White Paper

# The value of PET/CT for melanoma

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# Executive summary

PET/CT, a combination of contrasting and complimentary modalities of positron emission tomography (PET) and computed tomography (CT), is an extremely useful imaging tool in oncology, neurology, and cardiology. Tumors that are avid for Fludeoxyglucose F 18 ($^{18}$F FDG) injection,[a] an analogue of glucose, are very effectively assessed with this hybrid imaging modality. Melanoma is robustly $^{18}$F FDG-avid.[1] Accuracy of $^{18}$F FDG PET/CT increases with increasing tumor $^{18}$F FDG avidity. There is growing literature demonstrating remarkable utility of $^{18}$F FDG PET/CT in melanoma. This is very well reflected in the national cancer management guidelines as well as in the current reimbursement policies.

## Fludeoxyglucose F 18 5-10mCi as an IV injection

### Indications and usage

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- Oncology: For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together withmyocardial perfusion imaging.
- Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

### Important safety information

- Radiation Risks: Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker.
- Blood Glucose Abnormalities: In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.
- Adverse Reactions: Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available. Full prescribing information for Fludeoxyglucose F 18 Injection can be found at the conclusion of this publication.

### Dosage forms and strengths

multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanolas a stabilizer (approximately 15 to 50 mL volume) for intravenous administration. Fludeoxyglucose F 18 injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

[a] For indications and important safety information for Fludeoxyglucose F 18 injection ($^{18}$F FDG) see page 3. For full prescribing information see pages 17-19.

# Introduction

Melanoma is a malignant neoplasm of the skin, originating from the melanocyte. According to American Cancer Society's 2018 estimates, 91,270 new melanomas will be diagnosed (about 55,150 in men and 36,120 in women).[2] About 9,320 people are expected to die of melanoma (about 5,990 men and 3,330 women). Melanoma is more than 20 times more common in Caucasians than in African Americans. Overall, the lifetime risk of getting melanoma is about 2.6% (1 in 38) for Caucasians, 0.1% (1 in 1,000) for African Americans, and 0.58% (1 in 172) for Hispanics.

The risk of melanoma increases as people age. The average age of people when it is diagnosed is 63 years old; however, melanoma is not uncommon even among those younger than 30. In fact, it's one of the most common cancers in young adults (especially young women).[2]

Accounting for less than 5% of all skin cancers, melanoma is associated with approximately 75% of skin cancer–related mortality.[3] Although predominantly found in the skin, melanoma can also arise in other sites, including mucosal surfaces (anus, vaginal surfaces), ocular (uveal) locations, or meningeal surfaces.

Since the early 1990s, a major advance in the management of patients with cutaneous melanoma has involved the technique of lymphatic mapping and sentinel lymph node (SLN) biopsy.[4]

Increasing interest in understanding the biology and pathogenesis of melanoma has led to the discovery of vital signaling pathways and the development of mutation-driven therapy, immunotherapy, and targeted therapies, which have revolutionized the clinical history of this disease by dramatically improving the outcomes of patients with metastatic disease. Immunotherapy is mostly based on immune checkpoint inhibitors targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), and more recently programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) interaction.[5]

As discussed in detail below, PET/CT plays an increasingly important role in the appropriate clinical setting in both initial as well as subsequent treatment strategies in melanoma management.

# $^{18}$F FDG PET/CT imaging protocols for melanoma

Melanoma can metastasize to practically any organ. Metastases to skin/subcutaneous tissues as well as to both axial and appendicular skeleton can occur. Therefore, routine imaging from vertex to sole of feet may allow both accurate initial staging of the disease and subsequent detection of recurrences/metastases.[6]

If there are no contraindications, intravenous contrast may provide better anatomic definition of lesions, particularly in the solid organs and lymph nodes as well as the brain. PET sensitivity for metastatic lesions to the cerebral cortex may be compromised due to high physiologic background of $^{18}$F FDG. Brain magnetic resonance imaging (MRI) is superior in defining these lesions and may be indicated in the appropriate setting.

Oral contrast may be helpful in better anatomic delineation of gastrointestinal tract and in detection of small lymph nodes in close proximity to the bowel loops.

# PET/CT in initial treatment strategy

## Current status

SLN biopsy is now routinely used as a staging procedure for patients with T1b, T2, T3, and T4 primary cutaneous melanomas and clinically negative regional lymph nodes in most melanoma treatment centers throughout the world.[8,9]

The frequency of SLN metastasis increases with increasing tumor thickness and other adverse clinicopathological prognostic factors.[10]

Krug et al. published a comprehensive review article discussing the use of $^{18}$F FDG PET in initial staging of melanoma.[11] Based on 28 studies, the authors concluded that PET/CT is useful in detecting metastases, especially in patients with stages III and IV melanomas, with limited use in stages I and II diseases. The pooled sensitivity of PET/CT was 83%, and the pooled specificity was 85%. However, the authors note the preliminary nature of the presented results and recommend further prospective studies with defined clinical endpoints. Overall, PET/CT was superior to the other imaging modalities. Xing et al. investigated the use of CT, PET, and PET/CT in a large meta-analysis based on 74 studies and concluded that PET/CT is superior in the detection of the distant metastases in the primary stating compared with PET and CT alone (sensitivity of 86%, 82%, and 63%, respectively).[12]

The benefit of PET/CT in stages I and II diseases was evaluated in smaller case series, which found it to be of limited value.[13]

Singh et al. evaluated 52 patients with no palpable nodes. The sensitivity of $^{18}$F FDG PET/CT for predicting SN involvement was 14.3%. The positive predictive value was only 50%. They concluded that FDG PET/CT is not a substitute for SLN biopsy.[14]

Yancovitz et al. evaluated different presurgical imaging methods (chest radiograph, CT, and PET/CT) in 158 patients with melanoma (T1b–T3b). They discovered only one metastatic lesion in contrast to many false-positive results.[15]

