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Transitioning from Mobile to Fixed PET/CT Services

Jackson Kiser, MD, Roanoke, Virginia, USA

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The statements by Siemens' customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers wil achieve the same results.

***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 20-30.

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

****Sodium Fluoride F 18 Injection for Intravenous Use**

INDICATIONS AND USAGE

Sodium fluoride F 18 (^{18}F NaF) 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 pages 31-39.

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

*****AMMONIA N 13 INJECTION for Intravenous Use**

INDICATIONS AND USAGE

Ammonia N 13 (^{13}N NH_3) Injection is a radioactive diagnostic agent for Positron Emission Tomography (PET) indicated for diagnostic PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.

IMPORTANT SAFETY INFORMATION

- **Radiation Risks:** Ammonia N 13 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.
- **Adverse Reactions:** No adverse reactions have been reported for Ammonia N 13 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.

Siemens' PETNET Solutions is a manufacturer of Ammonia N 13 Injection. Indication and important safety information as approved by the US Food and Drug Administration can be found at the links below for ^{13}N Ammonia, adult dose 8-12 mCi, administered by intravenous injection.

Full Prescribing Information for Ammonia N 13 Injection can be found on pages 40-47.

Ammonia N 13 Injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

Introduction

PET/CT as a hybrid imaging modality has been available for over a decade and its importance as an imaging modality is rapidly being redefined. When PET was first approved as a modality for imaging by the Centers for Medicare and Medicaid Services (CMS), only 10 cancer diagnoses were approved for reimbursement.

Today, there are approved indications recognized for solid cancer diagnosis with the PET radiopharmaceutical fludeoxyglucose F 18 injection (^{18}F FDG).* CMS also allows PET/CT bone imaging with sodium fluoride F 18 injection (^{18}F NaF).** Oncology still represents the vast majority of scans for PET imaging and is the primary justification for investment in PET/CT. However, other opportunities for growth exist in cardiology and neurology. In the experience of Molecular Imaging and Therapy Consultants (MITC), most facilities that had their own scanner locate it in an outpatient facility almost exclusively for oncology. Mobile scanners are an ideal way to introduce the technology to facilities interested in exploring the potential for PET imaging and its capabilities.

In general, a mobile scanner is used for oncologic imaging to start. MITC first began using PET/CT when it was in its infancy and, at that time, there were only limited covered indications. In the current environment where CMS has waived any exclusion for the vast majority of oncologic indications, oncologic imaging is the foundation for developing a PET/CT program.

With this growth, hospital administration was convinced it was time for a fixed scanner when they determined that a mobile scanner could not deliver the type of consistent service needed to expand the various service lines beyond oncology. This decision was formed by the lead nuclear

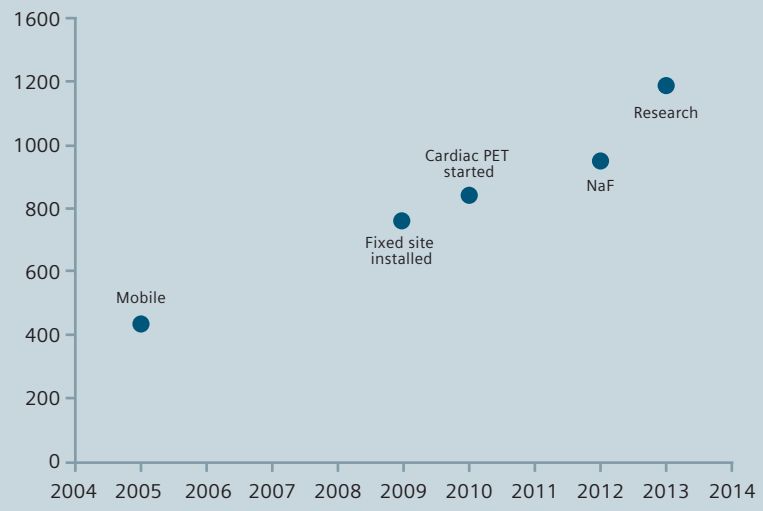


Figure 1

Figure 1: Annual department volumes from 2005 through 2013. The fixed scanner was installed in late 2009. Only a few of the ^{18}F FDG brain metabolism studies were performed prior to installing the fixed scanner. Cardiac PET began shortly after installation in 2010 when the scanner migrated in-house. Later, ^{18}F NaF and some research studies were added.

medicine physician, the lead nuclear medicine technologist and members of high level administration including the COO of the hospital. The decision to buy a fixed scanner was based on:

- The known volumes which were showing continuous growth
- The realization that more oncologic indications would be forthcoming largely by way of the National Oncology PET Registry (NOPR) program
- The need to expand the service beyond oncology
- The knowledge of new PET radiopharmaceuticals in development

An additional benefit would be the flexibility to manage the work schedule by not being relegated to a mobile service that was only available once or twice a week.

As an example, while still using a mobile unit, the department was faced with a patient referral from the cardiac surgery service where there was a question of myocardial viability in a patient who might need a cardiac bypass. There was a clinical concern of the benefit of bypass due to the uncertainty of myocardial viability, and cardiac MRI was inconclusive, leading to a request to perform a PET ^{18}F FDG viability study. Trying to find a slot to image this inpatient with a mobile service was very difficult due to the full schedule. To further complicate the problem, this patient was a diabetic and an insulin clamp technique had to be utilized so it was uncertain as to when the patient would be ready to be imaged. Right away, it was clear that performing this viability study on this patient would be very difficult on a mobile unit.

