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Current Role of PET/CT in Evaluation of Lung Cancer

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Introduction

Lung cancer is the second most common cancer in both men and women and the leading cause of death in the USA. Delayed detection and ineffective treatment therapies may lead to shorter survival rates. Lung cancer accounts for about 13% of all cancers. Approximately 221,000 new cases and 158,000 deaths from lung cancer are estimated for the year 2015 in the USA.[1] Early detection and accurate staging of lung tumors is key to appropriate therapy selection.

Five-year survival rates vary dramatically between early and advanced stages of lung cancer. Delayed detection and ineffective therapy may lead to shorter survival rates. Detection and assessment of primary tumor and of mediastinal nodal and distant metastases through a combination of imaging modalities is key to proper staging. Inaccurate delineation due to improper staging and missed metastases may also impact survival. PET/CT provides a combination of metabolic and morphological information which has a major impact on evaluation and therapy planning of primary and recurrent lung tumors.

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

INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection (^{18}F FDG) 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.

IMPORTANT SAFETY INFORMATION

- **Radiation Risk**: 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.
- **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.

Full prescribing information for Fludeoxyglucose F 18 Injection can be found on pages 18-20.

Fludeoxyglucose F 18 injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

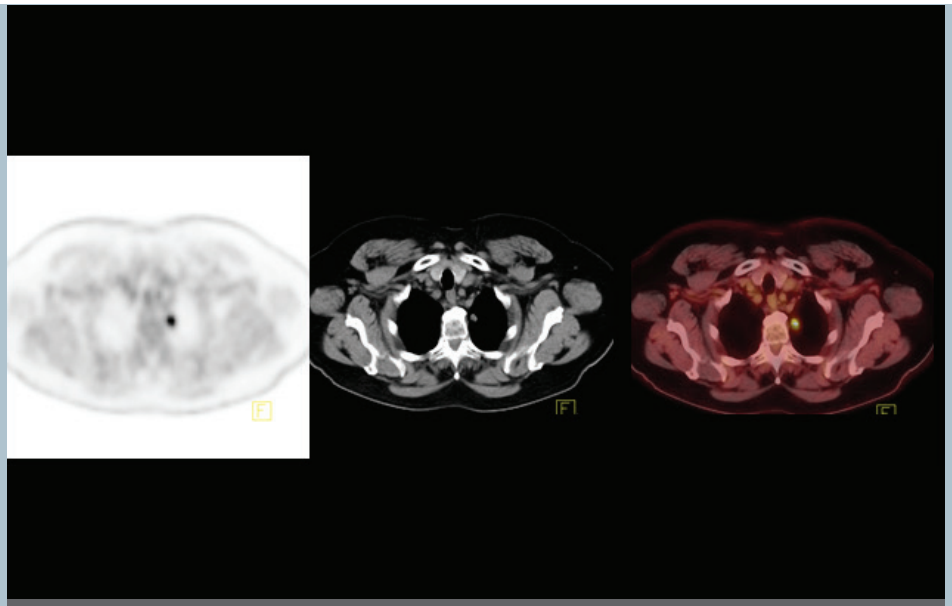

Figure 1

Figure 1: Solitary lung nodule <1 cm in diameter without characteristic CT findings like spiculated edges or calcification. High ^{18}F FDG uptake (SUV_{max} 5.4) strongly suggests malignant nodule.

Data courtesy of
Stanford Medical Center,
Stanford, California, USA

Lung Nodules

Lung cancer often presents as a solitary pulmonary nodule (SPN) on chest radiographs. SPN, defined as an opacity in the lung parenchyma up to 3 cm in diameter with no associated mediastinal adenopathy or atelectasis, is found incidentally on imaging studies unrelated to the respiratory system in 0.09-0.2% of all chest radiographs. [2] In one study of CT screening for lung cancer in smokers, 13% of patients had pulmonary nodules larger than 5 mm at baseline.[3] Lung nodules can be related to malignancy or granulomatous, inflammatory or infective pathologies. CT findings of smooth, regular borders and central calcification suggest benign origin while spiculated borders, eccentric calcification and contrast enhancement are often associated with malignant nodules. However, accurate differentiation is often not possible and a substantial number of patients are subjected to transthoracic or transbronchial biopsies and thoracotomies. A total of 25-39% of malignant nodules are inaccurately classified as benign based on radiologic assessments of size, margins and internal characteristics.[4] A total of 20% of pulmonary nodules present as ground glass or semi-solid opacities, which have a higher overall incidence of malignancy, commonly, bronchioalveolar carcinomas.[5]

Fludeoxyglucose F18 injection* (^{18}F FDG) PET/CT imaging of pulmonary nodules has been shown to have high sensitivity and specificity for characterization of lung nodules. In a study involving 89 patients with indeterminate solitary pulmonary nodules, ^{18}F FDG PET using a SUV_{max} cutoff of 2.5 showed an overall sensitivity of 92% and specificity of 90% for detection of malignant nodules. The sensitivity was slightly lower (80%) for nodules smaller than 1.5 cm.[6] There was significant correlation between tumor doubling time and Standard Uptake Value (SUV). Kim et al. [7] demonstrated a sensitivity of 97% and specificity of

Figure 2: Small solitary pulmonary nodule with moderate level of ^{18}F FDG uptake with respiratory motion-related blurring on non-gated PET/CT. Respiratory gated PET with optimal gating defined on the end expiratory portion of the respiratory cycle fused with CT shows sharper definition of the lung nodule with higher uptake due to elimination of respiratory motion-related blurring and partial volume effects. SUV_{max} within the nodule increased from 3.5 on non-gated to 5 on respiratory gated acquisitions. Respiratory gating may improve visualization of small nodules with low ^{18}F FDG uptake.

Data courtesy of University of Tennessee, Knoxville, Tennessee, USA

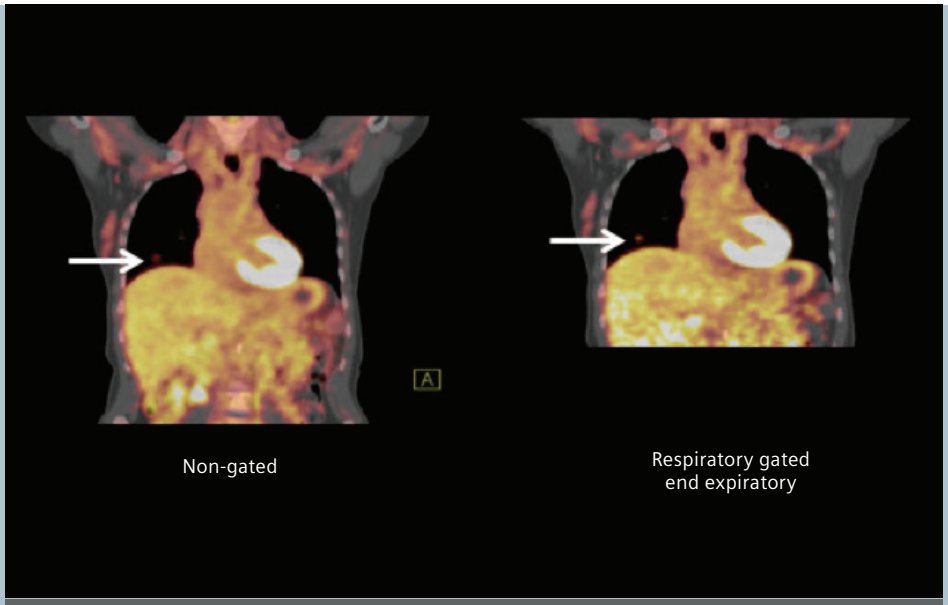

Figure 2

85% for characterization of pulmonary nodules into benign or malignant by visual evaluation. Several studies have demonstrated higher accuracy of PET in pulmonary nodules larger than 10 mm in diameter. Veronesi et al. [8] compared PET imaging in lung nodules 5-10 mm and >10 mm in diameter. Using SUV >2.0 as the threshold for positive, sensitivity for detection of malignancy for all nodules was 88% but was 100% in the subgroup of solid nodules with diameter more than 10 mm. Another study [9] evaluated 36 SPN with diameters less than 10 mm and detected malignancy with sensitivity of 93% but specificity of 77%.