**$^{18}$F FDG PET before completion lymphadenectomy in patients with positive SLN biopsy:** Horn et al. evaluated 80 patients with $^{18}$F FDG PET after a positive SLN and within 100 days of the SLN biopsy procedure. $^{18}$F FDG PET was suspicious of distant involvement in 13 patients but only four could be considered true-positive. In addition, four patients with negative $^{18}$F FDG PET manifested clinical recurrence within 6 months after SLN biopsy. PET was therefore considered false-negative in these patients.[16]

**$^{18}$F FDG PET prior to lymph node dissection in patients with palpable nodes:** Bastiaann et al. compared $^{18}$F FDG PET to CT in 251 patients with palpable lymph nodes prior to lymph node dissection. Significantly more metastatic sites were detected by $^{18}$F FDG PET than CT (120 vs 100; P 0.03). In particular, $^{18}$F FDG PET detected more bone/bone marrow and subcutaneous lesions.[17]

Aukema et al. evaluated role of $^{18}$F FDG PET/CT in 70 patients with palpable lymph nodes prior to lymph node dissection, with a sensitivity of 87% and positive predictive value of 97%. A change in management occurred in 26 patients (37%).

Distant metastases were discovered in 20 patients, lymphatic metastases in another nodal basin in three patients, and in-transit lesions in three patients.[7]

PET/CT in initial treatment strategy of melanoma: Conclusion

- $^{18}$F FDG PET/CT cannot replace SLN biopsy because of low sensitivity
- There is a controversial role in patients without palpable lymph nodes
- PET/CT is useful in patients with palpable lymph nodes as it reveals distant metastases or lymph node involvement in more regional basins

## Clinical guidelines

In patients with stage III disease, PET/CT scan may be more useful. In particular, PET/CT scans can help to further characterize lesions found to be indeterminate on CT scan, and can image areas of the body not studied by the routine body CT scans (i.e., arms and legs).[6]

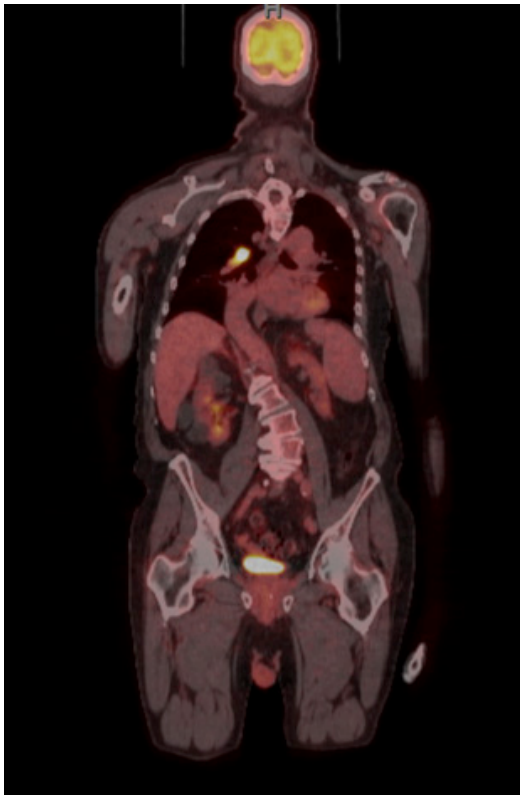
# PET/CT in subsequent treatment strategy of melanoma

**A. Detection of early recurrence**
**B. Assessment of treatment response**
**C. PET/CT as a potential prognostic marker**
**D: PET/CT in melanoma surveillance**

## A: Detection of early recurrence

Early identification of patients with oligometastasis to lung, soft tissue, or distant lymphatic site is important to identify for those patients with disease who might be amenable to surgical resection. Most initial distant recurrences occur in the first two or three years.[18, 19] This group of patients may achieve prolonged survival when distant lesions are completely resected.[20]

Koskivuoa et al. used whole-body PET/CT in the follow up of 110 asymptomatic patients with stage IIB-IIIB cutaneous melanoma and found occult disease in 11 asymptomatic patients (10%) with a single PET/CT. In 50 patients (45%), PET/CT findings were true negative. In 15 patients (14%), the PET/CT scan was a false positive leading to additional management or repetitive imaging. An earlier detection of occult metastases did not improve survival.[21]



Example of solitary metastatic lesion: right hilar lymph node

Data courtesy of Munir Ghesani, MD, FACNM, FACR, New York, NY, USA.

## B: Assessment of treatment response

The management of metastatic melanoma has been revolutionized with the introduction of immune checkpoint inhibitor therapy. Ipilimumab acts by blocking the immune checkpoint pathway involving the CTLA-4. In a recent study, it was reported that among patients with advanced melanoma, significantly longer overall survival occurred with combination therapy with nivolumab plus ipilimumab or with nivolumab alone than with ipilimumab alone.[22]

It should be noted that the mechanism of action of these agents is markedly different from that of cytotoxic chemotherapy, leading to atypical response patterns and several new immune-related adverse events. This raises the issue of appropriate evaluation of treatment response, leading to the introduction of a new set of response criteria based on the World Health Organization (WHO) criteria, the immune-related response criteria (irRC).[23]

Hodi et al. evaluated immunotherapy treatment response in 655 melanoma patients treated with pembrolizumab. Five percent of the patients had early pseudoprogression and 3% had delayed pseudoprogression.