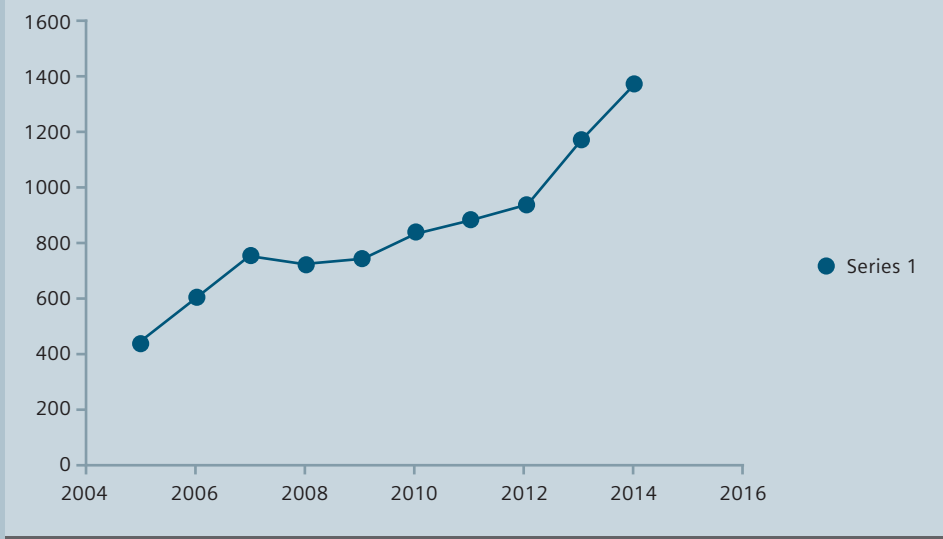


Figure 2

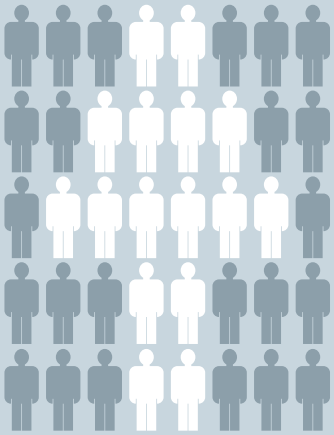
Figure 2: Graph demonstrates progressive increase in volume over time. Lowest volume was in 2005 at 435 exams. In 2014, 1,378 exams were performed.

Another major advantage was that a cyclotron was being sited just minutes from the hospital. Access to the cyclotron would ultimately allow quick access to not only ^{18}F FDG for oncology but would also provide access to short-lived isotopes, particularly Ammonia N 13 injection*** (^{13}N NH_3) for cardiac myocardial perfusion imaging. The potential volume impact this would have above that of the predictable oncology volume was unknown. ^{13}N NH_3 is a desirable perfusion agent and attenuation correction is always possible, which would prove very advantageous for imaging obese patients. Because of the short half-life, the duration of the rest and stress sequence is considerably shorter than other conventional cardiac imaging methods. Another consideration is the patient safety factor because ^{13}N NH_3 scans require pharmacological stress.

Another area of potential growth is PET/CT imaging of neurology patients. Reimbursement in this area has proven to be difficult and complex. CMS does cover certain aspects of neurological imaging when specific requirements are met but commercial coverage in this area varies.

The workflow to perform neurological imaging can be challenging as it is most desirable to have these patients

316%
increase in volume over 10 YEARS



in a setting of relative sensory deprivation so as not to activate the brain excessively. While using the mobile system, the hospital did not have the facilities to place patients in such a quiet setting near the trailer. When the fixed scanner was purchased, amyloid imaging radiopharmaceuticals were not yet available but there was ongoing evidence-based information that these would most likely gain acceptance.

These expanded applications were considerations when deciding to purchase a fixed scanner. As an added incentive, we were able to provide applications which could not or would not be offered by other hospitals in the area. Administration recognized that the cost of using a mobile service was self-defeating as PET/CT volumes began to increase due to higher patient demand. In our rural practicing area, high-level PET imaging techniques were scarce and MITC was the tertiary referral center for surrounding hospitals. Additionally, having a fixed PET/CT allowed MITC to serve this rural area with limited PET resources. Having a fixed scanner also allowed referrals from other facilities from outside our traditional service area. All these factors contributed to our ability to grow.

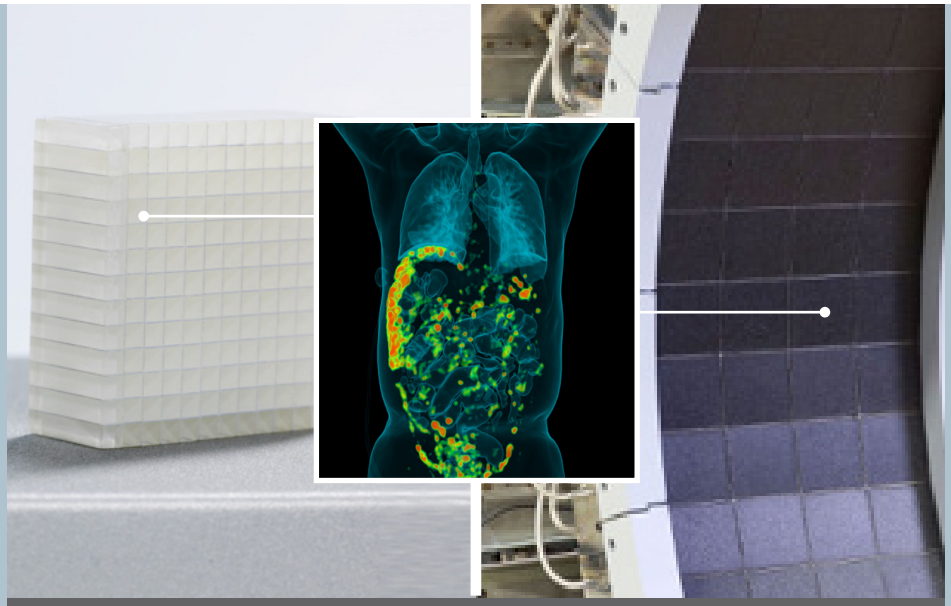


Figure 3

Figure 3: Fourth detector ring allows for larger FOV and shorter imaging times which is important for cardiac imaging. LSO is an ideal material for PET imaging.

Data courtesy of Keio University, Tokyo, Japan.