Bronchoalveolar carcinomas, most often represented by ground glass opacities are usually not ^{18}F FDG-avid and are most often not visualized on PET but delineated on thin-slice CT.[10]

Accurate estimation of SUV of a lung nodule, especially nodules with smaller diameter is key to proper characterization. Respiratory motion-related blurring and partial volume effect in PET/CT acquisition may lead to lower SUV levels in non-gated PET/CT acquisitions. PET respiratory gating has been used to improve the accuracy of SUV in small nodules with significant respiratory motion. In a study comparing standard 3D PET acquisition with respiratory gated PET (4D PET) in 32 lung nodules, [11] the mean SUV_{max} for 3D PET was 2.5 and the mean 4D-SUV_{max} was 3.2 . The mean percentage increase in SUV_{max} with respiratory gating was 38% for all patients but was higher (45%) in nodules <10 mm in size, compared to 31% in larger nodules. Malignant lesions showed mean 4D-SUV_{max} of 3.8. In this study, the standard cutoff SUV_{max} of 2.5 was not helpful in distinguishing between benign and malignant nodules, thereby suggesting that a different threshold be used for small nodules, especially when respiratory gated PET is used as routine for such evaluation.

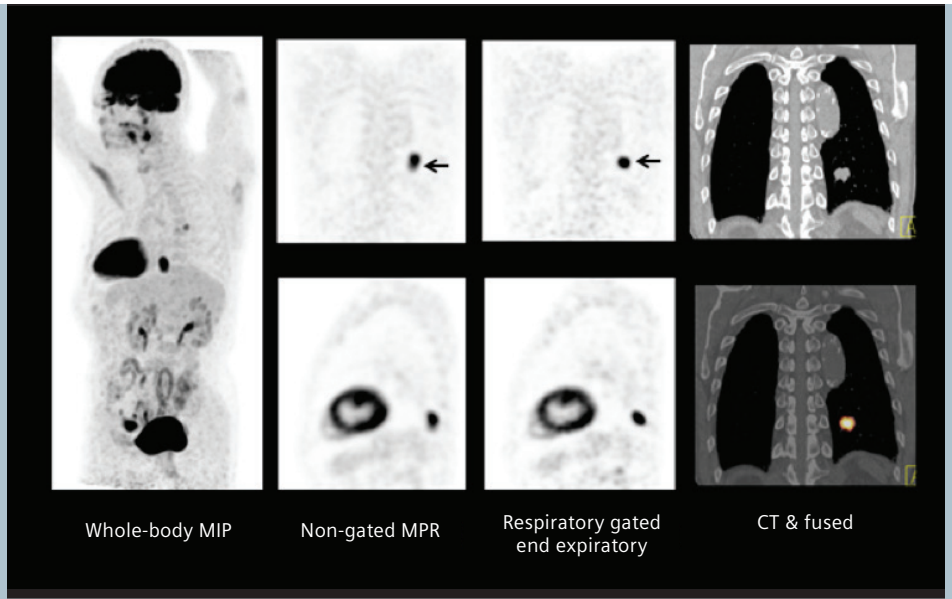

Figure 3

Figure 3: Large solitary lung nodule with high ^{18}F FDG uptake showing respiratory motion-related blurring on non-gated standard PET acquisition. Respiratory gated end expiratory images obtained using an optimal gating approach show smaller nodular size with sharp margins due to elimination of respiratory motion-related blurring. The CT shows irregular spiculated margin of the lung nodule which is suggestive of malignancy. Fusion images show high ^{18}F FDG uptake within the large irregular lung nodule which strongly indicated presence of malignancy. SUV_{max} was 11.5.

Data courtesy of
Keio University, Tokyo, Japan

Staging of Lung Cancer

Annual low-dose CT screening for lung cancer in adults aged 55 to 80 years who have a long smoking history has been recommended by the US Preventive Services task force.[12] Indeterminate pulmonary lesions identified by low-dose CT can potentially be characterized by ^{18}F FDG PET/CT leading to improved decision-making for which lesions to biopsy. In the Pittsburgh Lung Screening Study, (PLuSS) the population was screened for lung cancer with annual LDCT.[13] A total of 18.5% (n=17) of all 93 screen-detected lung cancers were indolent cancers with mean tumor size of 10 mm (range 7-22 mm) with mean SUV_{max} <1, whenever available. Median doubling time was significantly longer in this group when compared to the rest of the prevalence stage 1 cancers. Improved accuracy of SUV_{max} estimations secondary to respiratory gated PET may support accurate characterization of such low uptake indolent nodules.

NCCN guidelines recommend ^{18}F FDG PET/CT for solid or semi-solid solitary pulmonary nodules 8 mm or larger. In case PET/CT is suggestive of malignancy, a biopsy or surgical excision is recommended. In case biopsy is negative for malignancy, annual low-dose CT screening is recommended for the next two years.

Accurate staging of lung cancer is key to proper selection of therapy. Early stage tumors, especially tumors without segmental or hilar nodal metastases can be treated with surgery or stereotactic radiotherapy (SBRT) with significantly higher 5-year survival rates compared to advanced stage tumors. Detection of small metastatic mediastinal nodes are key to proper staging. A retrospective study of 84 lung cancer patients demonstrated significantly higher sensitivity with ^{18}F FDG PET/CT compared with CT alone in the delineation of lung tumors associated with atelectasis (91% vs 48%). However, the biggest impact of ^{18}F FDG PET/CT is its ability to detect metastatic lymph nodes even when they are normal in size on CT. Size criteria on CT alone (nodes >1 cm considered positive) is not reliable for staging of mediastinal nodes. A total of 15% of patients in clinical stage I disease have been shown to harbor metastases in normal-sized lymph nodes.[14] ^{18}F FDG PET/CT provides accurate delineation of primary tumor margins, differentiates viable tumor from atelectasis as well as delineates intratumoral necrotic zones with higher precision than CT, in some cases.

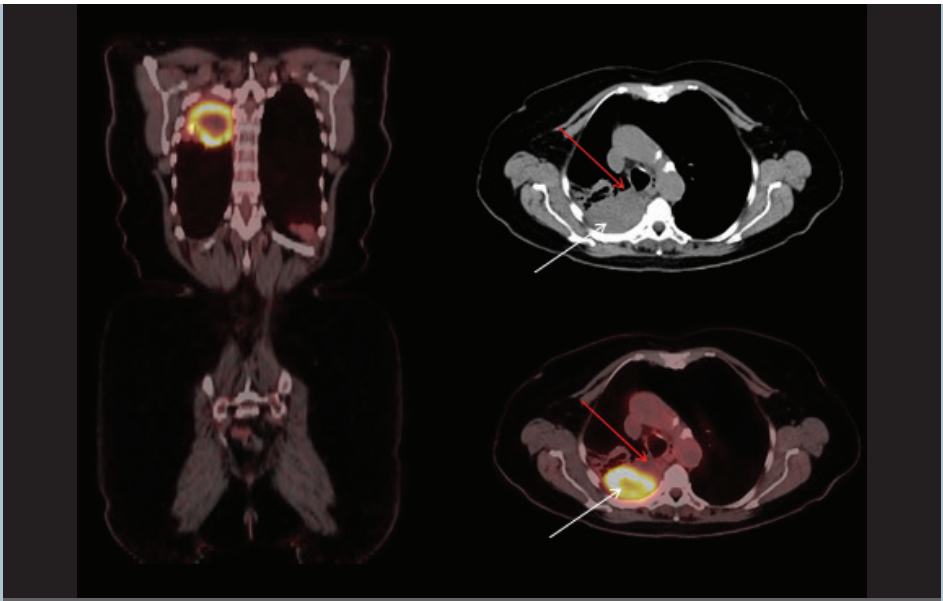

Figure 4

Figure 4: Primary lung carcinoma: ^{18}F FDG-avid large primary tumor (white arrows) with central necrosis defined by PET/CT. ^{18}F FDG PET/CT delineates metabolically active tumor and differentiates tumor from adjacent atelectatic lung (red arrow).

