

Use of Dual-Point Fluorodeoxyglucose Imaging to Enhance Sensitivity and Specificity

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Positron emission tomography (PET) and positron emission tomography/computed tomography imaging with fluorodeoxyglucose (FDG) are widely used as a powerful evaluation modality in oncological nuclear medicine not only for detecting tumors but also for staging and for therapy monitoring. Nevertheless, there are numerous causes of FDG uptake in benign processes seen on PET images. In fact, the degree of FDG uptake is related to the cellular metabolic rate and the number of glucose transporters. FDG accumulation in tumors is due, in part, to an increased number of glucose transporters in malignant cells. However, FDG is not specific for neoplasms: a similar situation exists in inflammation; activated inflammatory cells demonstrate increased expression of glucose transporters. Therefore, there is growing interest in improving the specificity of FDG-PET in patients with cancer. Preliminary studies showed that in several neoplasms, the uptake of FDG continues to increase for hours after radiopharmaceutical injection, and this difference in the time course of FDG uptake could be useful to improve the accuracy of PET to distinguish benign lesions from malignant ones. Also in experimental cultures, dual-point acquisition (early at 40-60 minutes postinjection and delayed at 90-270 minutes) demonstrated that it is able to differentiate inflammatory from neoplastic tissue. In general, inflammatory tissue is expected to reduce FDG uptake as the time goes by, whereas the uptake in the neoplastic lesions is supposed to be increasing. There is evidence in the recent literature of the clinical usefulness of dual-time-point FDG-PET imaging in a wide variety of malignancies, including those of head and neck, lung, breast, gallbladder, cervix, liver, and in brain tumors. A lesion is likely to be malignant if the standard uptake value increases over time, whereas it is likely to be benign if the standard uptake value is stable or decreases. It is worth noting that in many of these studies, dual-time-point PET improved not only the specificity but also the sensitivity in assessing breast, pulmonary, liver, and other tumors because of increased lesion-to-background ratio, as a consequence of FDG washout from the surrounding normal tissues and increasing neoplastic uptake.

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The introduction of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) in the clinical setting have substantially changed the diagnostic algorithm in oncology and the management of patients with cancer.^{1,2} The usefulness of this kind of images for the differential diagnosis of undefined lesions, initial tumor staging, detection of relapse, and therapeutic response monitoring has been extensively reported.³

Depending on the clinical needs, several radiopharmaceuticals are currently employed for functional imaging with PET; nevertheless, the most common radiotracer in use today is certainly ¹⁸F-fluorodeoxyglucose (FDG), which is a radio-labeled sugar able to detect sites of abnormal glucose metabolism and can localize many types of tumors.⁴ FDG is transported into cells by glucose transporters and is phosphorylated by hexokinase enzyme to ¹⁸F-2'-FDG-6 phosphate but is not metabolized. The degree of FDG uptake is related to the cellular metabolic rate and the number of glucose transporters. Enhanced FDG uptake in tumors is due, in part, to an increased number of glucose transporters in malignant cells.⁵

However, FDG is not specific for malignancies: a similar situation exists in inflammation; activated inflammatory cells demonstrate increased expression of glucose transporters.⁶

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In addition, in inflammatory conditions, the affinity of glucose transporters for deoxyglucose is apparently increased by various cytokines and growth factors. FDG uptake in infections is related to the granulocytes and mononuclear cells using large quantity of glucose by way of the hexose monophosphate shunt.^{6,7} As a matter of fact, because of the growing use of FDG-PET, there are also increasing literature data reporting nonspecific FDG accumulation in a wide spectrum of anatomical variants and physiological processes as well as in several benign pathologies.⁸ Therefore, FDG uptake in the unknown benign lesions gives rise to false-positive results when a patient is managed for a potential malignant disorder, with a decreased positive predictive value (PPV) of PET and PET/CT in such settings.⁹

In addition to visual assessment, various reports suggest standard uptake value (SUV) measurement as a useful tool for differentiating between benign and malignant lesions.¹⁰ Traditionally, a threshold for a single-time-point SUV of 2.5 has been proposed as the optimal one for separating malignant from benign lung lesions¹¹; subsequently, this threshold has been used by many groups also to diagnose other malignancies. However, a considerable overlap exists between the uptake values of malignant and benign lesions: there is a wide range of FDG accumulation among malignant processes, and also in inflammatory and infectious conditions, high SUVs can be observed.^{10,12}

About 10 years ago, dual-time-point (DP) FDG-PET imaging emerged as a possible strategy for distinguishing malignant from benign FDG-avid processes.¹⁰ This approach was based on the results of previous studies demonstrating that the uptake of FDG continues to increase in malignant tumors for several hours after the injection of the radiotracer.^{13,14} From these findings it has been deduced that the difference in the time course of FDG uptake could be used to improve the accuracy of PET to differentiate benign lesions from malignant ones (Fig. 1).

In the course of developing a clinical protocol for FDG-PET imaging of nonsmall cell lung cancer (NSCLC), Fischman and Alpert¹³ performed dynamic PET images in a series of patients to determine the optimal time for scanning. In most of the evaluated cases, even at 90 minutes after FDG administration, the plateau concentrations of radioactivity within the neoplasms were not achieved. These preliminary observations were confirmed in a following study aimed to evaluate the glucose metabolism in malignant tumors.¹⁴ In 8 patients with stage III NSCLC, quantitative dynamic FDG-PET before and after treatment was performed. It is worth noting that the tumor concentrations of FDG did not reach a plateau within the 90-minute imaging in any of the pretreatment studies and only in 1 case posttreatment. Moreover, the average time to reach 95% of the plateau value was 298 ± 42 minutes (range: 130-500) pretreatment and 154 ± 31 minutes (range: 65-24) posttreatment; the difference between the plateau and the 60-minute value was $46\% \pm 6\%$ pretreatment and $17\% \pm 5\%$ posttreatment, respectively.

In an article investing the accumulation of FDG in an experimentally induced inflammatory tissue, rats were subcutaneously inoculated with turpentine oil.¹⁵ The time-course

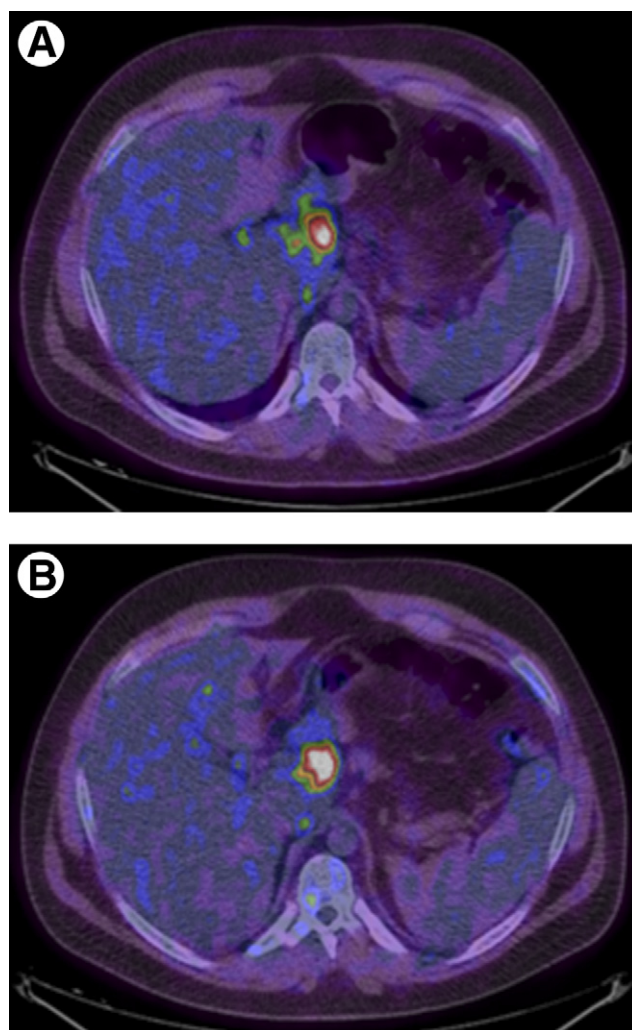


Figure 1 A 23-year-old young man with Hodgkin lymphoma, evaluated at initial staging. PET/CT fusion images (transaxial views) show a focal area of pathologic FDG uptake in a lymph node of the hepatic hilum, with standard uptake values (SUV) of 6.1 at 45-minute scan (A) and 13.8 at 105-minute scan (B), respectively. (Color version of figure is available online.)