Purchase, Utilization and Protocol Development

After exhaustive site visits and research, the decision came down to two vendors. The decision was made to purchase the PET/CT system with a combination of the most efficient detectors and largest Field of View (FOV). In MITC's situation, the PET component of the PET/CT was more important than the CT slice capability. This decision was based on several factors, most importantly of which was the LSO crystal technology. The crystal characteristics of the scanner selected far exceeded any other on the market and LSO has been proven to be a scintillation element due to its better emission spectra and its shorter decay constant. It also allows a smaller crystal to be used which increases resolution.

The other important feature was the fourth detector ring. The TrueV option is an additional detector ring that increases the axial FOV and sensitivity providing larger coverage and faster scans. The additional crystal ring is critical with cardiac imaging as one of the competitor scanner companies considered could not guarantee complete coverage of the heart with their configuration. Shorter imaging times, with very short-lived isotopes, would also become of critical importance. Also, with the added ring and extended coverage, it was decided to expand the usual "eyes-to-thighs" coverage typically used for oncology to include the entire head.

It should be noted that there was a lot of work after the purchase of the scanner. Simply having a scanner of high quality does not ensure that volume will grow or even stay the same. To capture current and, ultimately, increase volume, an additional investment had to be made...time. This was the time to start propagating the technology to referring physicians not only at the hospital but to other practices and hospitals in the region. In addition to marketing department assistance, the lead radiologist and lead technologist would take the time to speak with individual physicians and relevant staff. Visits were made to neurology, cardiology, oncology and urology offices to promote the new system. An open house was held where

the radiologist and technician, as well as other physicians, were on hand so the general public could ask questions about this technology. Multiple presentations in the form of lectures were given as another way to extend this knowledge. Case presentations and grand-rounds-style presentations were given at subspecialty conferences such as the cardiac catheterization conference.

The best and probably most productive way to disseminate this technology was to use the weekly tumor conference at the hospital as a vehicle. This is a weekly gathering of multiple subspecialists in the same room for one hour a week. The conference is regularly attended by medical and radiation oncologists, pulmonologists, urologists and other surgical subspecialties like gynecology, cardiothoracic and surgical oncology. It was important that not only the radiologist attend but also the lead molecular technologist. When the radiologist would be called on to present patient images, this became a time when physician education was possible. This was, in part, how sodium fluoride PET bone scanning was introduced to referring physicians.

Yet the role of the lead technologist became equally, if not more, important at this conference. One of the biggest barriers facilities face is getting pre-authorization for the PET/CT scan to be done at all. The lead technologist became the greatest resource in combatting this by explaining appropriate coding and indications. It became immediately apparent that referring physicians were very frustrated by the numerous denials for PET/CT imaging they ordered for their patients, as the insurance companies response was that PET imaging is “experimental” while there were numerous indications approved by CMS. Sodium fluoride scans were particularly problematic. By functioning in this capacity, the lead technologist developed a relationship with various physicians and gained their trust as an important resource to resolve these problems.

Figure 4: Example of dual time point PET/CT in a patient with SPN. Initial whole-body scan (bottom row) was followed by a delayed scan of the chest (top row). Comparison of both acquistions shows increase in SUV_{max} in the lung nodule on delayed images which indicates a higher likelihood of malignancy.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

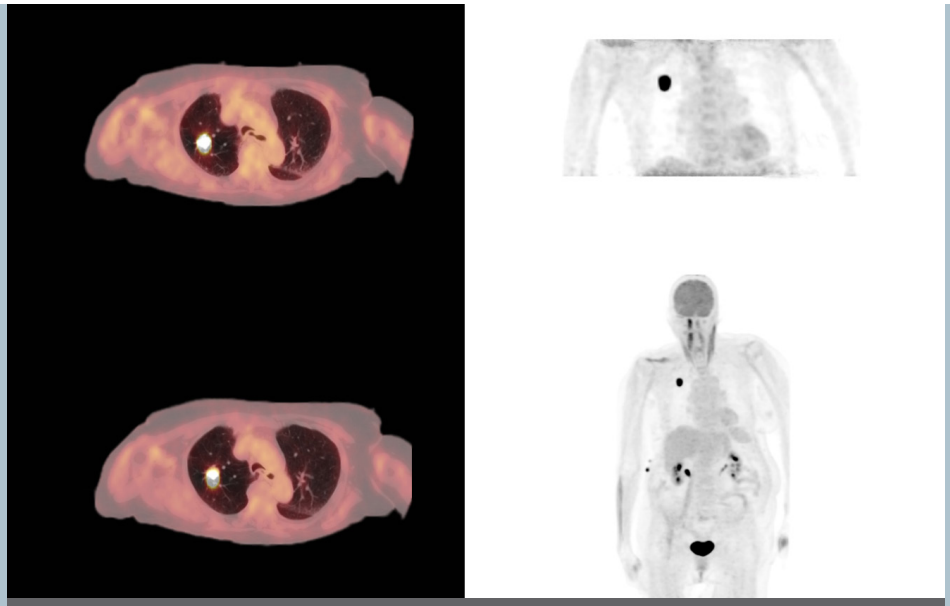


Figure 4

Oncology

Similar to most imaging facilities, the majority of PET/CT utilization is for oncology. MITC took advantage the scanner's fourth ring of detectors when imaging oncology patients. Instead of the standard skull base to thighs protocol generally used, the entire skull was included. This allows detection of unsuspected skull and brain metastases with little, if any, increase in the time required to complete the exam. For solitary pulmonary nodules (SPN), the protocol includes a single delayed acquisition of the chest over the area of interest after the initial scan to obtain a second time point. This allows for comparison of the initial maximum SUV to the delayed measurement, since malignant disease will typically show an increase on the delayed value, whereas benign disease will either remain the same or decrease. One additional protocol modification is that patients with head and neck cancer will have a high resolution acquisition of this area as an adjunct to the standard top of skull through the thighs. This is helpful especially in the event of a malignant cervical lymph node biopsy with an unknown primary.