Data courtesy of
National University Hospital,
Singapore

Mediastinal Staging

Hellwig et al., in a meta-analysis, found ^{18}F FDG PET to have 96% sensitivity and 80% specificity for diagnosis of malignant lung lesions. In this study, PET was superior to CT in evaluation of mediastinal lymph nodal and distant metastases and changed therapeutic management in 18% of all cases.[15] In a prospective study involving 122 potentially operable lung cancer patients, Yang et al. [16] demonstrated significantly higher accuracy for mediastinal lymph nodal staging with ^{18}F FDG PET/CT compared to CT alone. PET/CT correctly staged 80% (98 out of 122) of patients while CT correctly staged only 56% (68 out of 122). Sensitivity and specificity for lymph node staging for PET/CT was 86% and 85%, respectively, while the same for CT was 69% and 71%. Another study involving 200 patients with Stage I NSCLC who underwent PET/CT and radical surgery, showed very high negative predictive value (91%) for mediastinal lymph node metastases.[17] Kubota et al. [18] demonstrated that accuracy for detection of mediastinal lymph node metastases increased from 62.3% with contrast CT only to 79.2% when ^{18}F FDG PET was combined with contrast CT. Thus, the general consensus regarding mediastinal nodal staging favors ^{18}F FDG PET/CT over contrast CT only.

Impact on Management

The PLUS multi-center randomized trial [19] compared the impact of conventional workup and addition of PET in two randomized groups of NSCLC patients scheduled for surgery. Addition of PET avoided futile surgery in 1 in 5 patients (20%) and led to upstaging in 27%. Hicks et al. found that PET caused a major management change in 40 out of 63 (63%) patients who had previously undergone potentially curative surgery for NSCLS.[20]

^{18}F FDG is taken up in malignancy as well as inflammation. Granulomatous lung lesions and inflammatory nodes may appear ^{18}F FDG-avid and cause diagnostic dilemmas and false positives. In a study comparing ^{18}F FDG avidity and nodal size and macrophage accumulation, Shiraki et al. [21] observed that false positive nodes were always larger as compared to true negative nodes. Since sensitivity for ^{18}F FDG PET/CT is slightly lower in normal-sized mediastinal nodes and false positive but enlarged nodes may lead to upstaging, several groups have evaluated the value of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in early stage lung cancers which are candidates for SBRT, especially in PET/CT negative patients.[22]

****SODIUM FLUORIDE F 18 INJECTION for Intravenous Use**

Indication and usage

Sodium fluoride F 18 injection (10–200 mCi/mL) is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging bone to define areas of altered osteogenic activity.

IMPORTANT SAFETY INFORMATION

- **Allergic Reactions:** As with any injectable drug, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.
- **Cancer Risk:** Sodium fluoride F 18 injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and healthcare worker.
- **Adverse Reactions:** No adverse reactions have been reported based on a review of the published literature, publicly available reference sources and adverse drug reaction reporting systems. The completeness of the sources is not known.
- **Dosage Forms and Strengths:** Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) at EOS reference time of no-carrier-added sodium fluoride F18 in aqueous 0.9% sodium chloride solution. Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

Full prescribing information for Sodium Fluoride F 18 Injection can be found on page 21-23.

Sodium Fluoride F 18 Injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

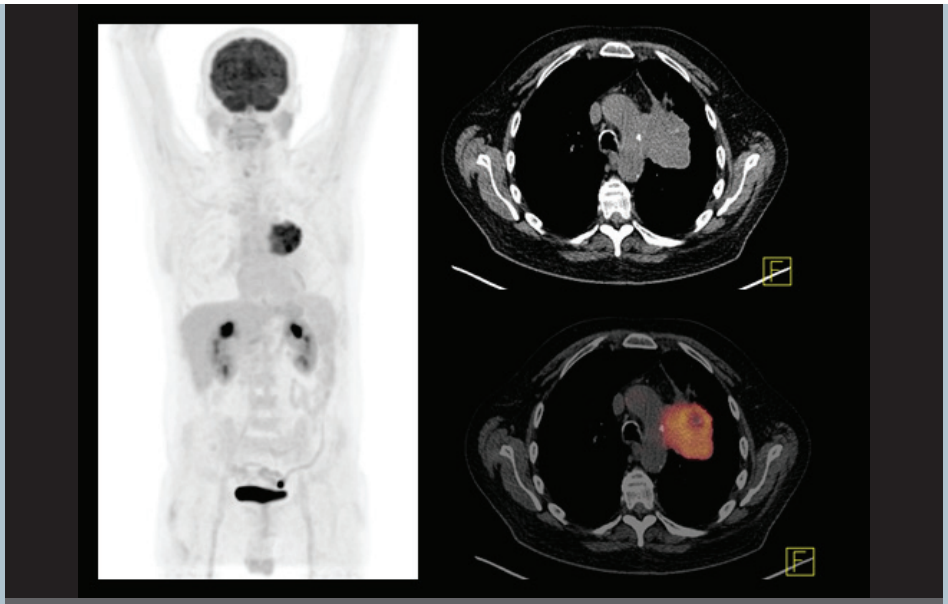

Figure 5

Figure 5: Large left suprahilar primary lung carcinoma showing high ^{18}F FDG avidity with central hypointensity reflecting central necrosis. No ^{18}F FDG-avid mediastinal lymph node metastases are visualized on PET/CT. In view of the absence of PET-positive mediastinal lymph node and distant metastases, the tumor is treated with SBRT.

Data courtesy of University of Geneva, Geneva, Switzerland

Evaluation of Distant Metastases

Evaluation of distant metastases is critical for proper therapy decision and for determining tumor resectability. The brain, bone, liver and adrenal glands are common sites for distant metastases. Metastases to the contralateral lung are also considered distant metastases. Occult metastases may be present in up to 30% of patients with adenocarcinoma or large cell carcinoma of the lung.[23] In a study by MacManus, [24] 24% of patients with clinical stage III cancer had previously undetected distant metastases demonstrated by ^{18}F FDG PET. A similar study by Pieterman [25] showed sensitivity and specificity of 92% and 83%, respectively, for the diagnosis of distant metastases. A total of 11% of patients had distant metastases detected by ^{18}F FDG PET that other modalities had failed to detect. Dinan et al., [26] in an analysis of a large series, demonstrated that with introduction of ^{18}F FDG PET into the workup of lung cancer, the proportion of patients staged with advanced disease increased from 44% to 50%. Upstaging of disease was accompanied by stage-specific improved survival.

^{18}F FDG PET/CT has been shown to have high accuracy in detecting bone metastases with sensitivity and specificity as high as 93.9% and 98.9%, respectively.[27] Cheran et al. [28] compared ^{18}F FDG PET to planar bone scan in a large series of patients with lung cancer. PET was far more sensitive (91%) compared to bone scan (75%) while specificities were similar (95%). In another similar study, PET/CT sensitivity was 94.3% compared to 78% for bone scintigraphy. PET/CT also showed lower incidence of false positive (1.2% vs. 2.9%) and false-negative results (5.7% vs. 21.9%) than bone scan.[29] In a study comparing ^{18}F FDG PET/CT, Sodium Fluoride F18 injection** (^{18}F) PET and ^{99m}Tc MDP planar bone scintigraphy, Kruger et al. [30] demonstrated ^{18}F FDG PET/CT to be slightly less sensitive than ^{18}F Fluoride PET but significantly superior to planar bone scan.