study of FDG tissue distribution showed that the uptake of the radiopharmaceutical in inflammatory tissue gradually increased until 60 minutes and then decreased. These results suggest a different trend between malignant and benign/inflammatory lesions with regard to FDG accumulation: the first ones show an increase with time, whereas the second ones a decrease. Based on this logic, Lodge et al¹⁶ performed a study of FDG uptake in soft tissue masses to investigate some of the methodological factors potentially affecting the ability of PET in assessing tumor malignancy. Twenty-nine patients with soft tissue masses were evaluated using a 6-hour scanning protocol, consisting of a 2-hour dynamic acquisition, which commenced immediately after tracer injection, followed by 2 further static scans, which started 4 and 6 hours after FDG administration. The histological evaluation of each biopsy specimen resulted in 17 benign masses and 12 soft tissue sarcomas (10 were high-grade and 2 low-grade tumors). The findings in high-grade soft tissue sarco-

mas confirmed the data of Hamberg et al,¹⁴ which had suggested that FDG uptake in certain malignant tumors does not reach a maximum until approximately 5 hours after injection. In fact, the time course of SUVs in benign lesions and high-grade sarcomas was significantly different, with the latter ones tending to demonstrate greater uptake than benign masses, and their time to reach a maximum was also greater. In particular, high-grade sarcomas reached a peak activity concentration approximately 4 hours after FDG injection, whereas benign lesions reached a maximum within 30 minutes. Therefore, measuring SUVs derived from images acquired at later times, an improved differentiation between these 2 kind of soft tissue masses, is achievable, with the SUV calculated 4 hours postinjection as an useful index of tumor malignancy. However, high-grade but not low-grade tumors could be distinguished from benign lesions.

The optimal scan time for FDG-PET was evaluated in a group of 29 patients with histologically proven primary breast cancer with a diameter of ≥ 2 cm.¹⁷ Images were acquired 0-40 minutes, 1.5 hours, and 3 hours after radiotracer injection; SUVs and tumor-to-nontumor and tumor-to-organ ratios were calculated. At visual analysis, the primary breast cancer was more clearly delineated on the later scans: 24 of 29 patients were diagnosed on the imaging at 1.5 hours and 27 on the scans acquired 3 hours after FDG injection. It is worth noting that 13 multifocal tumors appeared diffuse on the early scans but were clearly visualized on the 3-hour images, whereas lymph node metastases was correctly depicted in 18 of 18 patients on the later scans but only in 12 of 18 on the 1.5-hour images. Tumor-to-nontumor and tumor-to-organ ratios resulted significantly higher for the 3-hour images than for the 1.5 hour images, whereas SUVs did not rise to the same extent. Therefore, tumor contrast in breast cancer is improved by acquiring the PET images at 3 hours, with a primary lesion detectability of 93% compared with 83% in the 1.5-hour scans.

Subsequently, Hustinx et al¹⁸ studied the utility of DP imaging to differentiate malignancy from inflammation and normal tissue in the head and neck cancers. Twenty-one patients were submitted to PET at 70 minutes (range 47-112) and then at 98 minutes (range 77-142) after FDG injection, with a mean interval between scans of 28 minutes (range 13-49). Regions of interest were drawn on every focus of increased uptake and on a control contralateral location, and also for the tongue, larynx, and cerebellum, to measure initial SUVs and changes over time for both pathologic and normal structures. Tumor SUVs increased over time (by 12%), whereas the uptakes of normal and inflamed tissue remained almost unchanged on average. Moreover, the ratio tumor/contralateral SUV rose by 23% between early and delayed scans, whereas this ratio for inflamed sites increased by only 5%. These preliminary results indicated that the pattern of tumor uptake of FDG may be distinguishable from those of normal and inflamed tissues in the head and neck on DP PET, and so the acquisition of serial images could improve both the sensitivity and the specificity of FDG-PET in this oncological application.

The usefulness of delayed FDG-PET imaging was then evaluated in the pancreas in differentiating benign from ma-

lignant lesions in a group of 47 patients with suspected pancreatic carcinoma.¹⁹ All of them were imaged 1 and 2 hours after radiotracer administration; also, a subset of 19 patients was scanned at 3 hours postinjection. The SUV was determined, and the retention index (RI) was calculated by dividing the increase in the SUV between 1 and 2 hours by the SUV at 1 hours. The SUV increased 2 hours postinjection in 22 of 27 malignant lesions and decreased in 17 of 20 benign lesions; the SUVs at 3 hours were higher than those at 2 hours in 9 of 14 malignant and in 2 of 5 benign lesions, respectively. The difference of RIs between malignant (12.36) and benign (-7.05) lesions were statistically significant. These data suggested that a delayed FDG-PET scan at 2 hours could be useful for distinguishing malignant from benign pancreatic lesions, especially in those patients in whom routine PET findings at 1 hour are not conclusive.

The advantage of delayed whole-body FDG-PET imaging for tumor detection was subsequently confirmed by Kubota et al²⁰ in a group of 22 subjects, with different kind of cancers evaluated with images acquired both at 1 and at 2 hours. Most malignant tumors, especially those in the lung, mediastinum, and upper abdomen, showed significant increase in FDG uptake at 2 hours than at 1 hour, whereas benign lesions—with the exception of sarcoidosis—and normal tissues demonstrated lower uptake of FDG at 2 hours than at 1 hour. In particular, image interpretation was changed in 3 lesions (2 lung cancers and 1 malignant lymphoma) from equivocal on 1-hour scan to positive for cancer on delayed images. Therefore, patient-based sensitivity resulted improved from 78% to 94%, and lesion-based sensitivity from 92% to 98%, respectively.

After these previous reports, the first article on DP FDG-PET imaging for differentiating malignant from inflammatory processes, including in vitro, animal, and patients' studies, was published in 2001 by Zhuang et al.¹⁰ In the in vitro studies, the uptake by different tumor cell lines and peripheral blood mononuclear cells (isolated from healthy human volunteers) was measured 20 and 60 minutes after adding FDG into growth medium. The tumor cell lines tested showed significantly increased FDG uptake over time (+100.3%), whereas it decreased in inflammatory cells (-13%). In the animal studies, mice mesothelioma cells were implanted into the left flank of rats and a focal inflammatory reaction (mechanical irritation) was generated in the right flank; PET images were acquired at 45 and 90 minutes. The SUVs of tumors from 90-minute imaging were higher than those from 45-minute imaging (18%), whereas the SUVs of inflammatory lesions decreased over time (-17%). The average SUV of tumors was 3.49 for early and 4.12 for delayed images, whereas that of inflammatory processes was 2.33 for early and 1.93 for delayed, respectively. In the human studies, 76 patients who had DP FDG-PET imaging were retrospectively analyzed: 31 with malignant lesions, 12 with surgical pathology confirmed or clinical follow-up suggested, 12 with benign lung nodules showing increased FDG accumulation, 8 with inflammation caused by radiation therapy, and 25 with painful lower limb prostheses. PET acquisition began 48-63 minutes after FDG injection, and the average interval

between the first time point and the second time point scan was 52 minutes (range 41-65 minutes). The average SUV of the lesions in known cancer patients increased (19.2%) from 3.96 at the first time point to 4.72 at the second time point, whereas in benign lung nodules, it slightly decreased over time (-6.3%) from 2.37 to 2.22. The average SUVs of the inflammatory lesions due to radiotherapy were almost constant over time (1.2%), changing from 2.56 at the first time point to 2.59 at the second time point; similarly, the average SUVs of the lesions of painful lower limb prostheses resulted relatively stable over time (from 2.61 to 2.71). The results of this study, including an *in vitro* system, a small tumor-bearing animal model, and clinical patients, were consistent, and they clearly demonstrated that the analysis of change in SUV over time can improve the accuracy in separating malignant from benign abnormalities when compared with absolute SUV measurements at a single time. Moreover, the outcome of the human studies suggested that the changes of SUV over shorter intervals between the early and the delayed PET acquisition provide sufficient information for imaging interpretation.