The vast majority of the patients scanned were outpatients who presented with a known cancer diagnosis with PET/CT indications of staging, restaging and treatment moni-

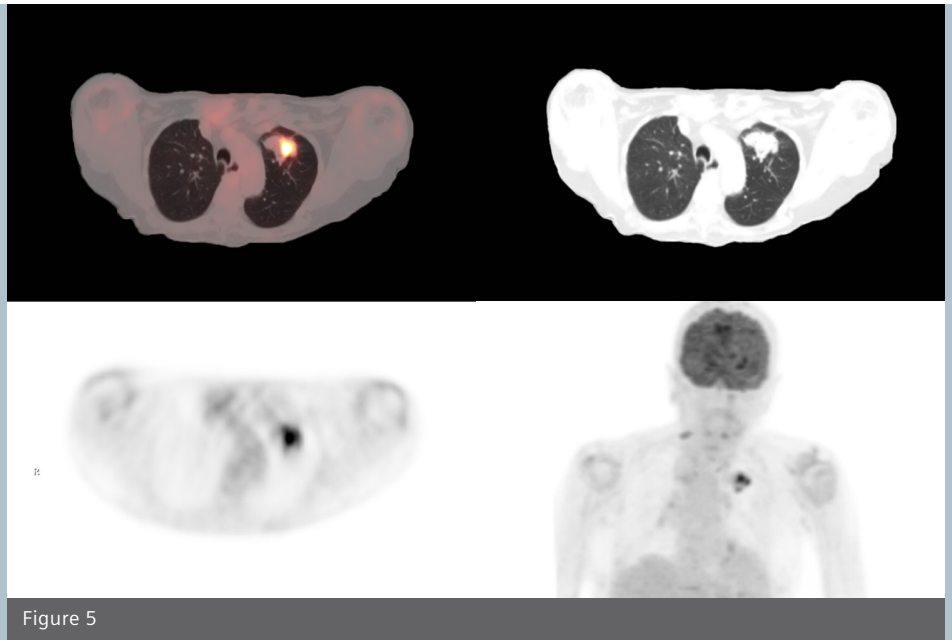


Figure 5

Figure 5: Where to biopsy. This is an example of how PET helped determine which part of a lung mass was metabolically active for diagnostic biopsy.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

toring. However, an immense improvement in patient management is realized, particularly in expediting diagnosis and treatment in patients who are admitted with suspected malignancy through the emergency room. The immediate impact is that performing PET/CT on those patients who become inpatients helps direct potential biopsy to the site expected to produce the highest yield for diagnosis as well as determining the safest and least invasive location. Beyond this, PET/CT also stages the patient for further therapy. Although, in most situations, PET/CT is not covered for inpatient imaging for any oncologic indication, it can be used as a guide to rapid diagnosis and optimal staging. As such, the downstream revenue offsets this downside. The use of PET/CT, therefore, helps expedite patient care and diagnosis. There have been instances where a biopsy has been performed by other services that were not guided by metabolic activity and it turned out to be non-diagnostic. Repeat biopsy by the radiology department guided by the metabolic activity ultimately led to a diagnosis.

An additional example of the advantage to PET/CT in the inpatient setting was a patient with a known cancer primary diagnosis who was being staged prior to definitive therapy and was found to have a second primary which completely changed the management of this patient. This

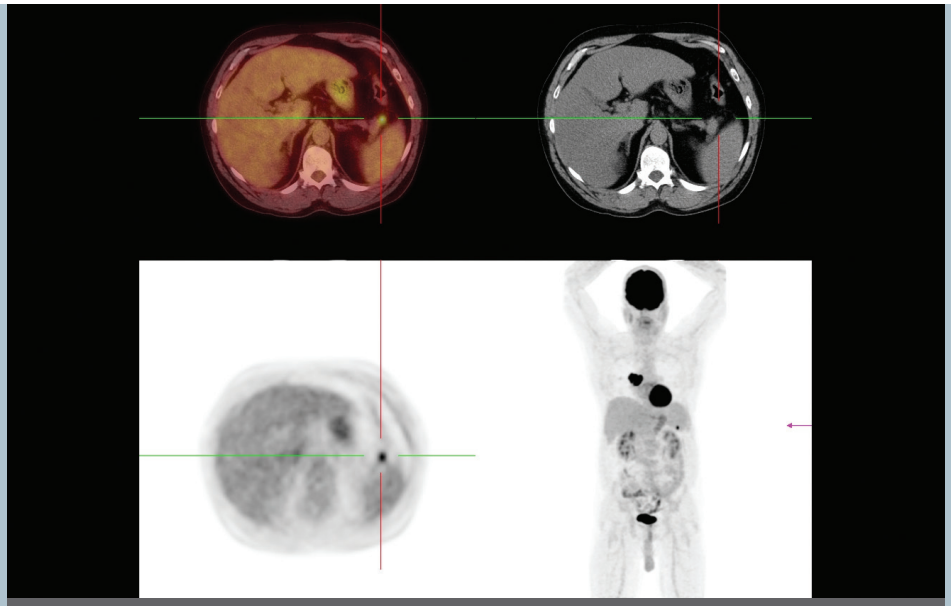


Figure 6

Figure 6: Example of a case of known lung cancer with incidental second malignancy in the pancreatic tail detected on PET/CT for staging.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

patient was being staged for a lung cancer and was found to have a second primary pancreatic lesion which had to be addressed before the other cancer was treated. Based on this, patients with a suspected or known diagnosis of cancer who have to be admitted for inpatient management could have a PET/CT scan, if there is a scanner available, to expedite staging, other diagnoses and treatment.

Sodium fluoride bone scan is another oncologic application performed regularly. The sensitivity of this scan far exceeds standard planar scintigraphy.[1] Although PET/CT is extremely sensitive detecting both benign and malignant abnormalities, the combination with CT helps increase specificity and reader confidence. As in conventional scintigraphy, ^{18}F NaF is best used with osteoblastic disease. Referring physicians who send a patient with a diagnosis of prostate cancer who are being staged or have a rising PSA are encouraged to use this advanced PET technology.