^{18}F FDG PET/CT is also accurate in the detection of extraosseous distant metastases compared to CT. Adrenal glands and liver are common sites of extrathoracic metastases. At

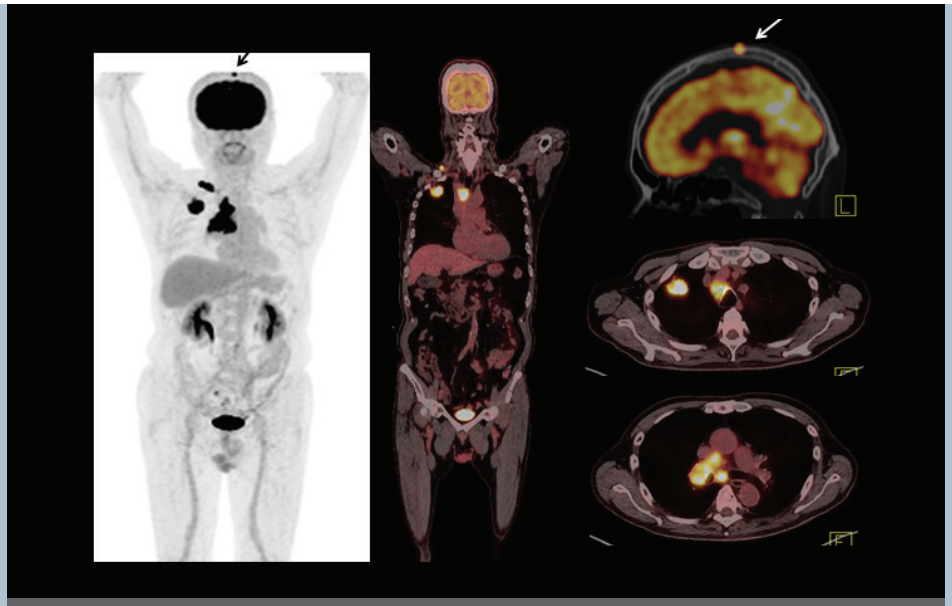

Figure 6

Figure 6: Primary squamous cell cancer of lung with extensive mediastinal and supraclavicular metastases. ^{18}F FDG PET/CT detects small metastases in the skull (arrows), thereby changing disease stage.

Data courtesy of
Keio University, Tokyo, Japan

the time of presentation, up to 10% of lung cancer patients may have an adrenal mass but approximately two-thirds of these masses will be benign.[31] ^{18}F FDG PET has been shown to have excellent sensitivity and specificity (100% and 94%, respectively) in characterization of adrenal lesions found by CT or MRI.[32] However, an ^{18}F FDG-avid adrenal lesion may represent a hyperfunctioning adenoma and may require a dedicated contrast CT or MRI for proper characterization.

Because of the high ^{18}F FDG uptake in normal brain parenchyma, PET has limited ability to detect early brain metastases. The current standard of care for all patients with clinical Stage >I B is to have a dedicated MRI of the brain.

NCCN Guidelines

^{18}F FDG PET/CT is recommended for pre-treatment evaluation in Stage I (A and B), Stage II, Stage II B and Stage III A, as well as Stage IV non-small cell lung cancer.

Prediction and Evaluation of Therapy Response

PET/CT is highly effective in the evaluation of tumor response to therapy, both for induction chemotherapy as well as radiation or chemoradiation therapy. Changes in tumor metabolism precede tumor shrinkage, and functional evaluation with PET/CT is a reliable indicator of tumor response to therapy and helps guide the decision to continue or modify therapy, depending on metabolic response. For early stage tumors, SBRT is an alternative to surgery in selected patients. Higher SUV_{max} in pre-treatment ^{18}F FDG PET/CT has been shown to be associated with poor recurrence-free survival and higher incidence of distant metastases in patients with Stage I lung cancer treated with SBRT. [33] Takeda et al. [34] demonstrated significantly higher local control rate in patients treated with SBRT with lower pre-treatment SUV_{max}. The two-year local control rate for tumors with SUV_{max} <6.0 was 93% while it was 42% for tumors with higher SUV_{max} (>6). This suggests that tumors with higher SUV_{max} may benefit from further dose escalation to improve local control.

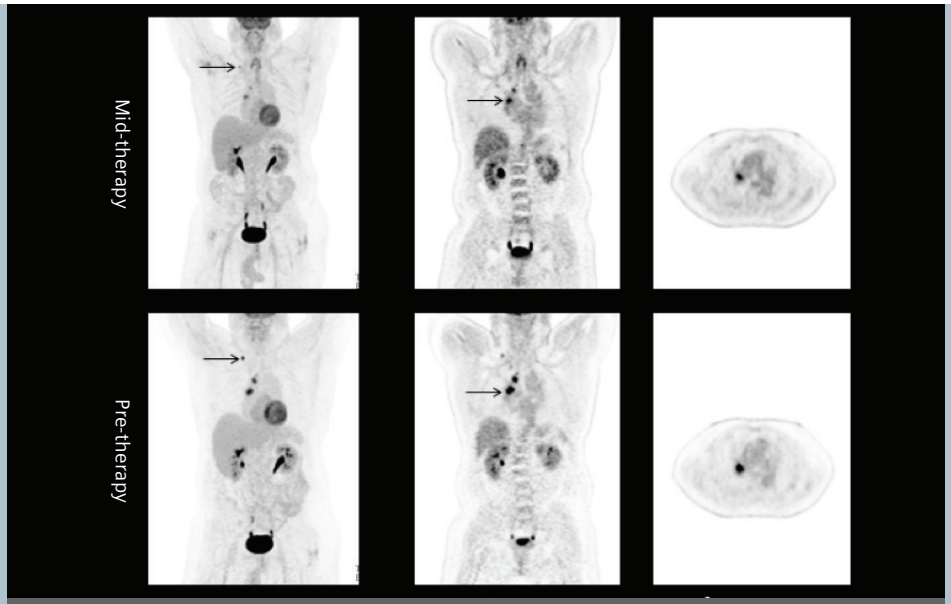

Figure 7

Figure 7: Primary suprahilar lung carcinoma with mediastinal and suprahilar metastases underwent ^{18}F FDG PET/CT before and upon completion of initial chemoradiation therapy. Post-therapy PET shows a significant decrease in uptake in the supraclavicular lesion (arrows) as well as a slight decrease in the uptake and lesion volume in the primary tumor (arrows) following chemoradiation.

Data courtesy of Stanford University Hospital, Stanford, California, USA

High pre-treatment SUV_{max} has been accepted as a poor prognostic factor in more advanced lung cancer as well. [35] In a series of lung cancer patients (T 1-4, N 0-2) treated with surgical resection alone, SUV_{max} <9 was associated with a 96% 2-year survival while it was 68% for tumors with SUV_{max} >9.

Pre- and post-treatment ^{18}F FDG PET has been compared with CT for prediction of response following chemoradiation and PET response was found to significantly correlate with survival compared to response on CT.[36] Poor prognosis has also been associated with higher volume of residual metabolically active tumor in post-therapy PET/CT.[37]

PET/CT has been shown to be of value in restaging after neoadjuvant therapy, for early assessment of response to therapy and restaging after completion of therapy. Induction chemotherapy is often used as neoadjuvant therapy prior to radiation. Decoster et al. [38] performed ^{18}F FDG PET at baseline and after 3 cycles of induction chemotherapy in 31 patients with unresectable Stage II lung cancer. A complete response demonstrated by ^{18}F FDG PET after induction chemotherapy was associated with significantly longer time to progression and overall survival. Percentage decrease of SUV_{max} on serial ^{18}F FDG PET studies performed at baseline, following induction chemotherapy and after chemoradiation, correlated significantly with histopathological response in patients who ultimately underwent surgical resection.[39] A >55% decrease in SUV_{max} after chemoradiation correlated best with histopathological response. Post-RT SUV_{max} below 4.1 in mediastinal lymph node was best associated with the absence of disease on histopathology.