The relationship between temporal changes in FDG uptake and expression of hexokinase or glucose transporter was then evaluated by Higashi et al²¹ in 21 patients with pancreatic cancer before surgery. The percentages of cells strongly expressing hexokinase type-II and glucose transporter-1 were visually analyzed by immunohistochemical staining of paraffin sections from the tumor specimens. In this series, the RI obtained from DP (1 and 2 hours) FDG-PET predicted hexokinase II and demonstrated that the SUV at 1 hour had a positive correlation with glucose transporter-1 expression but not with hexokinase II expression. Therefore, these results indicated that DP FDG-PET imaging can noninvasively evaluate 2 important factors in cellular glycolysis of cancers, as glucose transporters and glycolytic enzymes.

The findings of the previous mentioned articles have encouraged the acquisition of DP imaging to enhance both sensitivity and specificity of FDG-PET, and there is considerable evidence in the recent literature of the possible usefulness of this technique, which has been evaluated in a wide variety of tumors.²² The theoretical basis for this approach is that the dephosphorylation of FDG-6-phosphate in neoplastic cells is likely to be slower than in normal cells owing to the low glucose-6-phosphatase content.^{23,24} Therefore, in general, benign and inflammatory tissues are expected to reduce the FDG uptake as the time goes by, whereas the accumulation in the malignant tissue is supposed to be increasing. This article now deals with the clinical application of DP FDG-PET imaging in various kind of tumors.

Lung Cancer

One of the most common diagnostic indications for FDG-PET in lung cancer is the differentiation between benign and malignant pulmonary nodules.²⁵⁻²⁷ Matthies et al²⁸ compared the diagnostic accuracy of standard single-time FDG-PET imaging with those of DP acquisition in 36 patients with 38 suspected malignant pulmonary nodules. Patients under-

went chest PET at 70 minutes (point 1, range 56-110 minutes) and at 123 minutes (point 2, range 100-163 minutes) after FDG injection, with a mean interval between the 2 scans of 56 minutes (range 49-64 minutes). Surgical pathology and follow-up revealed 19 patients with 20 malignant tumors. Single-time-point PET (at time point 1) with a threshold SUV of 2.5 reached a sensitivity of 80% and a specificity of 94%; DP imaging (with a threshold value of 10% increase between scan 1 and scan 2) had a sensitivity of 100% and a specificity of 89%, respectively. In particular, 4 of 20 of malignant nodules had SUVs <2.5 on scan 1, whereas 2 lesions with a high likelihood of benign etiology showing increase >10% of their SUVs over time had very low uptake (0.43 and 0.63, respectively) on scan 1. These findings suggested that DP technique can improve the sensitivity of FDG-PET in the diagnosis of pulmonary nodules (Fig. 2); in contrast, this protocol might be useful to increase the specificity only for lung lesions with SUV >1 on scan 1.

Subsequently, a retrospective study including 265 patients with solitary pulmonary nodules (SPNs) on CT was conducted.²⁹ All underwent total-body FDG-PET 60 minutes after tracer injection, and 255 patients underwent a second FDG-PET for chest 100 minutes after injection. Partial volume correction for first time SUV (corrSUV1) was applied using recovery coefficient method adopted and modified from the literature.³⁰ Malignancy of pulmonary nodules was defined using the following criteria: (1) visual assessment, (2) SUV1 \geq 2.5, (3) corrSUV1 \geq 2.5, (4) SUV2 \geq 2.5, (5) any increase in SUV between the first and second scans (SUV2 > SUV1), (6) increase or no change between SUV1 and SUV2 (SUV2 \geq SUV1), and (7) combination of SUV1 \geq 2.5 and/or SUV2 \geq SUV1. All nodules with no FDG uptake that had SUVs equal to lung background activity were considered as benign in all criteria. Of the 265 SPNs evaluated, 72 (27%) proved to be malignant and 193 (73%) benign. In assessing the diagnostic value of FDG-PET, sensitivity, specificity, and accuracy were the following for each criterion used: (1) 97%, 58%, and 68%; (2) 65%, 92%, and 85%; (3) 90%, 80%, and 83%; (4) 84%, 91%, and 89%; (5) 84%, 95%, and 92%; (6) 92%, 92%, and 92%; (7) 95%, 90%, and 91%. The results obtained adopting the last 3 criteria—that have comparable accuracies—clearly showed the benefit of DP imaging in improving the sensitivity and maintaining good specificity (Fig. 3). However, in this series, there were several benign lung nodules characterized by FDG uptake: the pathologic diagnosis of these lesions, which had an increase or no change in SUV over time, included inflammation, granuloma, histoplasmosis, mycobacterial infection, and sarcoidosis. The outcomes of this article led the authors to suggest the inclusion of DP FDG-PET imaging in the clinical workup of patients with SPN, despite the increased length of each examination. In particular, this technique proved to be useful for detecting small lung lesions with lower SUVs.

We have recently performed a prospective study to compare the diagnostic accuracy of early, delayed and DP FDG-PET, and of contrast-enhanced CT within a PET/CT examination in the evaluation of SPN.³¹ Thirty patients underwent PET imaging at 50 minutes after FDG administration (early),

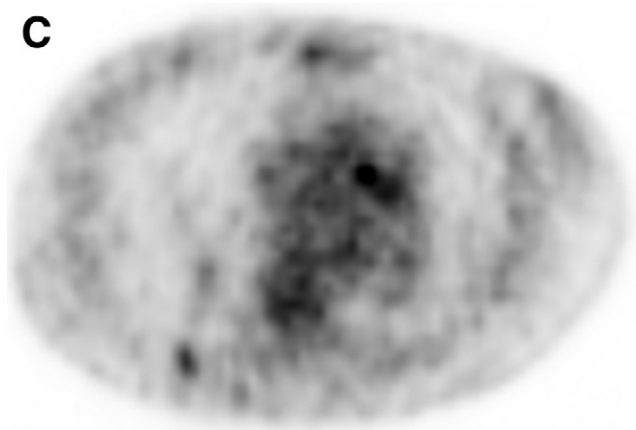
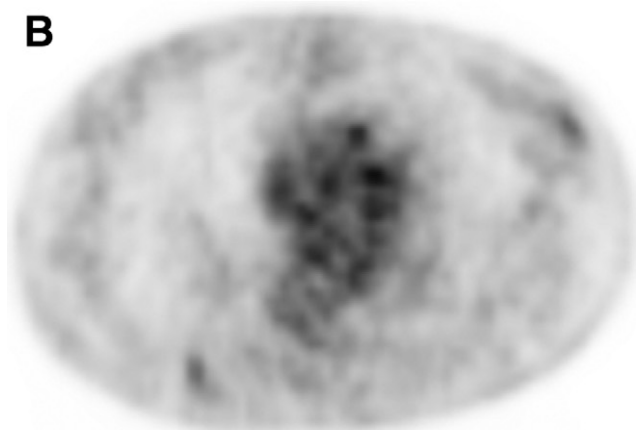
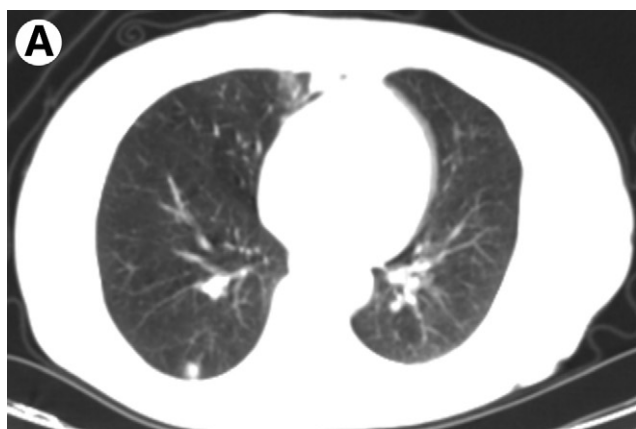