They concluded that traditional assessment using RECIST criteria would have underestimated treatment response in 15% of patients, probably leading unnecessarily to premature cessation of therapy.[24]

**Immunotherapy treatment response: irRC key points**

- Follow-up imaging studies be performed no less than 4 weeks after the first assessment
- The appearance of one new metastatic lesion is not necessarily related to tumor progression if the whole tumor volume has not increased by more than 25% from the baseline study[23]
- There are four immune response categories: complete response, partial response, stable disease, and progression of disease

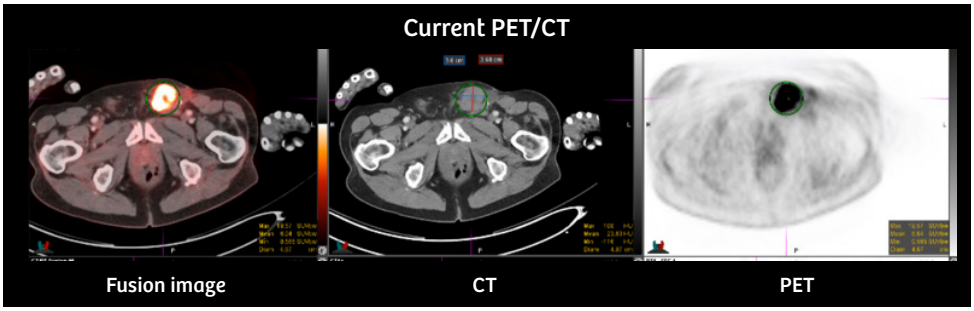
| | |
|---|---|
| **irCR** | Complete disappearance of all lesions (whether measurable or not, and no new lesions, and confirmation by a repeat consecutive assessment no less than 4 weeks from date first documented) |
| **irPR** | Decrease in tumor burden ≥ 50% relative to baseline confirmed by repeat consecutive assessment at least 4 weeks later |
| **irSD** | Not meeting criteria for irCR or irPR in absence of irPD |
| **irPD** | increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden) confirmed by repeat consective assessment at least 4 weeks later |

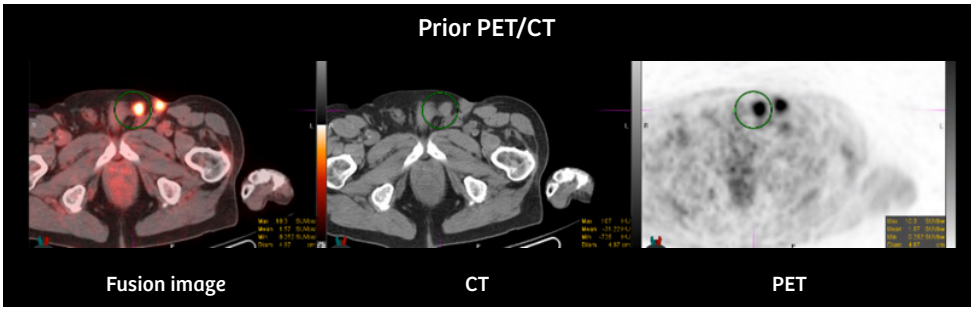
Data courtesy of Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS, 2009.

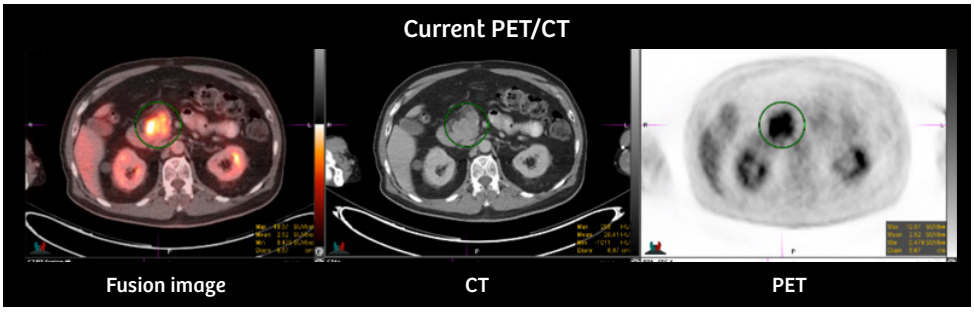
Legend: irCR = complete immune response
irPR = partial immune response
irSD = stable disease
irPD = progressive disease

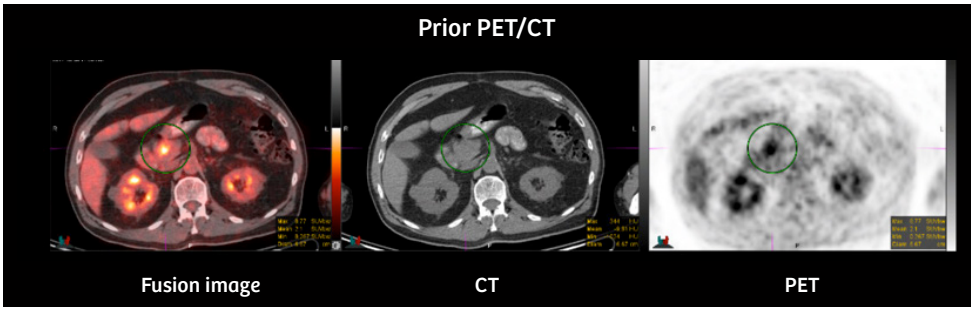
## Case #1:

Example of interval progression of metastases.



