images²⁷ (figs. 7 y 8).

Dual time point FDG-PET was coupled with kinetic modeling by Spence et al to investigate supratentorial gliomas. They reported that the estimated K4 (which estimates washout of FDG from the tumor or the normal grey matter) values for the tumors were not significantly different from the K4 values of cerebral gray matter on the images from the first time point 45 minutes after FDG injection, but were lower on FDG-PET images at the second time point obtained at 180, 240, 300, or 360 minutes after FDG injection²⁸.

An investigation of bone marrow lesions using dual time point FDG-PET was carried out by Houseni et al²⁹. 81 patients with suspected spinal bone marrow pathology were underwent FDG-PET as well as bone marrow histopathologic analysis. Three groups were delineated based upon histopathology: one with normal bone marrow, one with chemotherapy in the past 6 months, and one with malignant spinal bone marrow involvement. The percent change in SUV from early to delayed time point images was calculated for each group, and the results were compared across the three groups. The percent increase in SUV was significantly higher in the group with malignant involvement of the spinal bone marrow than in the group affected by chemotherapeutic agents. It was also noted that there is a substantial decrease in FDG uptake over time in normal bone marrow. It was concluded that the time course of FDG uptake is quite different in the various histopathological conditions of the spinal bone marrow²⁹.

**Limitations of dual time point FDG-PET imaging**

Dual time point FDG-PET has some limitations. For example, it has limited accuracy in the setting of bronchioloalveolar cell carcinoma and well differentiated adenocarcinoma, this may reflect the relatively benign nature of these tumors. However, one must keep in mind that these cancers will tend to be less aggressive than other less differentiated tumors, and therefore the results from dual time point ima-
ging may indirectly provide diagnostic information regarding patient prognosis in the setting of such cancers. This principle may be applicable to other malignancies that generally have a relatively indolent course and have associated relatively low levels of FDG uptake such as well-differentiated breast, lung prostate and neuroendocrine tumors, hepatomas, and thyroid cancers. Also, similar observations (low levels of uptake initially and minimal or no change over time) have been noted in certain infections such as that occurring in the setting of a painful lower limb prosthesis as well as in inflammation related to prior radiation therapy. Furthermore, brown fat may show increased accumulation of FDG over time on dual time point FDG-PET, although the typical symmetric and paravertebral distribution of brown fat as well as detection of corresponding fat attenuation on coregistered CT images will prevent a false positive diagnosis. Lastly, limitations with regard to the accuracy of the dual time point approach have also been reported in the evaluation of patients with suspicious focal abdominal uptake. However, there are some concerns about the methodologies employed by these investigators and also a recent presentation by Garrastachu et al clearly demonstrates that FDG-PET imaging performed at 1 and 2 hours improves the specificity of diagnosis in patients with these conditions.

Conclusions

The data published in the literature demonstrate that dual time point methodology is a useful and simple diagnostic tool that improves the sensitivity, specificity, and accuracy of FDG-PET for accurate characterization of malignant lesions. Dual time point imaging should be used in select patients, particularly when differentiation between benign and malignant processes is of clinical concern. Also, the degree of change of SUV over time may have prognostic value and may provide evidence for future behavior of the tumor.

References


Figure 8. Recurrence of autoimmune chronic pancreatitis: Focal uptake of FDG was observed at 1 hour postinjection, but the uptake was reduced at 2 hours postinjection (arrows). Reproduced from Nakamoto Y et al with permission from Cancer.