When ^{18}F NaF was first introduced, there was some confusion by the clinicians. Some did not understand that PET scanning could be performed with radiopharmaceuticals other than ^{18}F FDG. Often, when the radiologist would recommend a PET bone scan, the clinicians would request an ^{18}F FDG scan by mistake. To make things more complicated, the principle audience was urologists. This is a subspecialty that rarely orders PET scans for their prostate

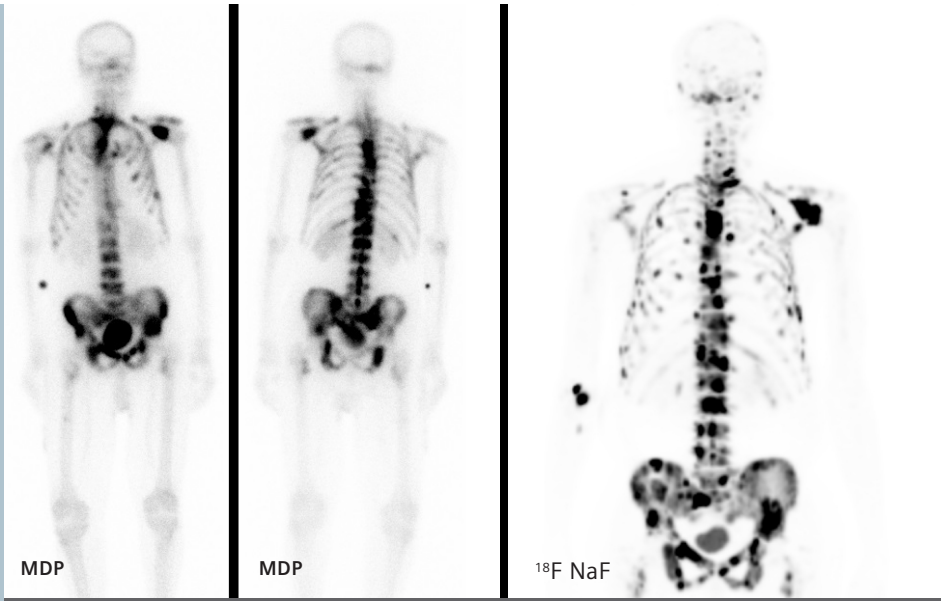


Figure 7

Figure 7: MDP and ^{18}F NaF bone scans studies performed about a week apart with ^{18}F NaF showing much more extensive disease that MDP.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

cancer patients. Despite best efforts to educate, requests for conventional bone scans continue to be seen. After several visits to the urologists' offices, it was eventually discovered that the urologist would order a "bone scan" and the nurses or clerical staff would just enter as a default a conventional bone scan. Once this was recognized, when a conventional bone scan was ordered by a urologist for a patient of Medicare age, this would prompt the department to call the office to ask the urologist if this could be switched to a ^{18}F NaF PET/CT bone scan. This was not the only hurdle to implementing PET bone scans. The other challenge to implementing PET bone scans was that NOPR (National Oncologic PET Registry) paperwork had to be filled out by both the urologist and the radiologist. But, once the referring physicians realized that PET bone scans can change staging more often than conventional bone scans, the technology utilization increased.

The other target subspecialty, who were more easily convinced, were the radiation oncologists. Because they have a working understanding of radiologic procedures, they could readily see the benefits of PET bone scan. During this period of ^{18}F NaF bone scan start-up, the use of Xofigo® (Radium 223), an alpha emitter, was approved for treatment of bone metastases in prostate cancer. A protocol was introduced whereby any patient who was to be treated with Xofigo would undergo initial PET ^{18}F NaF bone scan prior to treatment, as well as a follow-up scan at the end of the standard six cycles of therapy.

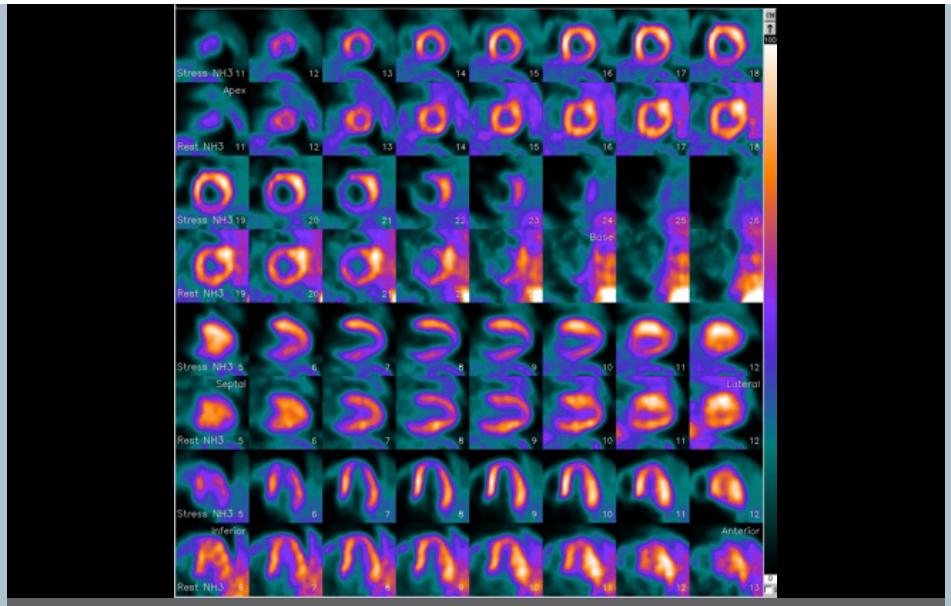


Figure 8

Figure 8: Rest and stress regadenoson $^{13}N\ NH_3$ ammonia myocardial perfusion images showing inferior wall ischemia.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

Cardiology

Probably the most advanced applications for which this facility used PET/CT imaging is myocardial perfusion imaging (MPI) and myocardial viability. The availability of $^{13}N\ NH_3$ ammonia has dramatically changed the way chest pain presentations are managed. As with most institutions, patients who are admitted with diagnosis of rule out myocardial infarction go to an observation unit for serial enzymes and then later undergo myocardial perfusion imaging. In most instances, these patients will be evaluated with standard SPECT/CT imaging with sestamibi. Those patients whose BMI exceeds 40 would historically undergo a 2-day study so that larger doses could be used for both rest and stress images to improve the count rate. Instead, $^{13}N\ NH_3$ ammonia is now routinely used for PET/CT imaging. Because the scanner has a weight limit of 500 pounds, these patients can be scanned with a high degree of accuracy. The PET/CT characteristics and the ability to image large patients also play a role in risk stratification in morbidly obese patients who need MPI pre-operative clearance before surgery. This is, at the time of this publication, the only facility capable of imaging obese patients in this region who need this clearance. This is particularly helpful in patients preparing for bariatric surgery who often have multiple risk factors such as hypertension and diabetes.