PET/CT performed early during chemotherapy or radiation may predict therapy response. Weber et al. [40] performed PET before and after 1 chemotherapy cycle in 57 patients with advanced lung cancer. Reduction of metabolic activity after one cycle closely correlated with the final outcome of therapy. A decrease in SUV_{max} of 20% after one cycle was 95% sensitive in predicting favorable long-term response. A poor response predicted disease progression within 3 months. Median time to progression was significantly longer for metabolic responders than for non-responders (163 vs. 54 days).

NCCN guidelines suggest use of PET/CT in restaging and therapy response assessment. PET is covered by CMS for restaging after the completion of treatment for the purpose of detecting residual disease, detecting suspected recurrence or determining the extent of a known recurrence. PET is covered for monitoring response to treatment when a change in therapy is anticipated. PET is not recommended for routine post-therapy surveillance by NCCN.

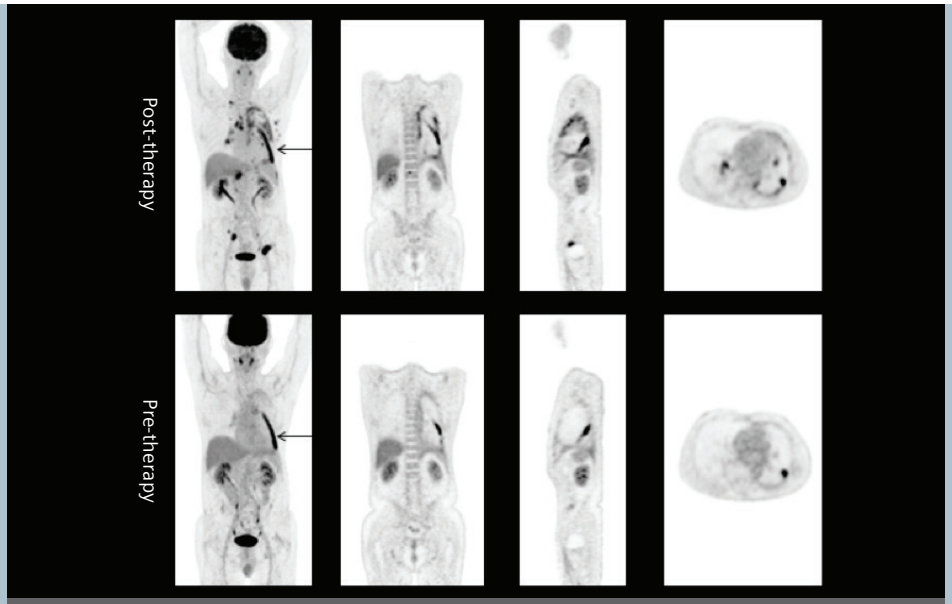

Figure 8

Figure 8: Mesothelioma in oblique fissure showing progression in spite of chemoradiation demonstrated by sequential ^{18}F FDG PET.

Data courtesy of National University Hospital, Singapore

Radiation Therapy Planning

Radiation therapy (RT) plays a major role in patients who are not candidates for surgery. Recent advances in radiation therapy for NSCLC, including intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and stereotactic body radiotherapy (SBRT), have enabled higher radiation doses to be delivered to tumors for increased tumor local control, while reducing doses to surrounding normal tissue, thereby reducing radiation-induced toxicities. Although CT-based planning is the standard approach, it only provides morphological information. Incorporating ^{18}F FDG PET/CT into radiation treatment planning adds a layer of biological information which leads to improved tumor targeting based on delineation of a metabolically active tumor and differentiation of viable tumor from atelectasis, tumor necrosis and fibrosis. PET/CT may lead the physician to alter the radiation field significantly by including ^{18}F FDG-avid non-enlarged metastatic lymph nodes within the treatment field. In view of the high negative predictive value of ^{18}F FDG PET/CT for nodal metastases (>90%), routine elective nodal radiation is no longer recommended.[41] There are reports indicating that it is safe to only irradiate PET-positive lymph nodes, thus reducing target volume and resulting in a higher tumor dose.[42] Selective mediastinal lymph node irradiation based on PET with ^{18}F FDG yielded a low rate of treatment failure for isolated nodes, suggesting that reducing the target volume does not result in poorer local control.[43]

PET/CT-based planning offers the potential of dose escalation to the tumor regions with the highest ^{18}F FDG uptake in order to achieve improved local control and reduce local failure rates. Areas of high ^{18}F FDG uptake on pre-radiotherapy PET/CT are at higher risk of relapse after radiotherapy and high SUV zones within the tumor may benefit from radiation dose escalation.[44] Gross tumor volumes (GTVs) drawn based on the hypermetabolic tumor have been shown to be significantly different from GTVs drawn on CT only.[45] In several planning studies, it was shown that GTV based on PET was, in general, smaller than with CT, thus leading to sufficiently decreased radiation exposure to the lungs and the esophagus as to allow for radiation-dose escalation.[46]

The Radiation Therapy Oncology Group (RTOG) 0515 was a phase II prospective trial designed to quantify the impact of PET/CT compared with CT alone on radiation treatment plans (RTPs) in NSCLC.[44] Forty-seven patients underwent definitive RT (>60 Gy) based on an ^{18}F FDG PET/CT-generated radiation plan. Mean follow-up was for 12.9 months. GTVs derived from PET/CT were significantly smaller than

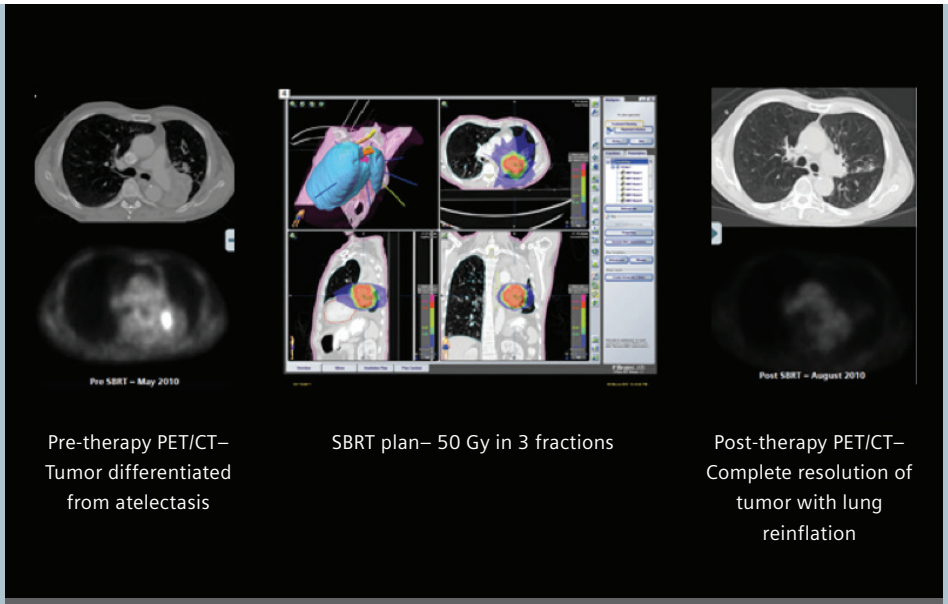

Figure 9

Figure 9: ^{18}F FDG PET differentiates hypermetabolic primary lung tumor from adjacent atelectasis on the pre-therapy PET/CT. Stereotactic body radiation therapy (SBRT) was planned on the PET/CT with hypo-fractionated dose escalation on the ^{18}F FDG-avid GTV (50 Gy in 3 fractions). Post-therapy PET/CT demonstrated complete resolution of tumor with reinflation of the atelectatic lung.