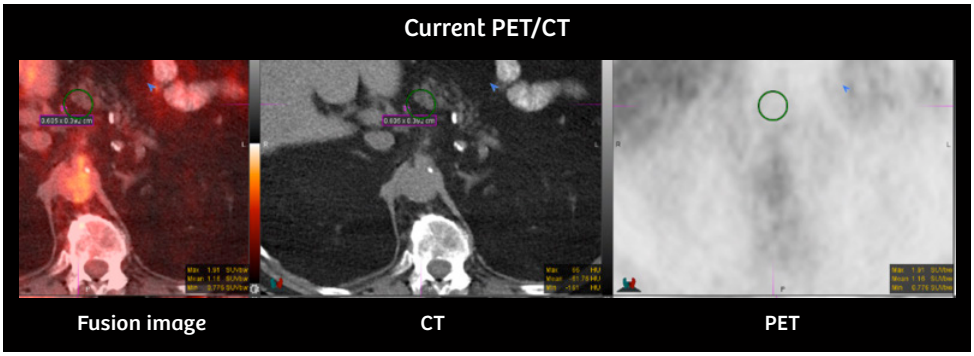



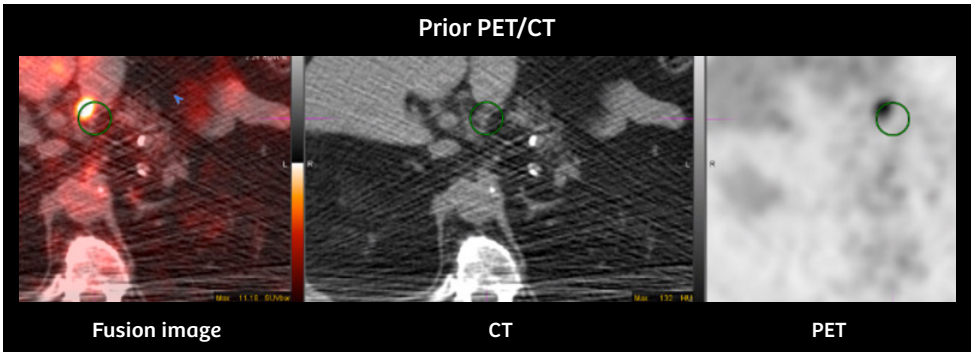



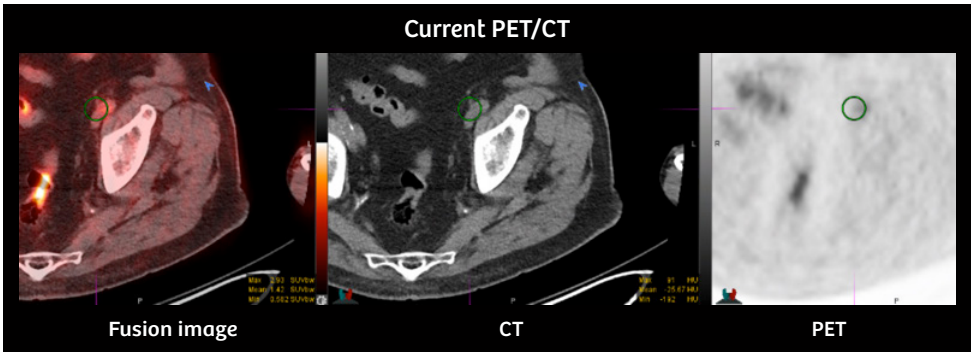

Data courtesy of Munir Ghesani, MD, FACNM, FACR, New York, NY, USA.

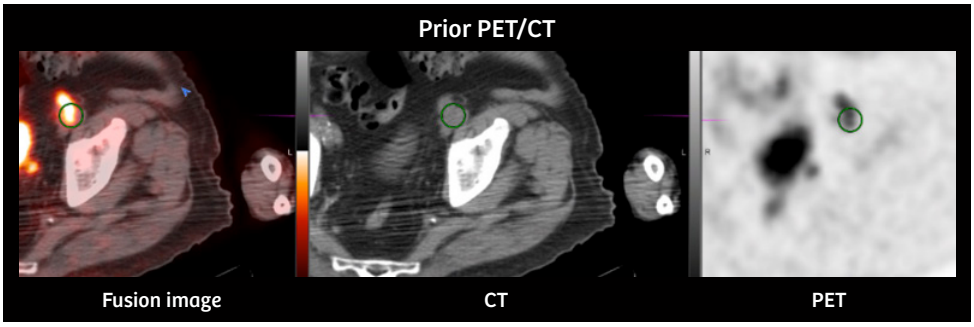
## Case #2:

Example of interval partial treatment response.



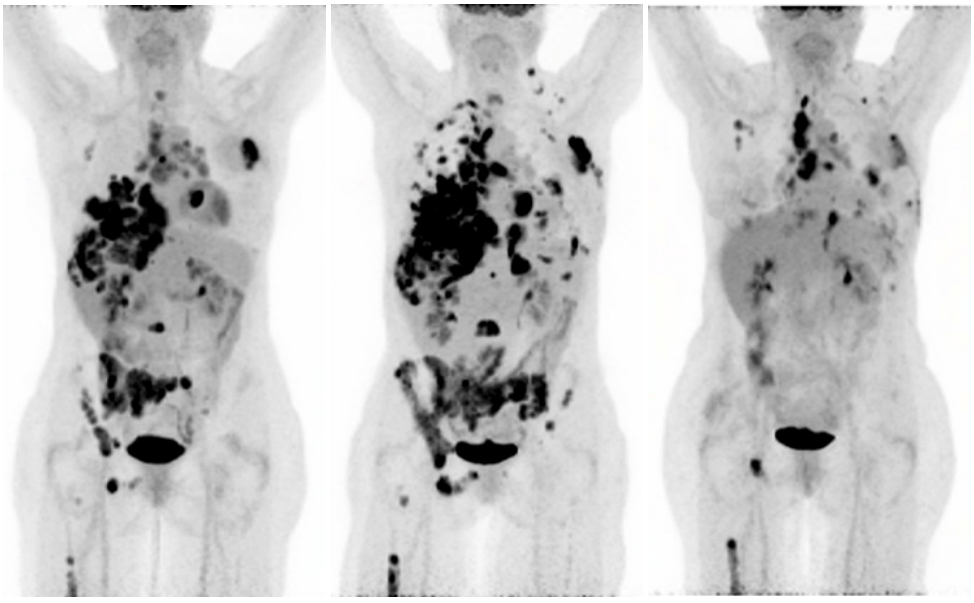




Data courtesy of Munir Ghesani, MD, FACNM, FACR, New York, NY, USA.

## Case #3:

Example of initial immune flare followed by partial treatment response.

**Maximum intensity projection (MIP) images**



**Initial scan** | **1 month post treatment** | **1 year follow-up**

Data courtesy of Munir Ghesani, MD, FACNM, FACR, New York, NY, USA.