Figure 2 Dual-point fluorodeoxyglucose (FDG)-PET imaging of 67-year-old woman with 0.9 cm solitary pulmonary nodule in the right lower lobe on CT (A). Early PET (B) shows a focal area with faint FDG uptake (SUV 1.2); delayed PET (C) shows more prominent FDG accumulation (SUV 1.6) in the solitary pulmonary nodule. Pathologic diagnosis of this nodule was lung adenocarcinoma.

and at 90 minutes after injection (delayed). SUV was calculated on both images, and lung nodules with $SUV \geq 2.5$ were considered malignant. SUV increasing $\geq 10\%$ (Δ SUV) was considered suggestive of malignancy. Absence of significant nodule enhancement ($<15 \Delta$ HU) at CT was considered strongly predictive of benignity. For the CT morphological assessment, the irregularity of the shape of each lesion was

rated. PET/CT results were related to histological assays and clinical records, and the diagnostic accuracy was assessed by area under the receiver operating characteristic curves (AUC) analysis. Eighteen of the 30 nodules (60%) were malignant, and 12 of 30 were benign (40%); both early and delayed SUV of malignant nodules were significantly higher than those of benign disease (early: 5.49 vs 2.15; delayed: 7.87 vs 2.27). Moreover, Δ SUVs of malignant lesions were significantly higher than those of benign ones (46.23% vs -2.17%). No statistical difference was found between nodule enhancement of malignant lesions versus enhancement of benign ones (36.22 vs 23.83), and no significant association was found between the CT morphologic categories and malignancy. The Δ HU sensitivity, specificity, PPV, and negative predictive value (NPV) resulted: 94%, 34%, 67%, and 96%, respectively; the CT morphologic evaluation obtained these results: sensitivity was 61%, specificity 46%, PPV 60%, and NPV 47%. SUVdelayed corresponding values were 77%, 66%, 74%, and 66%; SUVearly values were 77%, 91%, 79%, and 67%; DP SUV values were 83%, 70%, 75%, and 74%, respectively. The AUC for SUVearly was 0.79, for SUVdelayed 0.8, for DP SUV 0.85, for Δ HU 0.63, and for CT morphologic assessment 0.58. Therefore, our findings in this small series of patients indicated that early and delayed SUV showed comparable accuracies, whereas morphologic and contrast-enhanced CT evaluations had the lowest accuracies.

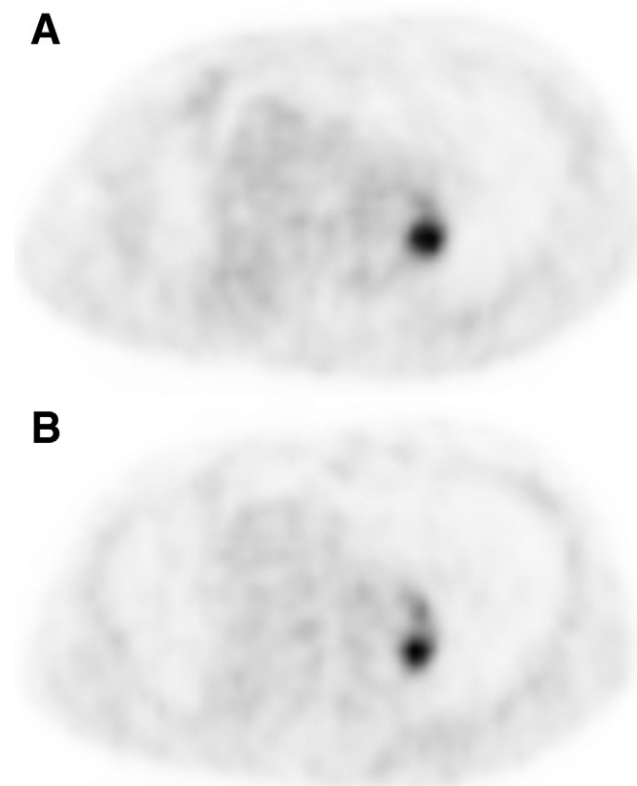


Figure 3 A 71-year-old man presented with 2.3-cm density in left lower lobe. SUV was not significantly different between early PET at 55 minutes after FDG injection (A) and delayed imaging at 120 minutes (B): 6.1 and 5.8, respectively. Excised lesion was granuloma.

It is worth noting that DP SUV showed the largest AUC. However, DP SUV was most sensitive, whereas single-time-point SUV was most specific.

The role of DP FDG-PET imaging in the evaluation of CT detected SPNs with an initial only mild metabolic activity (ie, SUV <2.5 at 60 minutes) was recently investigated in 36 patients.³² Delayed scanning included 3-4 bed positions in the thorax only, approximately 180 minutes after FDG injection. Two methods of interpreting delayed PET imaging were applied: the first one analyzed the SUV of SPNs on 180-minute scan, in which a SUV of 2.5 or more was regarded as a criterion for malignancy; the second one was based on the calculation of RI, in which an increase of 10% or more in SUV between the initial and delayed images was considered an indication of malignancy. The sensitivity, specificity, and accuracy of using a SUV of 2.5 or more as a criterion for malignancy on the delayed acquisition resulted 36%, 96%, and 78%, respectively; when a RI of >10% between the initial and delayed images was used, the sensitivity, specificity, and accuracy was 73%, 80%, and 78%, respectively.

These findings are similar to those previously reported by Xiu et al,³³ whose second image acquisition occurred earlier, on average 114 minutes after tracer injection, and despite a different prevalence of granulomatous disease between the 2 study populations. In fact, sensitivity, specificity, and accuracy resulted 44%, 87%, and 72% when using the criterion of delayed SUV \geq 2.5, and 81%, 87%, and 85% when applying a RI of >10%, respectively.

Nevertheless, in geographic regions with epidemic granulomatous disease, such as tuberculosis or in patients at high risk of granulomatous inflammation, delayed FDG-PET did not prove useful for differentiating malignant from benign pulmonary nodules with an initial mean SUV <2.5.³⁴ DP FDG-PET studies were conducted with imaging 1 and 2 hours after radiopharmaceutical injection in 27 patients with 31 lesions. The differences in 1-hour SUV, 2-hour SUV, RI, and size between the benign (n = 15) and malignant (n = 16) lung pulmonary nodules were not statistically significant, and the AUC did not differ from 0.5. In particular, 60% of the benign lesions had a RI >10% and 62% of the malignant lesions showed a RI >10%. Therefore, according to these data, for pulmonary lesions with an initial mean SUV <2.5, further increases in FDG uptake are frequent in granulomatous inflammation.