Data courtesy of UCLA, Los Angeles, California, USA

that from CT alone (mean GTV volume of 86.2 vs. 98.7 ml). PET/CT changed nodal GTV contours in 51% of patients. The elective nodal failure rate for GTVs derived by PET/CT was quite low, thereby supporting the approach of limiting the target volume to the metabolically active primary tumor and involved nodes.

Tumor size and metabolic activity changes during the course of radiation therapy and modification of GTV based on PET/CT performed during the course of RT may potentially help dose escalation to the viable tumor. Adaptive radiotherapy has shown promise in achieving higher tumor dose with reduced toxicities. Kong et al. [47] performed ^{18}F FDG PET/CT in 14 patients with Stage I-III NSCLC before RT and in mid-RT (after 40-50 Gy). Mid-RT PET volumes were used to design boost fields. Mid-therapy PET scan-based modification of radiation therapy plans allowed meaningful dose escalation of 30-102 Gy (mean 58 Gy) and a decrease in esophageal toxicity. There was a mean decrease in viable tumor volume after 40-50 Gy of 26% on CT and 44% on PET/CT. The study concluded that tumor metabolic activity and volume changes significantly after 40-50 Gy and adaptation of RT GTV based on mid-treatment PET/CT helps to escalate dose to active tumor, as well as reduce toxicity. Randomized Phase II Trial of Individualized Adaptive Radiotherapy Using During-Treatment ^{18}F FDG PET/CT and Modern Technology in Locally Advanced Non-Small Cell Lung Cancer (RTOG 1106/ACRIN 6697) is currently underway to test these findings with the goal of advancing the concept of PET-guided individualized adaptive radiotherapy.

NCCN guidelines recommend PET/CT for planning radiation therapy for NSCLC as part of initial treatment strategy determination and also recommend PET/CT be performed in treatment position.

PET/CT acquisition that would be used for radiation planning is ideally performed using a flat table top with the patient in treatment position with the arms up, in contrast to PET/CT studies for initial staging for primary lung tumor which are usually performed using the standard PET/CT bed. Reimbursement for additional PET/CT studies exclusively for the purpose of radiation therapy planning is often declined if a diagnostic PET/CT had been performed previously. Thus, the recommendation for initial staging PET/CT studies in lung cancer patients would coordinate such studies with the simulation staff in radiation therapy in order to use a flat table top so that the same study may be used for radiation planning if the tumor requires such therapy. Another point to consider during acquisition of the initial PET/CT is to put the patient in treatment position with arms up as compared to arms down since PET/CT acquired in treatment position may further help radiation planning.

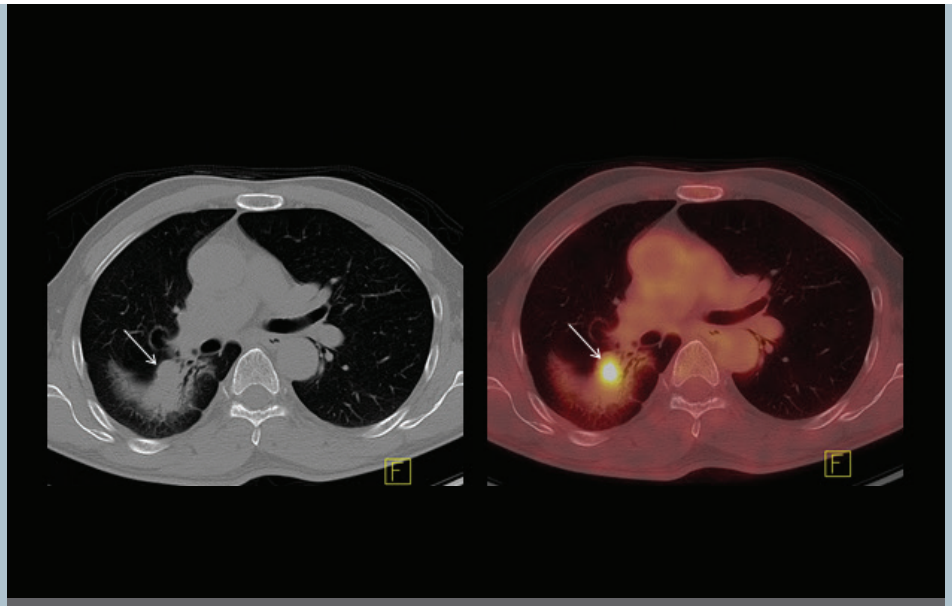

Figure 10

Figure 10: Recurrence of lung carcinoma within a region with post-radiation fibrosis. ^{18}F FDG PET shows hypermetabolism within recurrent tumor (white arrow) with adjacent fibrotic changes secondary to radiation therapy visualized on CT and showing low ^{18}F FDG uptake on PET/CT. ^{18}F FDG PET/CT delineates the extent of recurrent tumor and differentiates tumor margins from adjacent post-radiation fibrosis.

Data courtesy of
Raffles Hospital, Singapore

Follow-up and Surveillance

PET/CT is highly sensitive for detection of a metabolically active recurrent tumor. Although CT has been the mainstay in routine post-therapy surveillance of NSCLC, it is difficult to distinguish locoregional recurrence from radiation fibrosis, atelectasis and consolidation using standard CT while PET/CT can differentiate viable tumors. Although inflammation related to radiation therapy also shows ^{18}F FDG avidity, PET/CT has been demonstrated to have a very high accuracy for NSCLC relapse. Hicks et al., [20] in a series of 63 patients with NSCLC and suspected relapse, reported 98% sensitivity and 82% specificity for relapse detection with ^{18}F FDG PET. No disease was evident during a minimum follow-up of 12 months in 14 of 15 patients with clinically suspected relapse but negative PET findings (negative predictive value, 93%). PET induced a major management change in 63% patients, including change in treatment from curative to palliative or vice versa. In view of the ^{18}F FDG avidity shown by inflammation, PET-positive areas suggestive of recurrence should be correlated with histopathological analysis, whenever feasible.

^{18}F FDG PET is useful for detection of recurrence following SBRT since ^{18}F FDG positivity 12 months following therapy in Stage I tumor is associated with high local recurrence rate. [48] However, there may be persistent hypermetabolism in the tumor bed up to 6 months following SBRT due to more persistent inflammation secondary to hypofractionated therapy compared to conventional fractionation. Thus, early recurrence following SBRT using PET/CT should be interpreted with caution. However, 2-year local control rates have been reported to be as high as 98.5% with SBRT in Stage I lung carcinoma.

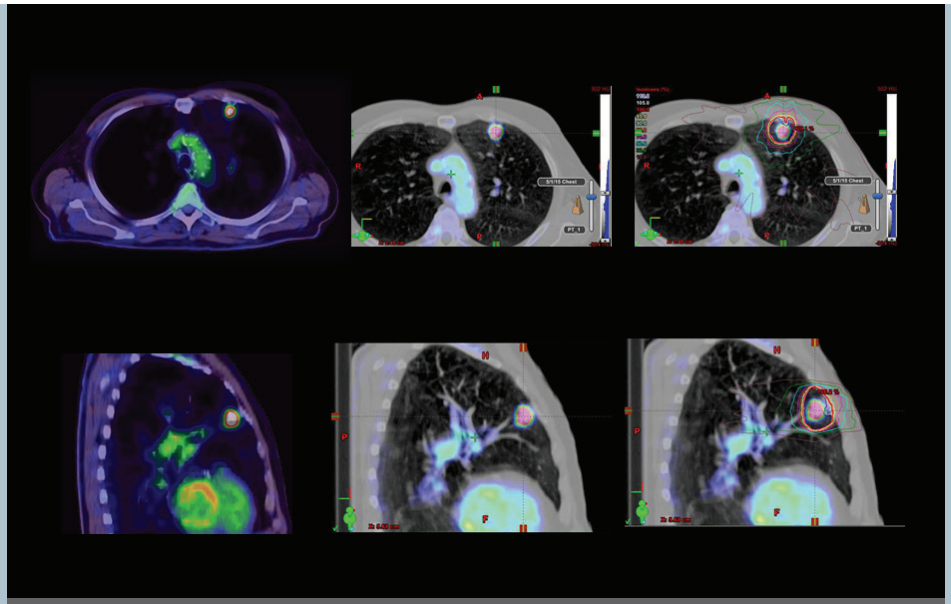

Figure 11

Figure 11: Peripheral lung carcinoma without lymph node metastases. ^{18}F FDG PET/CT shows high uptake with SUV_{max} of 9.3. SBRT contours generated from PET/CT data. 70 Gy delivered in 5 fractions with mean lung dose kept to less than 20 Gy. Patient had complete local tumor control with absence of significant toxicity and mild radiation pneumonitis.