## C: PET/CT as a potential prognostic marker

$^{18}$F FDG PET/CT has also been recently proposed as a potential marker to aid predicting patients' prognosis in different tumors, by using the various PET metabolic parameters, such as the $SUV_{max}$, metabolic tumor volume (MTV), and total lesion glycolysis (TLG).[25]

$SUV_{max}$ is a semiquantitative measure of tumor $^{18}$F FDG uptake, whereas MTV refers to volumetric measurement of tumor cells with high glycolytic activity; TLG is the sum of SUVs within the tumor, calculated as MTV X $SUV_{mean}$. In the setting of melanoma, Kang et al. reported that the $SUV_{max}$ from $^{18}$F FDG PET/CT can provide important information for predicting recurrence.[26]

Using PET volumetric parameters, Son et al. retrospectively conducted a review study including 41 patients with a histologic diagnosis of cutaneous melanoma who underwent pretreatment $^{18}$F FDG PET/CT scans; $SUV_{max}$ and TLG were found to be significantly higher in patients with recurrence than in patients without, and $SUV_{max}$ and TLG were also found to be significantly higher in nonsurvivors than in survivors.[27]

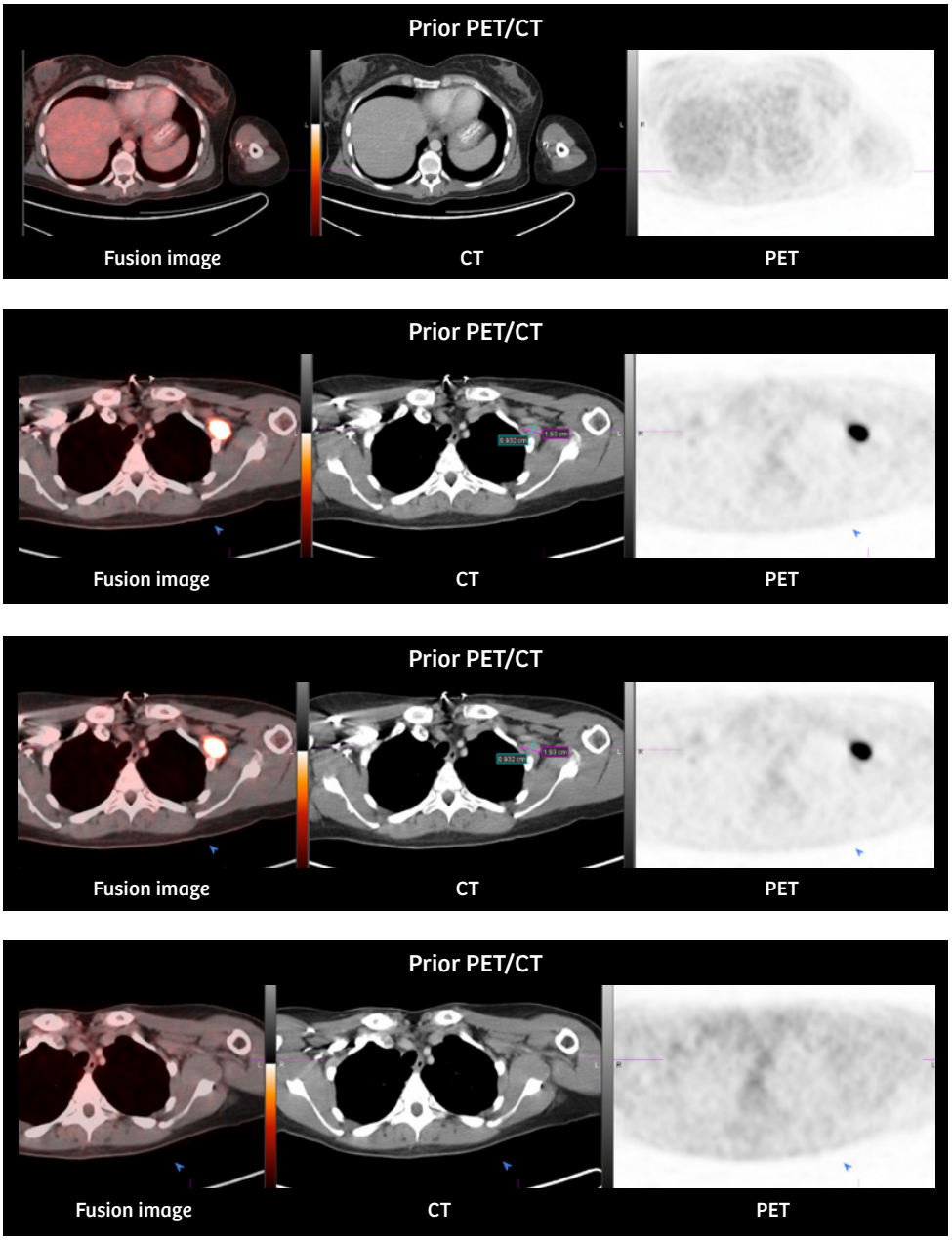
## D: PET/CT in melanoma surveillance

There are limited data on the follow-up of patients with melanoma. Recommendations on routine surveillance are therefore controversial. It may be reasonable to perform follow up evaluation of high risk patients. Vensby et al. evaluated 238 patients (526 scans).[28]

PET/CT findings were compared to histology, MRI or fine needle aspiration. They discovered that a negative PET/CT excludes relapse with a high degree of certainty. However, the frequency of false positive findings was relatively high, especially among patients undergoing a "routine" PET/CT with no clinical suspicion of relapse.

### Case #3:

Examples of recurrence detected on surveillance.