A comprehensive meta-analysis evaluating the diagnostic performance of DP FDG-PET in the diagnosis of pulmonary nodules has been recently made, including studies published between January 2000 and January 2011, which used pathology or clinical follow-up as the reference standard, and absolute number of true-positive, true-negative, false-positive, and false-negative results or stated sufficient data to derive these values.³⁵ Ten publications^{28,29,31,33,34,36-40} fulfilled all of the inclusion criteria, with a total of 816 patients and 890 pulmonary nodules. Multiple different thresholds were used to define a pulmonary nodule as malignant between the initial and later images. DP FDG-PET demonstrated a summary sensitivity of 85% and a summary specificity of 77%. Based on these outcomes, the authors' conclusion is that the accuracy of DP FDG-

PET is not superior to single-time-point imaging in determining benign versus malignant etiology of pulmonary nodules because the obtained values for sensitivity and specificity are similar to those reported in a previous meta-analysis of single-time-point FDG-PET.²⁷ For the authors, the main reasons for evaluating as questionable the additive value of the DP FDG-PET in the diagnosis of lung nodules are the significant overlap of benign and malignant nodule FDG-PET characteristics and the lack of consensus criteria for quantitative thresholds to define nodules as malignant.

DP FDG-PET has been proposed also for staging lung cancer and for differentiating metastatic from nonmetastatic lung cancer lesions.⁴¹ In a group of 153 lung cancer patients with known or suspected mediastinal and hilar lymph node involvement or distant metastases, total-body FDG-PET was acquired at 60 minutes (early imaging) and at 180 minutes (delayed imaging). A strong correlation between the RI SUV of the primary lesion and the metastatic lesions was found; FDG uptake in metastases was almost indistinguishable from that in nonmetastatic lesions on both early and delayed scans, and there was no relationship between the RI SUV results of primary lesions and those of nonmetastatic lesions. The accuracy in detecting lymph node and distant metastases was improved when RI SUV was used because of the significant increase in specificity relative to early and delayed SUV. In fact, patient-by-patient analysis for nodal metastasis staging gave these results: early imaging sensitivity 93%, specificity 64%, and accuracy 76%; delayed images sensitivity 97%, specificity 73%, and accuracy 82%; RI SUV sensitivity 100%, specificity 98%, and accuracy 99%. For distant metastasis staging, these values were: early imaging sensitivity 100%, specificity 59%, and accuracy 77%; delayed images sensitivity 100%, specificity 66%, and accuracy 81%; RI SUV sensitivity 100%, specificity 98%, and accuracy 99%. Therefore, these results suggested that RI SUV is able to raise the accuracy for diagnosis of metastases and was superior to early and delayed imaging for the differentiation of malignancy from nonmetastatic uptake.

In 34 patients with NSCLC, the diagnostic capacity of DP FDG-PET/CT for staging intrathoracic lymph node metastases was determined.⁴² Images were acquired 60 minutes (early) and 2 hours (delayed) after tracer administration. Significant differences were detected between metastatic and nonmetastatic lymph nodes and between metastatic and inflammatory lymph nodes for early and delayed SUV and RI, whereas no difference was found between nonmetastatic and inflammatory lymph nodes in early and delayed SUV and RI. For early SUV, the cut-off value for highest accuracy with metastatic lymph nodes was 3.61, yielding a sensitivity of 87% and a specificity of 88%; for delayed SUV, the cut-off value was 4, yielding a sensitivity of 92% and specificity of 93%. For RI, the cut-off value resulted 20.91%, yielding a sensitivity of 74%, and specificity of 76%. These findings indicated that in patients with NSCLC, the 2-hour images have the potential to improve the accuracy of FDG-PET/CT for intrathoracic lymph node staging.

Nevertheless, the usefulness of DP FDG-PET for regional lymph nodes staging in NSCLC cancer is still controversial.

As a matter of fact, Kim et al⁴³ reported a limited predictive value of DP (1 and 2 hours) FDG-PET/CT in the evaluation of pathologic N1 status in 70 patients with stage I and II NSCLC. Lymph node metastases (N1) were present in 15 of 70 patients (21.4%). The N1 group showed statistically significant higher value of both early and delayed SUV than N0 group; nevertheless, the Δ SUV did not result statistically different between pathologic N1 and N0 groups. Yen et al⁴⁴ demonstrated that in tuberculosis endemic country, PET is more accurate than CT in staging chest lymph node in NSCLC, but semiquantitative indices of DP FDG-PET do not have better diagnostic accuracy than visual analysis of PET images. Furthermore, Kasai et al⁴⁵ reported that single-time imaging of FDG-PET/CT is sufficiently useful for diagnosing mediastinal and hilar lymph node metastases in NSCLC patients.

In a recent study aimed to evaluate the efficacy of an additional CT attenuation and a DP scan in determining the status of regional lymph nodes in NSCLC, 39 nodal groups with positive FDG uptake in the initial scan underwent DP imaging, and the difference in the RI between benign and malignant groups showed no statistical significance.⁴⁶ However, in patients with NSCLC with lung comorbidity, DP FDG-PET/CT was more effective for mediastinal nodal staging than single-time-point imaging.⁴⁷ In fact, on a per patient basis, the sensitivity, specificity, accuracy, PPV, and NPV of single-time-point scan were 87%, 59%, 68%, 48%, and 92%, and those values of DP imaging resulted 94%, 68%, 75%, 56%, and 96%, respectively. On a per nodal station basis, the specificity, accuracy, and PPV of DP scan were statistically better than those of single point.

DP FDG-PET can improve the diagnostic accuracy in differentiating benign from malignant pleural disease and

would help to avoid many unnecessary biopsies. In a retrospective study, including 61 NSCLC patients with pleural effusion,⁴⁸ all of them were submitted to total-body FDG-PET/CT imaging at 60 ± 10 minutes after tracer injection, and 31 patients had second delayed imaging for the chest (at 90 ± 10 minutes). In this series, the change in SUVs over time calculated with DP technique was helpful in differentiating malignant pleural disease from benign inflammatory process (sensitivity 100%, specificity 94%, and accuracy 97%).

Conflicting results have been reported on the possible role of DP FDG-PET as a prognostic factor for lung cancer. In a retrospective analysis of 100 consecutive patients with newly diagnosed lung adenocarcinoma, pretherapy SUV change over time between the early (~ 60 minutes) and the delayed (~ 90 minutes) PET was a strong independent predictor of outcome.⁴⁹ A cutoff of 25% change for SUV over time showed the best discriminative value: patients with $>25\%$ increase in SUV had a median survival of 15 months, compared with 39 months for those with $<25\%$ increase in SUV (Fig. 4). Another retrospective review of 66 patients with surgically resected early (stage I and II) NSCLC investigated the prognostic value of DP (at 60 and 120 minutes) FDG-PET/CT at cancer diagnosis.⁵⁰ The overall survival and disease-free survival (DFS) resulted better in patients with early tumor SUV ≥ 5.75 than in the patients with early tumor SUV ≤ 5.75 . Seventeen (51.5%) patients with a delayed tumor SUV ≥ 6.8 and 4 (12.1%) patients with a delayed tumor SUV ≤ 6.8 recurred during follow-up period. The median DFS of the patients with delayed tumor SUV ≥ 6.8 was 31.7 months and was significantly worse than the patients with delayed tumor SUV ≤ 6.8 . However, the Δ SUV did not have prognostic values for overall survival and DFS. Both early and delayed