Data courtesy of University of Tennessee Medical Center, Knoxville, Tennessee, USA

Conclusion

^{18}F FDG PET/CT plays an instrumental role in all aspects of management of lung carcinoma, especially in staging and restaging, as well as in radiation planning and therapy response assessment due to its ability to provide superior accuracy for delineation of a viable tumor, differentiate tumor from atelectasis and fibrosis and detect metastatic lymph nodes which appear normal on conventional imaging. Although pitfalls exist, particularly related to uptake of ^{18}F FDG in inflammatory lesions leading to false positives and lower sensitivity for small lesions and lesions with significant respiratory motion, newer technologies such as use of Time of Flight and high resolution PET and respiratory gating for motion management promise to further improve the accuracy and impact of PET/CT in lung cancer.

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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

WARNINGS AND PRECAUTIONS

- Radiation risks: use smallest dose necessary for imaging (5.1).
- Blood glucose abnormalities: 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: 1/2011

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.

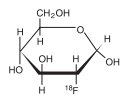
8.4 Pediatric Use

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. Pricipal 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 al-

teration 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 conditions, 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 in duration, 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. 18F-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 7.40 GBq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-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

PN0002262 Rev. A

March 1, 2011

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SODIUM FLUORIDE F 18 INJECTION
For Intravenous Use
Initial U.S. Approval: January 2011

INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging of bone to define areas of altered osteogenic activity (1).

DOSAGE AND ADMINISTRATION

- Sodium Fluoride F18 Injection emits radiation and must be handled with appropriate safety measures (2.1).
- Administer 300-450 MBq (8–12 mCi) as an intravenous injection in adults (2.4).
- Administer approximately 2.1 MBq/kg in children with a minimum of 19 MBq (0.5 mCi) and a maximum of 148 MBq (4 mCi) as an intravenous injection (2.5).
- Imaging can begin 1–2 hours after administration; optimally at one hour post administration (2.7).
- Encourage patients to void immediately prior to imaging the lumbar spine and bony pelvis (2.7).

DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) of no-carrier-added sodium fluoride F18 at the end of synthesis (EOS) reference time in aqueous 0.9% sodium chloride solution (3). Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Allergic Reactions: As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available (5.1).
- Cancer Risk: Sodium Fluoride F 18 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker (5.2).

ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems (6).

To report SUSPECTED ADVERSE REACTIONS, contact NCI/DCTD/CIP at 1-301-496-9531 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Any radiopharmaceutical, including Sodium Fluoride F18 injection, may cause fetal harm. Use only if clearly needed (8.1)
- Nursing: A decision should be made whether to interrupt nursing after Sodium Fluoride F 18 Injection administration or not to administer Sodium Fluoride F 18 Injection taking into consideration the importance of the drug to the mother. (8.3)
- Pediatrics: Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection (8.4).

See 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety – Drug Handling

- Wear waterproof gloves and effective shielding when handling Sodium Fluoride F 18 Injection. Use appropriate safety measures, including shielding, consistent with proper patient management 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.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Sodium Fluoride F 18 Injection.
- The dose of Sodium Fluoride F 18 Injection should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.
- The final dose for the patient should be calculated using proper decay factors from the time of End of Synthesis (EOS), and measured by a suitable radioactivity calibration system before administration [see Description (11.2)].

2.2 Radiation Safety - Patient Preparation

- To minimize the radiation-absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to ingest at least 500 mL of fluid immediately prior and subsequent to the administration of Sodium Fluoride F 18 Injection.
- Encourage the patient to void one-half hour after administration of Sodium Fluoride F 18 Injection and as frequently thereafter as possible for the next 12 hours.

2.3 Drug Preparation and Administration

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

2.4 Recommended Dose for Adults

- Administer 300–450 MBq (8–12 mCi) as an intravenous injection.

2.5 Recommended Dose for Pediatric Patients

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi–4 mCi) were used.

2.6 Radiation Dosimetry

The age/weight-based estimated absorbed radiation doses (mGy/MBq) from intravenous injection of Sodium Fluoride F 18 Injection are shown in Table 1. These estimates were calculated based on human data and using the data published by the Nuclear Regulatory Commission [1] and the International Commission on Radiological Protection for Sodium Fluoride Injection [2]. The bone, bone marrow and urinary bladder are considered target and critical organs.

Table 1: Estimated Absorbed Radiation Doses after Intravenous Administration of Sodium Fluoride F 18 Injection

Organ		Estimated Radiation Dose mGy/MBq				
		Adult 70 kg[1]	**15 year 56.8 kg[2]**	**10 year 33.2 kg[2]**	**5 year 19.8 kg[2]**	**1 year 9.7 kg[2]**
Adrenals		0.0062	0.012	0.018	0.028	0.052
Brain		0.0056	N/A	N/A	N/A	N/A
Bone surfaces		0.060	0.050	0.079	0.13	0.30
GI	Breasts	0.0028	0.0061	0.0097	0.015	0.030
	Gallbladder wall	0.0044	N/A	N/A	N/A	N/A
	Stomach wall	0.0038	0.008	0.013	0.019	0.036
	Small intestine	0.0066	0.012	0.018	0.028	0.052
	Upper large intestine wall	0.0058	0.010	0.016	0.026	0.046
	Lower large intestine wall	0.012	0.016	0.025	0.037	0.063
Heart wall		0.0039	N/A	N/A	N/A	N/A
Kidneys		0.019	0.025	0.036	0.053	0.097
Liver		0.0040	0.0084	0.013	0.021	0.039
Lungs		0.0041	0.0084	0.013	0.020	0.039
Muscle		0.0060	N/A	N/A	N/A	N/A
Ovaries		0.011	0.016	0.023	0.036	0.063
Pancreas		0.0048	0.0096	0.015	0.023	0.044
Red marrow		0.028	0.053	0.088	0.18	0.38
Skin		0.0040	N/A	N/A	N/A	N/A
Spleen		0.0042	0.0088	0.014	0.021	0.041
Testes		0.0078	0.013	0.021	0.033	0.062
Thymus		0.0035	N/A	N/A	N/A	N/A
Thyroid		0.0044	0.0084	0.013	0.020	0.036
Urinary bladder wall		0.25	0.27	0.4	0.61	1.1
Uterus		0.019	0.023	0.037	0.057	0.099
Other tissue		N/A	0.010	0.015	0.024	0.044
Effective Dose Equivalent mSv/MBq		0.027	0.034	0.052	0.086	0.17

1 Data from Nuclear Regulatory Commission Report, *Radiation Dose Estimates for Radiopharmaceuticals*, NUREG/CR-6345, page 10, 1996.