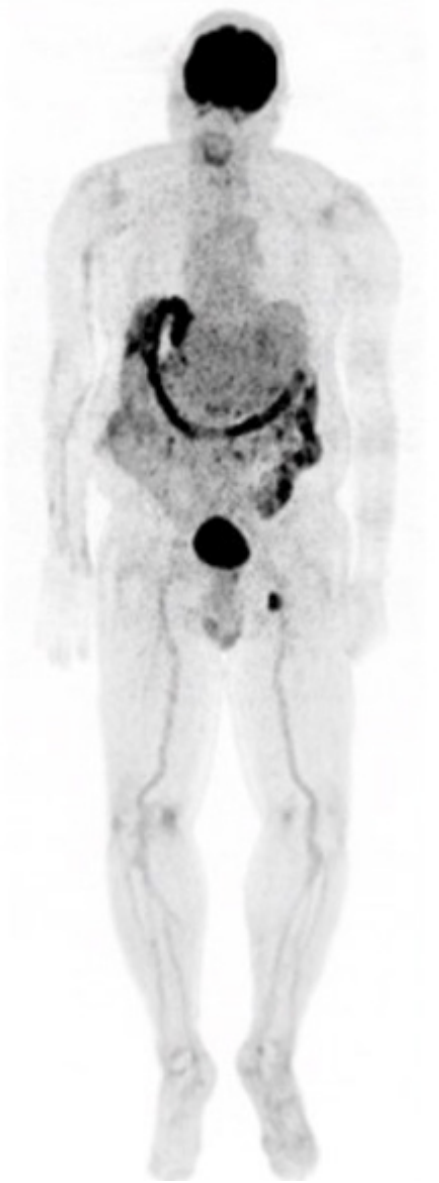


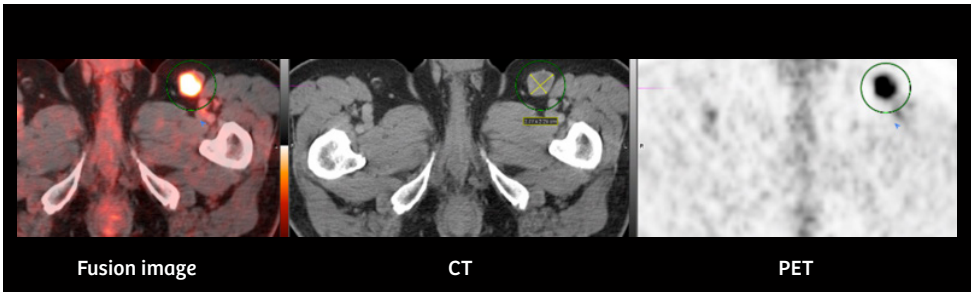

History of left upper extremity melanoma, surveillance scan following resection of in-transit metastasis in left forearm now demonstrates metastatic disease in left subpectoral station.

Data courtesy of Munir Ghesani, MD, FACNM, FACR, New York, NY, USA.

## Case #4:

MIP image






Left lower extremity melanoma.
Left inguinal recurrence on PET/CT, subsequently proven by biopsy.

Data courtesy of Munir Ghesani, MD, FACNM, FACR, New York, NY, USA.

### Clinical guidelines

A large meta-analysis compared ultrasound imaging CT, PET, and PET/CT, for the staging and surveillance of patients with melanoma.[29] Data from 74 studies containing 10,528 patients were included. For both staging and surveillance purposes, ultrasound was found to be associated with the highest sensitivity and specificity for lymph node metastases, while PET/CT was superior for detecting distant metastases. The safety of CT and PET/CT is a significant concern, however, because large population-based studies have shown that cumulative radiation exposure from repeated CT and nuclear medicine imaging tests may be associated with an increased risk of cancer.[6]

# Current reimbursement pathways for PET/CT imaging in melanoma

Melanoma was one of the first few cancers to receive Centers for Medicare and Medicaid (CMS) approval for $^{18}$F FDG PET imaging. Similar to many other cancer types, the revised CMS policy provides reimbursement of PET/CT in melanoma as part of initial and subsequent treatment strategies. Since there is strong literature supporting the use of PET/CT in melanoma, third-party carriers therefore readily approve its use, and follow CMS guidelines. In the setting of early T stage melanoma and no palpable lymph nodes sentinel lymph node biopsy is more sensitive than PET/CT. In this setting, PET/CT is generally not indicated.

# Conclusion

Melanoma in general is robustly FDG-avid. $^{18}$F FDG PET/CT is more sensitive than anatomic modalities, such as CT or MRI, and at least equally specific. In the setting of early T stage melanoma and no palpable lymph nodes PET/CT is generally not indicated. In the assessment of treatment response PET/CT is shown to be a very valuable imaging tool. In the application of PET/CT in treatment response assessment, one needs to be aware of atypical response patterns in the setting of immunotherapy. Immune response criteria should be used in this setting. Recommendations on routine surveillance of melanoma with PET/CT are controversial. However, in high risk patients, PET/CT detects recurrences with high sensitivity and may help identify resectable oligometastatic lesions. So far, it has not been shown to improve survival.

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Fludeoxyglucose F 18 Injection safely and effectively. See full prescribing information for Fludeoxyglucose F 18 Injection.**

**Fludeoxyglucose F 18 Injection, USP**
**For intravenous use**
**Initial U.S. Approval: 2005**

**RECENT MAJOR CHANGES**

| | |
|---|---|
| Warnings and Precautions (5.1, 5.2) | 7/2010 |
| Adverse Reactions ( 6 ) | 7/2010 |

**INDICATIONS AND USAGE**

Fludeoxyglucose F18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- Oncology: For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures (1).

**DOSAGE AND ADMINISTRATION**

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

- In the oncology and neurology settings, instruct patients to fast for 4 to 6 hours prior to the drug's injection. Consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to the drug's administration (5.2).
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection facilitates localization of cardiac ischemia (2.3).

Aseptically withdraw Fludeoxyglucose F 18 Injection from its container and administer by intravenous injection (2).

The recommended dose:

- for adults is 5 to 10 mCi (185 to 370 MBq), in all indicated clinical settings (2.1).
- for pediatric patients is 2.6 mCi in the neurology setting (2.2).

Initiate imaging within 40 minutes following drug injection; acquire static emission images 30 to 100 minutes from time of injection (2).

**DOSAGE FORMS AND STRENGTHS**

Multi-dose 30mL and 50mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose F 18 Injection and 4.5mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration (3).

**CONTRAINDICATIONS**

None (4)

**WARNINGS AND PRECAUTIONS**

- Radiation risks: use smallest dose necessary for imaging (5.1).
- Blood glucose adnormalities: may cause suboptimal imaging (5.2).

**ADVERSE REACTIONS**

Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available (6).

**To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**USE IN SPECIFIC POPULATIONS**

Pregnancy Category C: No human or animal data. Consider alternative diagnostics; use only if clearly needed (8.1).