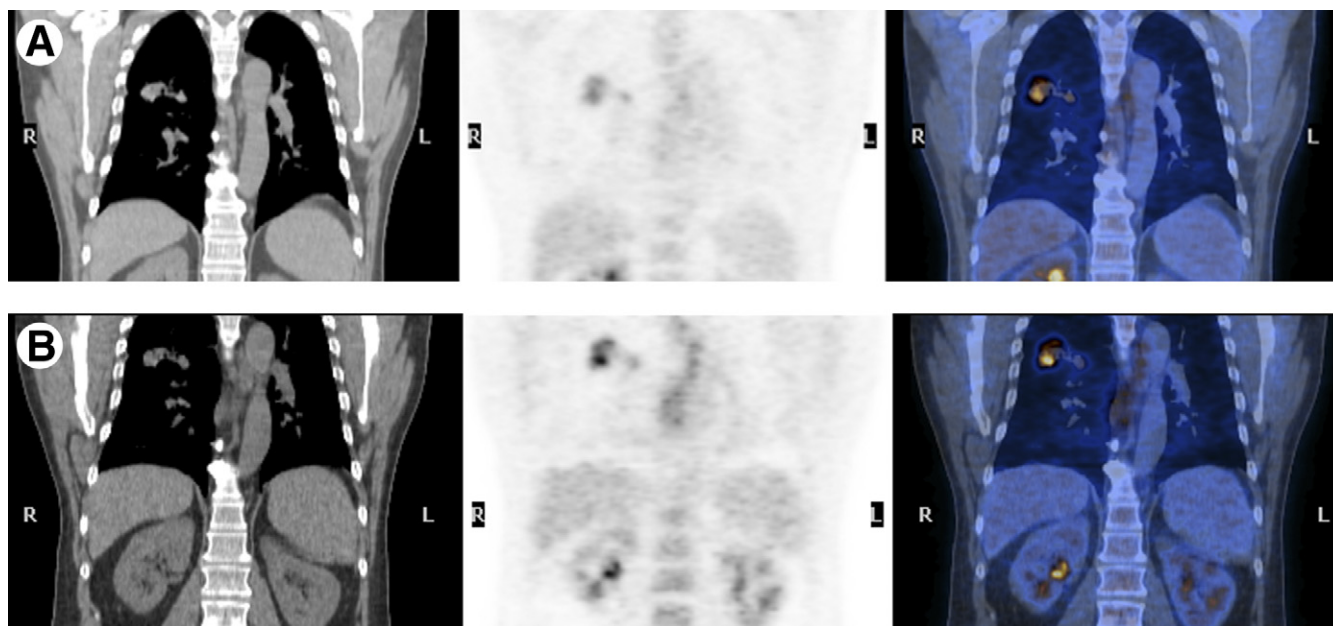


Figure 4 Coronal CT, PET, and PET/CT fusion images of a 58-year-old patient: early (A) and delayed (B) scans. Histopathology was moderately differentiated adenocarcinoma of the right upper lobe. Percentage change of SUV, between early and delayed images, measures 44%, and survival was 11 months. (Color version of figure is available online.)

SUVs were predictors for overall survival; early SUV was also a predictor of DFS. Therefore, these data indicated that Δ SUV calculated by DP FDG-PET/CT might not have a prognostic value for overall survival and DFS in surgically resected early stage NSCLC.

Breast Cancer

After the aforementioned manuscript of Boerner et al,¹⁷ a study was conducted to measure how SUV changes over time in breast cancer.⁵¹ FDG-PET was performed as 60-minute dynamic imaging with an additional image acquired at ~75 minutes after injection in 20 newly diagnosed untreated locally advanced breast cancer patients. In this group, SUV changed approximately linearly after 27 minutes at a rate ranging from -0.02 to 0.15 per minutes, and the rate of SUV change was linearly correlated with the instantaneous SUV measured at different times after injection.

Subsequently, the potential clinical usefulness of DP (at ~63 and ~101 minutes) FDG-PET for identifying malignant lesions in the breast was evaluated in 54 patients with 57 breast lesions.⁵² Among the 39 invasive carcinoma lesions, 33 (85%) showed an increase and 6 (15%) showed either no change or a decrease in SUVs over time; the change in SUVs from time point 1 to time point 2 were $12.6\% \pm 11.4\%$. Of the 18 inflammatory lesions, 3 (17%) showed an increase and 15 (83%) showed either no change or a decrease in SUVs; the change in SUVs from time point 1 to time point 2 resulted $-10.2\% \pm 16.5\%$. Of the 57 normal contralateral breasts, 2 (3.5%) showed an increase and 55 (96.5%) showed either no change or a decrease in SUVs, and the change in SUVs over time was $-15.8\% \pm 17\%$. These data indicated that over time, there is an increase in the uptake of FDG in breast malignancies, whereas the uptake in inflammatory lesions and normal breast tissues decreases. A percentage change of 3.75 or more in SUV differentiated inflammatory lesions from malignant ones. The same group then used the DP technique in a prospective study aimed to assess the utility of this kind of imaging in detecting primary breast cancer and to determine whether there is a relationship FDG uptake and its change over time and the histopathologic subtypes.⁵³ One hundred fifty-two patients with newly diagnosed breast cancer were divided into 2 groups according to histopathology as invasive and noninvasive. The mean early SUV, delayed SUV, and the Δ SUV were 3.9 ± 3.7 , 4.3 ± 4.0 , and $8.3\% \pm 11.5\%$ for invasive; 2.0 ± 0.6 , 2.1 ± 0.6 , and $3.4\% \pm 13\%$ for noninvasive; and 1.2 ± 0.3 , $1.1\% \pm 0.2\%$, and $-10\% \pm 10.8\%$ for the contralateral normal breasts, respectively. Moreover, DP was especially useful in detecting noninvasive (carcinoma in situ) breast cancer, invasive small lesions (<10 mm), and invasive lobular and mixed types of carcinomas. No data are actually available on the possible role of DP FDG-PET imaging in patients with suspicious recurrent breast cancer (Fig. 5).

The value of the reacquisition of PET/CT images 3 hours after FDG administration in the diagnostic evaluation of suspicious breast lesions has been then confirmed in a series of 48 patients.⁵⁴ Malignant breast lesions showed an increase in

FDG uptake over time; in contrast, benign lesions demonstrated a reduction. In particular, the DP acquisition yielded an accuracy of 85% for lesions with a $SUV \geq 2.5$ and/or positive Δ SUV, with sensitivity and specificity values of 81% and 100%, compared with 69%, 63%, and 100%, respectively, for the single-point acquisition.

The accuracy of DP FDG-PET/CT in primary breast cancer with minimally increased FDG uptake ($SUV \leq 2.5$) has been evaluated in a group of 49 patients,⁵⁵ who underwent 2 sequential PET/CT scans (55-60 and 100-120 minutes after tracer injection). Statistical analysis indicated that early SUV and delayed SUV singular measurements were unsatisfactory for discriminating between breast cancer with minimal FDG uptake and normal breast tissue, whereas the % change in SUV over time was adequate for the discrimination of cancer lesions. The highest accuracy for the characterization of malignant breast lesions was obtained when a Δ SUV cut-off value 0% was used as criteria for malignant FDG uptake change over time (sensitivity 76%, false-positive rate 20%).

A recent article has reported that DP imaging is not able to improve the overall performance of FDG-PET/CT in the detection axillary lymph node metastasis in breast cancer patients.⁵⁶ The study included 171 patients who underwent preoperative DP FDG-PET/CT (1 and 3 hours after radiotracer injection). Where FDG uptake in the axilla was perceptibly increased, the SUVs for both time points and the RI were calculated. The results of early and delayed PET/CT images in detecting axillary lymph nodes were equal, with sensitivity 60% and specificity 85%. Sixty patients showed increased FDG uptake in the axillas on 1- or 3-hour images, but there was no significant difference in RI between the metastatic group and the lymph node-negative group. The AUC for early SUV was 0.90 and 0.87 for delayed SUV.

Digestive System Tumors

In the liver, it has been reported that the acquisition of delayed images improves the hepatic detection of pathologic FDG uptake.⁵⁷ In a series of 95 consecutive patients previously treated for neoplastic disease and with suspected liver metastases, a DP PET/CT was acquired (1 and 2 hours after FDG injection). Thirty-seven of 95 patients (38.9%) presented liver lesions at both PET/CT scans, whereas there were 2 (2.2%) only at the second PET/CT. Eighty-one liver lesions were identified at both PET studies, whereas there were 9 (11.1%) only at the second PET. Moreover, at the second PET, a statistically significant reduction of background SUV and an increase of lesions' SUV were observed. These findings demonstrated that acquiring a delayed PET scan allows both a better visualization of liver pathologic uptake and a sensitivity increase—the second acquisition is particularly useful in patients with clinically suspected liver metastases when the first PET scan is negative (Fig. 6).