2 Data from ICRP publication 53, Radiation Dose to Patients from *Radiopharmaceuticals*, Ann ICRP, Volume 18, pages 15 and 74, 1987

2.7 Imaging Guidelines

- Imaging of Sodium Fluoride F 18 Injection can begin 1–2 hours after administration; optimally at 1 hour post administration.
- Encourage the patient to void immediately prior to imaging the fluoride F18 radioactivity in the lumbar spine or bony pelvis.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) at EOS reference time of no-carrier-added sodium fluoride F 18 in aqueous 0.9% sodium chloride solution. Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.

5.2 Radiation Risks

Sodium Fluoride F 18 Injection may increase the risk of cancer. Carcinogenic and mutagenic studies with Sodium Fluoride F 18 injection have not been performed. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.1)].

6 ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

7 DRUG INTERACTIONS

The possibility of interactions of Sodium Fluoride 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

Any radiopharmaceutical including Sodium Fluoride F 18 Injection has a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the radionuclide dose. Animal reproductive and developmental toxicity studies have not been conducted with Sodium Fluoride F 18 Injection. Prior to the administration of Sodium Fluoride F 18 Injection to women of childbearing potential, assess for presence of pregnancy. Sodium Fluoride F 18 Injection should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Sodium Fluoride F 18 Injection is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to interrupt nursing after administration of Sodium Fluoride F 18 Injection or not to administer Sodium Fluoride F 18 Injection, taking into account the importance of the drug to the mother. The body of scientific information related to radioactivity decay, drug tissue distribution and drug elimination shows that less than 0.01% of the radioactivity administered remains in the body after 24 hours (10 half-lives). To minimize the risks to a nursing infant, interrupt nursing for at least 24 hours.

8.4 Pediatric Use

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi – 4 mCi) were used. Sodium Fluoride F18 was shown to localize to areas of bone turnover including rapidly growing epiphyses in developing long bones. Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection.

11 DESCRIPTION

11.1 Chemical Characteristics

Sodium Fluoride F 18 Injection is a positron emitting radiopharmaceutical, containing nocarrier-added, radioactive fluoride F18 that is used for diagnostic purposes in conjunction with PET imaging. It is administered by intravenous injection. The active ingredient, sodium fluoride F18, has the molecular formula Na[^{18}F] with a molecular weight of 40.99, and has the following chemical structure: **Na + ^{18}F**
Sodium Fluoride F 18 Injection is provided as a ready-to-use, isotonic, sterile, pyrogen-free, preservative-free, clear and colorless solution. Each mL of the solution contains between 370 MBq to 7,400 MBq (10 mCi to 200 mCi) sodium fluoride F18, at the EOS reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8. The solution is presented in 30 mL multiple- dose glass vials with variable total volume and total radioactivity in each vial.

11.2 Physical Characteristics

Fluoride F 18 decays by positron (ß+) emission and has a half-life of 109.7 minutes. Ninety-seven percent of the decay results in emission of a positron with a maximum energy of 633 keV and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 2). Fluorine F18 atom decays to stable ^{18}O-oxygen.

Table 2: Principal Emission Data for Fluoride F18

Radiation/Emission	% per Disintegration	Mean Energy
Positron (ß+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

*Produced by positron annihilation

[3] Kocher, D.C. Radioactive Decay Data Tables DOE/TIC-11026, 69, 1981.

The specific gamma ray constant for fluoride F18 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 4.1 mm lead (Pb). A range of values for the attenuation of radiation results from the interposition of various thickness of Pb. The range of attenuation coefficients for this radionuclide is shown in Table 3. For example, the interposition of an 8.3 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 Fluoride F18

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

Table 4 lists the fraction of radioactivity remaining at selected time intervals for the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4: Physical Decay Chart for Fluoride F18

Time Since Calibration	Fraction Remaining
0*	1.00
15 minutes	0.909
30 minutes	0.826
60 minutes	0.683
110	0.500
220 minutes	0.250
440 minutes	0.060
12 hiurs	0.011
24 hours	0.0001

* Calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluoride F18 ion normally accumulates in the skeleton in an even fashion, with greater deposition in the axial skeleton (e.g. vertebrae and pelvis) than in the appendicular skeleton and greater deposition in the bones around joints than in the shafts of long bones.

12.2 Pharmacodynamics

Increased fluoride F18 ion deposition in bone can occur in areas of increased osteogenic activity during growth, infection, malignancy (primary or metastatic) following trauma, or inflammation of bone.

12.3 Pharmacokinetics

After intravenous administration, fluoride F18 ion is rapidly cleared from the plasma in a biexponential manner. The first phase has a half-life of 0.4 h, and the second phase has a half-life of 2.6 h. Essentially all the fluoride F18 that is delivered to bone by the blood is retained in the bone. One hour after administration of fluoride, F18 only about 10% of the injected dose remains in the blood. Fluoride F18 diffuses through capillaries into bone extracellular fluid space, where it becomes bound by chemisorption at the surface of bone crystals, preferentially at sites of newly mineralizing bone. Deposition of fluoride F18 in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the fluoride F18. Fluoride F18 does not appear to be bound to serum proteins. In patients with normal renal function, 20% or more of the fluorine ion is cleared from the body in the urine within the first 2 hours after intravenous administration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess reproductive toxicity, mutagenesis and carcinogenesis potential of Sodium Fluoride F 18 Injection have not been performed.

14 CLINICAL STUDIES

14.1 Metastatic Bone Disease

The doses used in reported studies ranged from 2.7 mCi to 20 mCi (100 MBq to 740 MBq), with an average median dose of 10 mCi (370 MBq) and an average mean dose of 9.2 mCi (340 MBq). In PET imaging of bone metastases with Sodium Fluoride F 18 Injection, focally increased tracer uptake is seen in both osteolytic and osteoblastic bone lesions. Negative PET imaging results with Sodium Fluoride F 18 Injection do not preclude the diagnosis of bone metastases. Also, as benign bone lesions are also detected by Sodium Fluoride F 18 Injection, positive PET imaging results cannot replace biopsy to confirm a diagnosis of cancer.

14.2 Other Bone Disorders

The doses used in reported studies ranged from 2.43 mCi to 15 mCi (90 MBq to 555 MBq), with an average median dose of 8.0 mCi (300 MBq) and an average mean dose of 7.6 mCi (280 MBq).

15 REFERENCES

1. Stabin, M.G., Stubbs, J.B. and Toohey R.E., Radiation Dose Estimates for Radiopharmaceuticals, U.S. Nuclear Regulatory Commission report NUREG/CR¬6345, page 10, 1996.
2. Radiation Dose to Patients from Radiopharmaceuticals, ICRP publication 53, Ann ICRP, 18 pages 15 and 74, 1987
3. Kocher, D.C., "Radioactive Decay Data Tables: A Handbook of decay data for application to radiation dosimetry and radiological assessments" DOE/TIC-11026, page 69, 1981.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sodium Fluoride F 18 Injection is supplied in a multiple-dose Type I glass vial with elastomeric stopper and aluminum crimp seal containing between 370 and 7,400 MBq/mL (10–200 mCi/mL) of no carrier-added sodium fluoride F18, at the EOS reference time, in aqueous 0.9% sodium chloride solution. The total volume and total radioactivity per vial are variable. Each vial is enclosed in a shielded container of appropriate thickness. The product is available in a 30 mL vial configuration with a variable fill volume. The NDC number is: 40028-512-30 (30 mL

Storage

Store at 25°C (77°F) in a shielded container; excursions permitted to 15–30°C (59–86°F). Use the solution within 12 hours of the EOS reference time.

Handling

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.

17 PATIENT COUNSELING INFORMATION

17.1 Pre-study Hydration

Encourage patients to drink at least 500 mL of water prior to drug administration.

17.2 Post-study Voiding

To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible, use a toilet and flush several times after each use; wash hands thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, wash the clothing separately.

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PN0002262 Rev. A

March 1, 2011

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