- Nursing mothers: Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding (8.3).
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings (8.4).

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 1/2016**

**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

**1.1 Oncology**

For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

**1.2 Cardiology**

For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

**1.3 Neurology**

For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

**2 DOSAGE AND ADMINISTRATION**

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].

**2.1 Recommended Dose for Adults**

Within the oncology, cardiology and neurology settings, the recommended dose for adults is 5 to 10 mCi (185 to 370 MBq) as an intravenous injection.

**2.2 Recommended Dose for Pediatric Patients**

Within the neurology setting, the recommended dose for pediatric patients is 2.6 mCi, as an intravenous injection. The optimal dose adjustment on the basis of body size or weight has not been determined [see *Use in Special Populations (8.4)*].

**2.3 Patient Preparation**

- To minimize the radiation absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [see *Warnings and Precautions (5.2)*]. Prior to Fludeoxyglucose F 18 PET imaging in the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug's injection.
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F18 Injection facilitates localization of cardiac ischemia

**2.4 Radiation Dosimetry**

The estimated human absorbed radiation doses (rem/mCi) to a newborn (3.4 kg), 1-year old (9.8 kg), 5-year old (19 kg), 10-year old (32 kg), 15-year old (57 kg), and adult (70 kg) from intravenous administration of Fludeoxyglucose F 18 Injection are shown in Table 1. These estimates were calculated based on human[2] data and using the data published by the International Commission on Radiological Protection[4] for Fludeoxyglucose $^{18}$ F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated are the urinary bladder, heart, pancreas, spleen, and lungs.

**Table 1. Estimated Absorbed Radiation Doses (rem/mCi) After Intravenous Administration of Fludeoxyglucose F-18 Injection[a]**

| Organ | Newborn (3.4 kg) | 1-year old (9.8 kg) | 5-year old (19 kg) | 10-year old (32 kg) | 15-year old (57 kg) | Adult (70 kg) |
|---|---|---|---|---|---|---|
| Bladder wall[b] | 4.3 | 1.7 | 0.93 | 0.60 | 0.40 | 0.32 |
| Heart wall | 2.4 | 1.2 | 0.70 | 0.44 | 0.29 | 0.22 |
| Pancreas | 2.2 | 0.68 | 0.33 | 0.25 | 0.13 | 0.096 |
| Spleen | 2.2 | 0.84 | 0.46 | 0.29 | 0.19 | 0.14 |
| Lungs | 0.96 | 0.38 | 0.20 | 0.13 | 0.092 | 0.064 |
| Kidneys | 0.81 | 0.34 | 0.19 | 0.13 | 0.089 | 0.074 |
| Ovaries | 0.80 | 0.8 | 0.19 | 0.11 | 0.058 | 0.053 |
| Uterus | 0.79 | 0.35 | 0.19 | 0.12 | 0.076 | 0.062 |
| LLI wall * | 0.69 | 0.28 | 0.15 | 0.097 | 0.060 | 0.051 |
| Liver | 0.69 | 0.31 | 0.17 | 0.11 | 0.076 | 0.058 |
| Gallbladder wall | 0.69 | 0.26 | 0.14 | 0.093 | 0.059 | 0.049 |
| Small intestine | 0.68 | 0.29 | 0.15 | 0.096 | 0.060 | 0.047 |
| ULI wall ** | 0.67 | 0.27 | 0.15 | 0.090 | 0.057 | 0.046 |
| Stomach wall | 0.65 | 0.27 | 0.14 | 0.089 | 0.057 | 0.047 |
| Adrenals | 0.65 | 0.28 | 0.15 | 0.095 | 0.061 | 0.048 |
| Testes | 0.64 | 0.27 | 0.14 | 0.085 | 0.052 | 0.041 |
| Red marrow | 0.62 | 0.26 | 0.14 | 0.089 | 0.057 | 0.047 |
| Thymus | 0.61 | 0.26 | 0.14 | 0.086 | 0.056 | 0.044 |
| Thyroid | 0.61 | 0.26 | 0.13 | 0.080 | 0.049 | 0.039 |
| Muscle | 0.58 | 0.25 | 0.13 | 0.078 | 0.049 | 0.039 |
| Bone surface | 0.57 | 0.24 | 0.12 | 0.079 | 0.052 | 0.041 |
| Breast | 0.54 | 0.22 | 0.11 | 0.068 | 0.043 | 0.034 |
| Skin | 0.49 | 0.20 | 0.10 | 0.060 | 0.037 | 0.030 |
| Brain | 0.29 | 0.13 | 0.09 | 0.078 | 0.072 | 0.070 |
| Other tissues | 0.59 | 0.25 | 0.13 | 0.083 | 0.052 | 0.042 |

[a] MIRDOSE 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Gallagher et al.[1] and Jones et al.[2]

[b] The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used. *LLI = lower large intestine; **ULI = upper large intestine

**2.5 Radiation Safety – Drug Handling**

- Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F 18 Injection to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see *Description (11.2)*].
- The dose of Fludeoxyglucose F 18 used in a given patient should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.

**2.6 Drug Preparation and Administration**

- Calculate the necessary volume to administer based on calibration time and dose.
- Aseptically withdraw Fludeoxyglucose F 18 Injection from its container.
- Inspect Fludeoxyglucose F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer the drug if it contains particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

**2.7 Imaging Guidelines**

- Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
- Acquire static emission images 30 to 100 minutes from the time of injection.

**3 DOSAGE FORMS AND STRENGTHS**

Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration.

**4 CONTRAINDICATIONS**

None

**5 WARNINGS AND PRECAUTIONS**

**5.1 Radiation Risks**

Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see *Dosage and Administration (2.5)*].

**5.2 Blood Glucose Abnormalities**

In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

**6 ADVERSE REACTIONS**

Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting. Have emergency resuscitation equipment and personnel immediately available.

**7 DRUG INTERACTIONS**

The possibility of interactions of Fludeoxyglucose F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

*Pregnancy Category C*

Animal reproduction studies have not been conducted with Fludeoxyglucose F 18 Injection. It is also not known whether Fludeoxyglucose F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Consider alternative diagnostic tests in a pregnant woman; administer Fludeoxyglucose F 18 Injection only if clearly needed.