Initially, only patients who were in-house and had a BMI of or greater than 40 would undergo PET MPI. With the approval of the chief medical officer and the medical executive staff of the hospital, the BMI was lowered to 35. There were occasional exceptions for scanning patients with BMI less than 35. There was also a period of time when there was limited availability of technetium for cardiac SPECT imaging. When this occurred, many patients underwent cardiac PET MPI regardless of BMI. There were also times when there would be failure of one of the SPECT cameras and patients were moved to cardiac PET. One additional scenario was when referring physicians would order a cardiac MPI scan and a ventilation-perfusion scan for the same day on an inpatient. Rather than spread these two procedures over 2 days to allow for radioactive decay of the technetium, these patients would undergo V/Q scan first followed by PET cardiac MPI on the same day to help avert an extra day in the hospital.

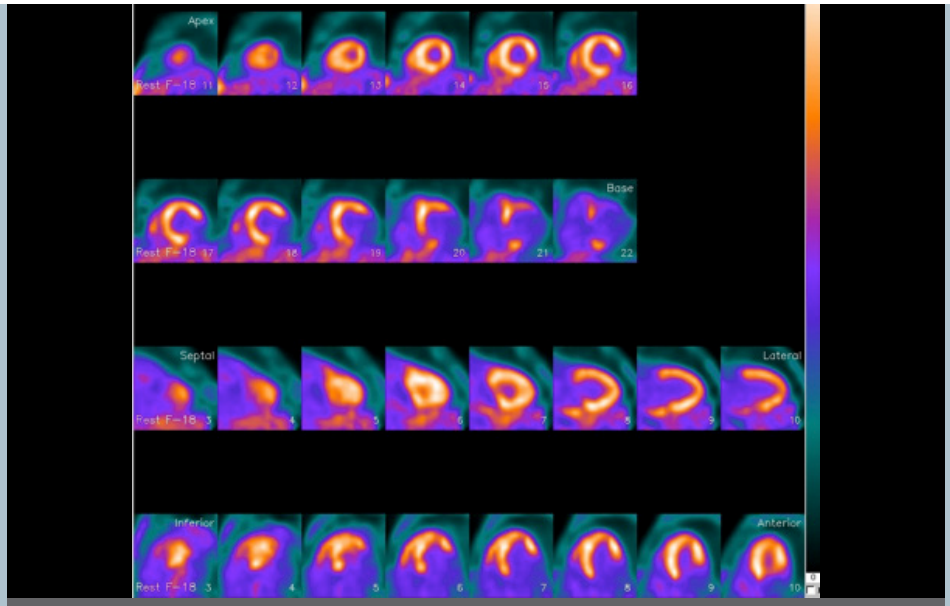


Figure 9

Figure 9: ^{18}F FDG PET shows hibernating myocardium in anteroseptal wall in a patient with resting ischemia.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

The advantages of the technology became immediately apparent following a scan of the first high BMI patient. An ischemic territory was found that would likely have been missed by conventional SPECT. The patient had inferior wall ischemia which was subsequently confirmed with cardiac catheterization. Since that time, this facility has advocated the benefits of PET MPI for patients with high BMI. This has multiplied volume accordingly. Because of this capability, competitive cardiology providers have reluctantly sent their patients to this facility. Fortunately, for the sake of patient care, providers are aware that PET MPI produces more reliable imaging than conventional SPECT in large patients. As this program evolved, coronary flow reserve software was accessed which allowed further manipulation of the data derived from the dynamic list mode data acquisition. This provided a weapon against the elusive balanced triple vessel disease. The guidelines for radiation dosage were also being scrutinized during this time and the additional dose advantage over conventional SPECT was realized.

An additional benefit is that the rest and stress scan time is reduced to about one hour compared to the SPECT study which may take up to 4 hours or, as already mentioned in the case of obese patients, may require rest and stress imaging on 2 separate days. In the era of timed admissions where prompt discharge is critical, this expedites diagnosis and management. Having PET/CT available for 23-hour observation has allowed for greater flexibility and maximized patient care compared with the standard myocardial imaging with SPECT. The four-ring detector design offered by the Siemens scanner ensures that the entire extent of the heart will be covered opposed to other vendors explored who could not do this. Higher reimbursement rates have also been realized using PET/CT instead of SPECT for inpatient and outpatient MPI.

Besides the clear image quality and resolution advantages that PET afforded, it became clear that PET had a clear dose advantage. Even using a 30 mCi dose for both rest and stress, the dose savings was considerable compared to sestamibi. As a way of further reducing dose, the rest

Figure 10: Initial 99m TC-MIBI (^{99m}TC MIBI) resting myocardial perfusion study (Figure 10a) shows gross resting hypoperfusion in anteroseptal wall which was determined to be viable hibernating myocardium by ^{18}F FDG PET study (Figure 9). A stress and rest ^{99m}TC MIBI MPI study perfomed a few months following bypass surgery (Figure 10b) shows improved perfusion to most of the anteroseptal wall with minor residual ischemia.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