The previous reported results have been subsequently confirmed in a recent article, including 39 with colorectal cancer and suspicion of hepatic metastases.⁵⁸ The first whole-body PET/CT scan was performed 67 ± 11 minutes after FDG injection; the delayed regional PET/CT scan was ac-

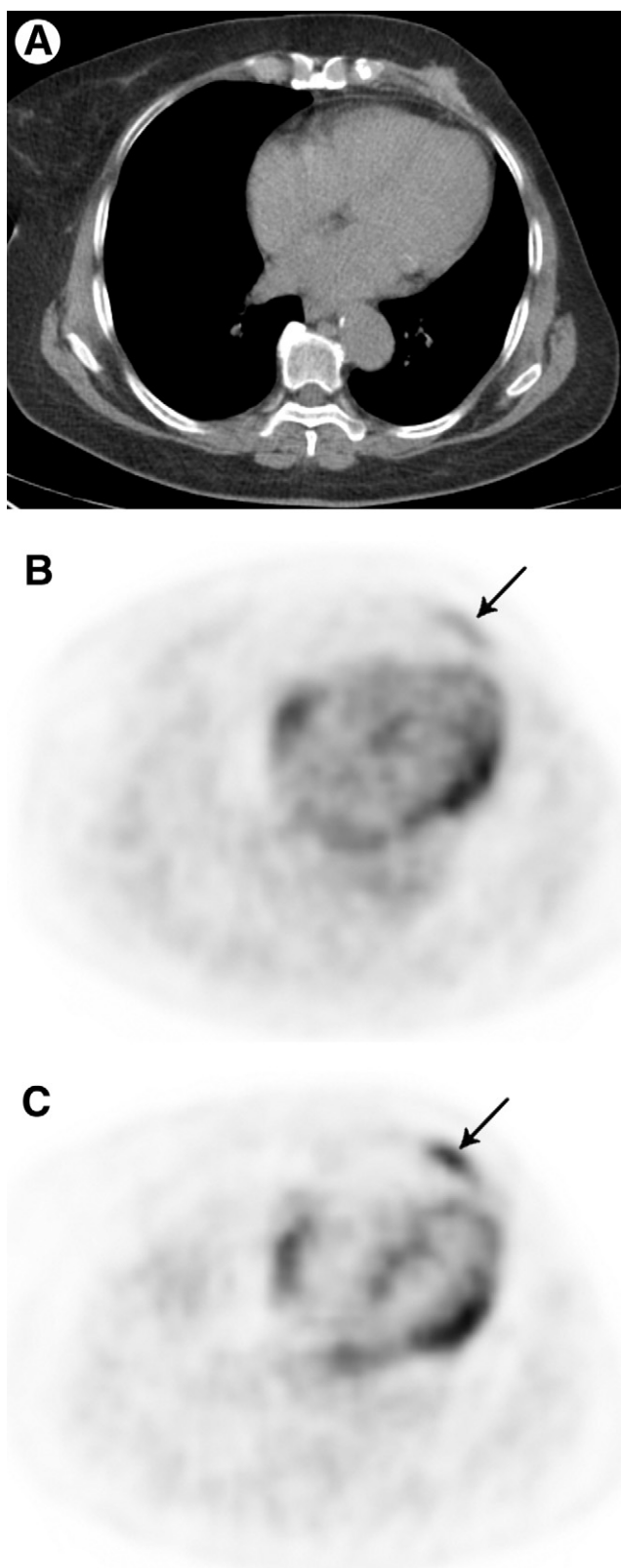


Figure 5 Dual-point FDG-PET imaging of 68-year-old woman, previously submitted to left mastectomy for breast cancer. CT scan (A) shows a suspicious local recurrence. Early PET (B) depicts an area of faint FDG uptake (arrow) that is more prominent in the delayed imaging (C). Pathologic diagnosis was relapsing invasive ductal breast carcinoma.

quired 113 ± 20 minutes after tracer administration. A total of 91 hepatic lesions were detected in 39 patients, and 86 lesions in 34 patients were histopathologically proven to be hepatic metastases; visual analysis detected 77% of them on the first scan and 87% on the delayed images. The SUV and tumor-to-liver uptake ratio (TLR) of the metastatic lesions on the delayed images were higher than those on the early scan; moreover, the TLR and SUV of the delayed scan showed the highest detection rates (92% and 88%, respectively).

The importance of acquiring a delayed PET/CT scan for all hepatic lesions with indeterminate FDG uptake on routine 60-minute images has been highlighted in a case report describing the pattern of FDG accumulation in a patient with hepatic epithelioid hemangioendothelioma, which demonstrated no pathologic uptake in the 60-minute scans, whereas the 3-hour PET/CT images showed intense FDG accumulation in the liver masses.⁵⁹

In patients with suspected gallbladder carcinoma, delayed FDG-PET scans were more helpful than early imaging for evaluating malignant lesions because of increased lesion uptake and lesion-to-background contrast.⁶⁰ In fact, both SUV and TLRs derived from delayed images were significantly higher than the ratios from early images. When a RI of -8 was chosen as arbitrary cut-off for differentiating between malignant and benign conditions, the accuracy was 84%. Nevertheless, it is interesting to highlight that the diagnostic performance of FDG-PET was highly dependent on C-reactive protein (CRP) levels (specificity was 80% in the group with a normal level of CRP and 0% in the group with an elevated CRP level, respectively).

In patients with esophageal squamous cell carcinoma, DP PET/CT demonstrated limited value in detection of primary tumor and locoregional lymph nodes metastasis; however, for the distant metastasis, the sensitivity improved if RI $\geq 10\%$ was used as a supplemental criterion.⁶¹

In pancreatic cancer, after the study of Nakamoto et al,¹⁹ it has been recently reported that FDG-PET with DP (1 and 2-hours) evaluation is a useful modality for the detection of small invasive ductal carcinomas with a diameter of <20 mm.⁶² Moreover, the RI calculated with DP FDG-PET can be used not only as a tool for initial diagnosis and staging of pancreatic cancer but also as a strong independent prognostic parameter for an accurate identification of those patients who will benefit from intensive therapy at different stages of the disease.⁶³ In particular, when combined with tumor stage, RI allowed even more precise prognostic evaluation: patients at stage I-III with RI $>10\%$ survived longer than did patients at the same stage with RI $<10\%$ (15.3 vs 11.5 months), patients at stage IV with RI $>10\%$ had an intermediate prognosis (median survival of 9.5 months), and patients at stage IV with RI $<10\%$ showed the worst prognosis (4.9 months).