**8.3 Nursing Mothers**

It is not known whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in women who are breast-feeding. Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding.

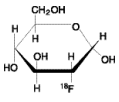
**8.4 Pediatric Use**

The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined. In the oncology or cardiology settings, the safety and effectiveness of Fludeoxyglucose F 18 Injection have not been established in pediatric patients.

**11 DESCRIPTION**

**11.1 Chemical Characteristics**

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[$^{18}$F]fluoro-D-glucose has the molecular formula of $C_6H_{11}{}^{18}FO_5$ with a molecular weight of 181.26, and has the following chemical structure:




Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.40GBq (20.0 to 200 mCi) of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

**11.2 Physical Characteristics**

Fluorine F 18 decays by emitting positron to Oxygen O 16 (stable) and has a physical half-life of 109.7 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons, that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 2).

**Table 2. Principal Radiation Emission Data for Fluorine F18**

| Radiation/Emission | % Per Disintegration | Mean Energy |
|---|---|---|
| Positron (b+) | 96.73 | 249.8 keV |
| Gamma (±)* | 193.46 | 511.0 keV |

*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-I 1026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 R/hr/mCi (1.35 x $10^{-6}$ Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb). The range of attenuation coefficients for this radionuclide as a function of lead shield thickness is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

**Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding**

| Shield thickness (Pb) mm | Coefficient of attenuation |
|---|---|
| 0 | 0.00 |
| 4 | 0.50 |
| 8 | 0.25 |
| 13 | 0.10 |
| 26 | 0.01 |
| 39 | 0.001 |
| 52 | 0.0001 |

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.

**Table 4. Physical Decay Chart for Fluorine F18**

| Minutes | Fraction Remaining |
|---|---|
| 0* | 1.000 |
| 15 | 0.909 |
| 30 | 0.826 |
| 60 | 0.683 |
| 110 | 0.500 |
| 220 | 0.250 |

*calibration time

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Fludeoxyglucose F 18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [$^{18}$F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose F 18 transport and phosphorylation (expressed as the ‚lumped constant" ratio), Fludeoxyglucose F 18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

**12.2 Pharmacodynamics**

Fludeoxyglucose F 18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial sub strate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these condi-

tions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging.

In the brain, cells normally rely on aerobic metabolism. In epilepsy, the glucose metabolism varies. Generally, during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

**12.3 Pharmacokinetics**

*Distribution:* In four healthy male volunteers, receiving an intravenous administration of 30 seconds induration, the arterial blood level profile for Fludeoxyglucose F 18 decayed triexponentially. The effective half-life ranges of the three phases were 0.2 to 0.3 minutes, 10 to 13 minutes with a mean and standard deviation (STD) of 11.6 (±) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 4 min.

Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

Metabolism: Fludeoxyglucose F 18 is transported into cells and phosphorylated to [$^{18}$F]-FDG-6- phosphate at a rate proportional to the rate of glucose utilization within that tissue. [F18]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[F18]fluoro-6-phospho-D-mannose([F 18]FDM-6-phosphate).

Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (ClDG)). Biodistribution and metabolism of ClDG are presumed to be similar to Fludeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (ClDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, ClDG, and ClDM) presumably leave cells by passive diffusion. Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose F 18 that is not involved in glucose metabolism in any tissue is then excreted in the urine.

*Elimination:* Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Three elimination phases have been identified in the reviewed literature. Within 33 minutes, a mean of 3.9% of the administrated radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

*Special Populations:*

The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in renally-impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained [*see Warnings and Precautions (5.2)*].

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Animal studies have not been performed to evaluate the Fludeoxyglucose F 18 Injection carcinogenic potential, mutagenic potential or effects on fertility.

**14 CLINICAL STUDIES**

**14.1 Oncology**

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fludeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq.

In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false-positive scans. The efficacy of Fludeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

**14.2 Cardiology**

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects).

Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is more limited.

**14.3 Neurology**

In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185 to 370 MBq (5 to 10 mCi). The mean age was 16.4 years (range: 4 months to 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (14/87) of the patients; in 34% (30/87) of the patients, Fludeoxyglucose F 18 Injection PET images provided new findings. In 32% (27/87), imaging with Fludeoxyglucose F 18 Injection was inconclusive. The impact of these imaging findings on clinical outcomes is not known.

Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

**15 REFERENCES**


1. Gallagher B.M., Ansari A., Atkins H., Casella V., Christman D.R., Fowler J.S., Ido T., MacGregor R.R., Som P., Wan C.N., Wolf A.P., Kuhl D.E., and Reivich M. "Radiopharmaceuticals XXVII. $^{18}$F-labeled 2-deoxy-2-fluoro-d-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: tissue distribution and imaging studies in animals," J Nucl Med, 1977; 18, 990-6.
2. Jones S.C., Alavi, A., Christman D., Montanez, I., Wolf, A.P., and Reivich M. "The radiation dosimetry of 2 [F-18] fluoro-2-deoxy-D-glucose in man," J Nucl Med, 1982; 23, 613-617.
3. Kocher, D.C. "Radioactive Decay Tables: A handbook of decay data for application to radiation dosimetry and radiological assessments," 1981, DOE/TIC-I 1026, 89.
4. ICRP Publication 53, Volume 18, No. I-4,1987, pages 75-76.


**16 HOW SUPPLIED/STORAGE AND DRUG HANDLING**

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL glass vial containing between 0.740 to 7.40GBq/mL (20 to 200 mCi/mL), of no carrier added 2deoxy-2-[F 18] fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 40028-511-30; 40028-511-50

Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

Store the Fludeoxyglucose F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store and dispose of Fludeoxyglucose F 18 Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.

The expiration date and time are provided on the container label. Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS time.

**17 PATIENT COUNSELING INFORMATION**

Instruct patients in procedures that increase renal clearance of radioactivity. Encourage patients to:

- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.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**PETNET** Solutions

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