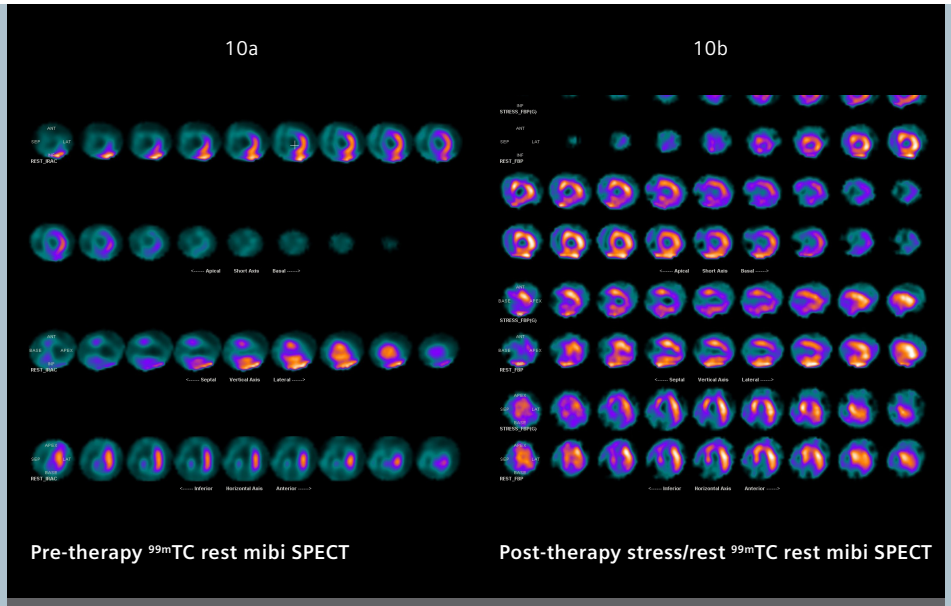


Figure 10

dose of ammonia was decreased to about 5-7 mCi and the stress dose to 20-25 mCi. The total dose to the patient with these modifications became on the order of a mammogram. This technique was validated with several patients in whom ischemia was reported and subsequent cardiac catheterization confirmed stenoses in the abnormal areas.

As volumes grew, the practicality of using a rubidium generator was considered. Due to the cost of each generator which typically has a four-week yield, it is necessary to have adequate volume to justify this cost. Accordingly, an imaging facility should perform around thirty exams per month to break even on the cost of doses. For centers who are not in close proximity to a cyclotron, the use of a rubidium offers an alternative to short-lived ^{13}N NH3 ammonia. ^{18}F-labeled agents are also being developed which offer yet another alternative and allow more widespread availability with unit capability.

Myocardial viability is the other application which can have a tremendous impact to an imaging facility. Using ^{18}F FDG, detection of viable and hibernating myocardium is possible. In patients with cardiomyopathy, PET viability is used to determine if revascularization is an appropriate treatment option. Many institutions choose to use MRI for this purpose but this requires a very robust scanner which is currently not available at many institutions. In patients with New York Heart Association (NYHA) class 4 heart failure who are very unstable, MRI is often a challenge during breath hold sequences. Furthermore, there are other patient limitations and contraindications to MRI such as pacemakers, claustrophobia and poor renal function. MRI is very sensitive for the detection of infarcted myocardium but is not always reliable when determining viability. And while the sensitivity may be less than MRI, the procedure is generally better tolerated by patients. It should be noted that failures do occur with PET, largely due to the diabetic population and poor myocardial uptake of ^{18}F FDG.

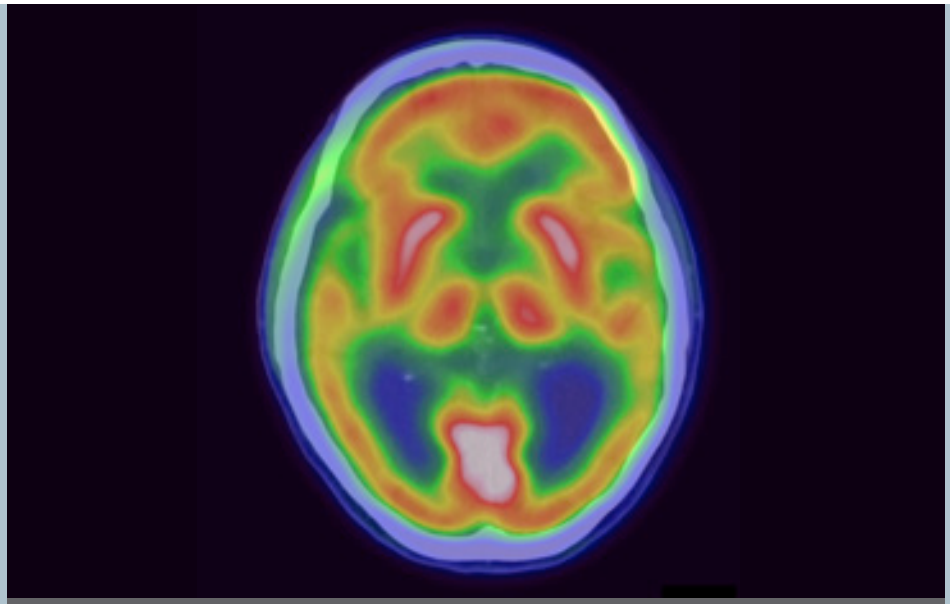


Figure 11

Figure 11: Example of Lewy body disease.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

Neurology

^{18}F FDG brain PET/CT is currently being performed as an adjunct for determining types of clinically atypical presentations of dementia. Based on patterns of hypometabolism, a diagnosis of a particular type of dementia can be inferred such as Alzheimer's disease, frontotemporal dementia, Lewy body disease and vascular dementia. The molecular imaging center was designed around PET/CT, with part of that design to include uptake rooms. One of these rooms is specifically for ^{18}F FDG uptake in patients undergoing brain scans which provides a greater degree of sensory deprivation. This room is only several feet from the scanner so that patients will not undergo too much unnecessary stimulation before the scan is commenced. This was not an option with a mobile PET provider. Protocol is for the patient to be injected with ^{18}F FDG and scanned about 30-60 minutes later. The images are processed and sent to a workstation where analysis is performed using a quantitative application (Scenium). Experience with florbetapir for imaging amyloid plaque deposition has been gained and CMS approval could be forthcoming for this agent so that it can be used more frequently.