The normal variants of the physiological FDG uptake in DP imaging have been described in a retrospective review of 206 consecutive asymptomatic subjects who underwent whole-body FDG-PET/CT for medical checkup.⁶⁴ The findings of this study indicated that physiological FDG uptake in the colon increases from the early (50 minutes) to the delayed

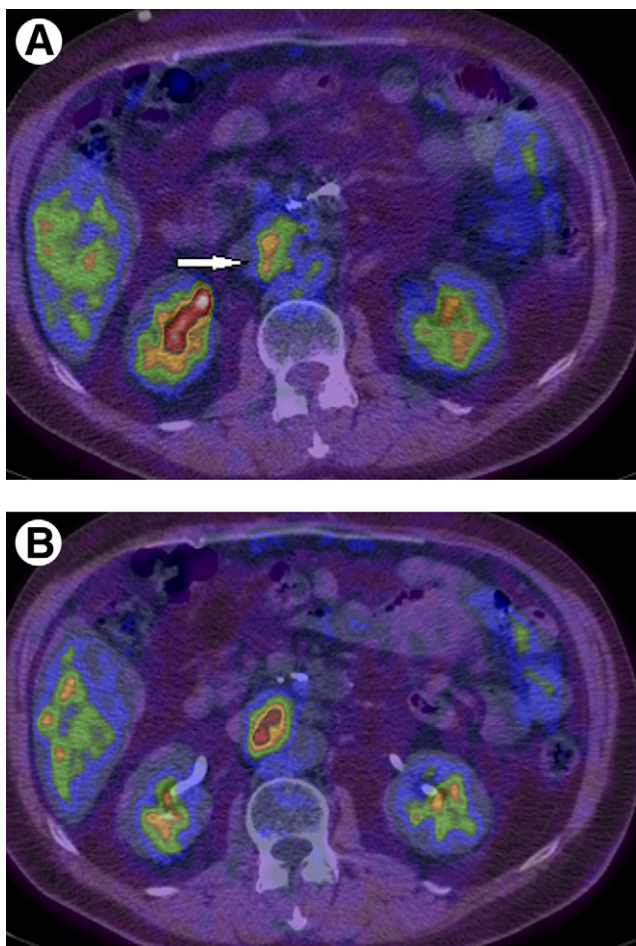


Figure 7 A 52-year-old male patient with previously resected pancreatic cancer. Early (60 minutes) PET/CT (A) shows a moderate FDG uptake in an enlarged abdominal lymph node (arrow, SUV 2.8), which increases in the delayed imaging (110 minutes, SUV 3.3) (B). The final diagnosis was lymph node metastasis.

ful to enhance the detectability of tiny residual skull base osteosarcoma initially concealed by adjacent high physiological brain activity.⁷²

In evaluating the locoregional status of nasopharyngeal carcinoma, the results of a prospective study, including 84 patients, indicated that FDG-PET is superior to MRI in identifying lower neck nodal metastasis, but 3-hour scans did not give further information in detecting both primary tumors or locoregional metastatic nodes with respect to 40-minute images.⁷³ Nevertheless, it is worth noting that in this study, diazepam 5 mg per os, was routinely given before FDG injection, and this fact might decrease the hexokinase/glucose-6-phosphatase ratio and so render the DP technique ineffective under these circumstances.⁷⁴ In fact, diazepam can reduce phosphorylation of glucose by inhibiting hexokinase activity, and its effect after orally administration commences approximately 30 minutes after ingestion and lasts many hours; therefore, it will likely minimally affect the early images (within the first hour), whereas it will significantly influence the FDG uptake on delayed images.⁷⁴

The accuracy of DP FDG-PET for the diagnosis of the various subtypes of thymic epithelial tumors based on the WHO classification was assessed in 23 patients.⁷⁵ High SUV values suggested the presence of high-risk tumors, and a very high SUV value (early >7.1) was useful for the differentiation of thymic carcinomas from other types of tumors. The delayed SUV values were higher than the early SUV values in all types of tumors.

In patients with incidentally detected thyroid nodules during FDG-PET/CT, the DP protocol (60 and 120 minutes) was of limited value for differentiating malignant from benign nodules.⁷⁶

Conclusions

Now FDG-PET and PET/CT imaging plays a fundamental role in oncology; however, with its wide application throughout the world, a growing number of limitations have been found. One of the main causes is certainly the nonspecificity of FDG uptake in tumor; it is well known that false-positive results could be because of inflammation, infection, or other unknown benign tumors,^{77,78} and so, it is really difficult to

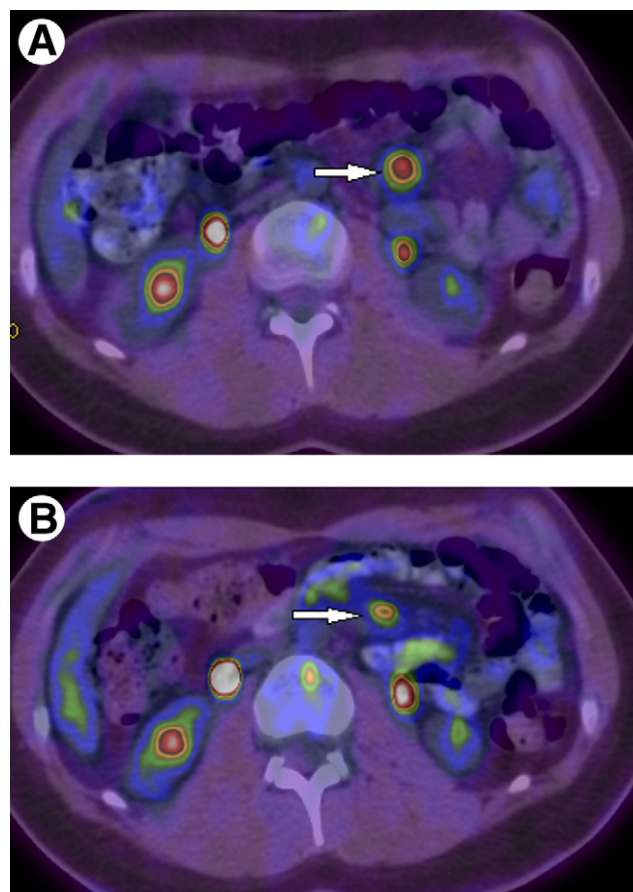


Figure 8 A 24-year-old young female patient with Hodgkin lymphoma, evaluated after chemotherapy. Early (60 minutes) PET/CT (A) demonstrated a focal area of FDG uptake in an abdominal lymph node (arrow, SUV 3.5), which decreases (SUV 2.9) in the later imaging at 120 minutes (B). This pattern is strongly suggestive for the presence of inflammatory tissue rather than for residual disease.

distinguish malignant from benign lesions in such clinical situations.

Several experimental approaches both in vitro and through PET images in vivo suggest that the time-activity of FDG uptake between malignant and benign lesions is different—tumor uptake increases for hours, whereas in inflammatory lesions it decreases gradually from 60 minutes after injection. Therefore, this difference in the time course could be useful to improve the specificity of FDG studies for differentiating benign from malignant lesions by means of the acquisitions of delayed scans. Moreover, it is important to highlight that in many of these studies, the DP technique was able to improve the sensitivity of PET in assessing various tumors. This can be explained by 2 factors: first, there may be clearance of background activity between the 2 time points, improving target-to-background ratio, that leads to higher sensitivity; second, a significant increase in SUV within malignant lesions over time might also improves lesion detectability.

Nevertheless, some points should be clarified before suggesting the inclusion of DP imaging in routine FDG-PET/CT protocols for cancer patients.⁷⁹ In particular, further investigations are needed to identify patient populations that would most benefit from this technique. As a matter of fact, in a recent article assessing the utility of DP FDG-PET/CT in the Australian population, this approach differentiated malignant from benign intra-abdominal lesions (Figs. 7 and 8) but did not improve the overall evaluation of pulmonary lesions.⁸⁰

If imaging should be performed as late as reasonably possible after FDG injection to increase tumor to background contrast and thereby improve the sensitivity in demonstrating additional sites of disease, it is clear that the various tumor types may be affected differently by delayed scans. Tumor-specific studies would be useful to assess the optimal timing of imaging for tumors, which could have differing levels of hexokinase/glucose-6-phosphatase ratio (eg, hematological malignancy, sarcoma, breast and other carcinoma subtypes). Therefore, the most appropriate time for a delayed scan should be defined for each kind of neoplasm⁸¹; moreover, the method of SUV calculation should be standardized, as well as the criteria for quantitative thresholds to define lesions as malignant, for example, for the lung nodules. Finally, larger prospective studies may be helpful to better evaluate the clinical role of DP FDG-PET/CT imaging in oncology patients, in particular taking into account any possible resulting change in management.

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