There have been a few instances where PET/CT has been used for treatment monitoring of neoplastic brain disease. In particular, this is when MRI is inconclusive as to whether findings after therapy represent radiation necrosis or viable tumor. This option is reserved for patients with large lesions as it can be difficult to assess small lesions due to the normal cortical accumulation of ^{18}F FDG. In the future, we hope to have other agents available.

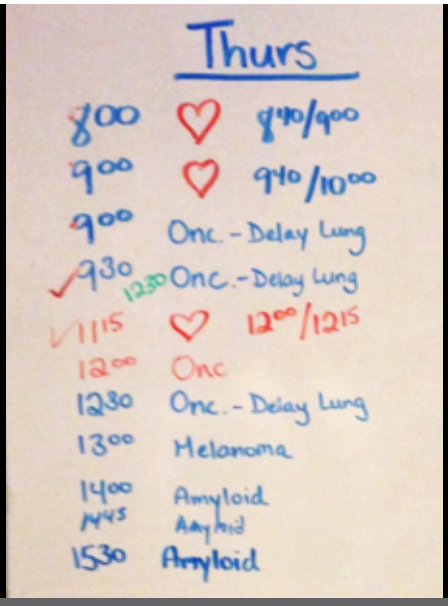


Figure 12

Figure 12: Integrating various types of procedures into a manageable workflow can be a challenge. This is an example of a workflow schedule for a particularly unusual day.

Data courtesy of Jackson W. Kiser, MD, Molecular Imaging and Therapy Consultants of Virginia, Virginia, USA.

Daily Workflow

Unlike most PET/CT facilities, MITC's experience has grown beyond the use of only ^{18}F FDG. Inasmuch, this has introduced workflow challenges as result of multiple radiopharmaceuticals which can have different decay characteristics. Exams using multiple radiopharmaceuticals cannot simply be performed back to back as is the case when only ^{18}F FDG oncology exams are being performed. The foundation for success is the education of the technologists about the different agents whether they be ^{18}F FDG, ^{18}F NaF, ^{13}N NH_3 or amyloid agents. With the understanding of the agent characteristics and that the indication for the exam which may change protocol and length of the exam (i.e., solitary pulmonary nodule will be imaged at 60 and 90 minutes after injection or melanoma patients will all receive whole-body imaging), the technical staff can craft the workflow schedule to take into account these and many other considerations. At this facility, the technologists must control and design the schedule rather than utilize a centralized scheduling process. Figure 12 is an example of one of the daily work schedules.

As more radioisotopes become available, more creative scheduling will necessarily evolve. The technologists, as well as the interpreting physician, must work very closely as these new agents come to market as it will generally be these individuals who will need to be armed with enough information to help guide referring physicians to the right test and the right agent. It is anticipated that, as molecular imaging becomes more complex, referring physicians may simply have to schedule the patient for a "molecular imaging exam" and the team of technologists and the physician will determine the best test and radiotracer to answer the question at hand.

Conclusion

The purchase of a fixed PET/CT scanner has markedly changed the way this hospital faces many of the challenges presented in the current healthcare environment. This facility is the only hospital in the western part of Virginia to offer "out-of-the-ordinary" procedures. It is also the only facility in the region beyond some of the academic centers that is able to offer or is willing to perform ^{18}F FDG myocardial viability, ^{18}F FDG brain metabolism, amyloid imaging and ^{13}N NH_3 myocardial perfusion imaging. The advanced applications have captured referrals well beyond the scope of oncology and further growth of this technology is expected with the scanner as more radiopharmaceuticals and isotopes are approved for clinical use.

With current emphasis on radiation exposure to patients, PET has allowed drastically lower dose compared to SPECT. Furthermore, it helped manage through the technetium shortage that happened several years ago and allowed MPI to be performed when other hospitals were having difficulty with dose availability. Expanded applications such as coronary flow reserve will add further vigor to advanced cardiac imaging. There is still much to learn about the power of this technique but there is a hope that this may help break through the barrier of balanced triple vessel disease. With this application, it may also be possible to do risk assessment in patients with coronary risk factors such as hypertension, hyperlipidemia and premetabolic syndrome.

Going forward, the availability of numerous novel tracers in development is anticipated, which might allow determination of the extent of disease, response to treatment and provide a vehicle for simultaneous treatment in the realm of theranostics.

For any hospital or radiology group that is just starting or in the early phases of a molecular imaging program with PET/CT, starting with a mobile scanner makes the most sense obviously with an emphasis on oncologic imaging. When to move to a fixed scanner will vary from institution to institution. Nonetheless, any facility that is considering this option should weigh several variables. These include, but are not limited to patient volumes, mobile scanner availability and cost of this service, COPN (certificate of public need) restrictions in place in some states and patient backlogs. It is important to consider how the scanner would be utilized. Many facilities probably consider the purchase of a fixed scanner to be used in a high volume single-specialty setting such as oncology or cardiology. MITC wanted to offer a wide array of imaging options to encompass multiple disciplines. Administrators were convinced that satisfactory growth of this type of practice could not be achieved on a mobile scanner for the reasons described throughout this case study.

Having this scanner available at any time has helped expedite patient care and diagnosis. By using the scanner in this way, the plan for patient care is frequently impacted or changed. This is often seen when brain metabolism studies or amyloid imaging are performed because a type of dementia is in question clinically. As described already, myocardial viability helps decide whether a patient would benefit from revascularization. ^{13}N NH_3 ammonia MPI has also helped clarify indeterminate SPECT studies which often occur in large patients. And, of course, changes in patients' cancer stage are frequently seen when ^{18}F FDG and, occasionally, sodium fluoride PET is used. The future will likely hold more new applications and radiotracers to further expand molecular imaging for improved patient care.

About the Author

Jackson W. Kiser, MD

Dr. Kiser received his medical degree from the Medical College of Virginia and subsequently completed internal medicine and radiology residencies at the University of Florida. He achieved board certification in internal medicine by the American Board of Internal Medicine, and radiology certification and special competency in nuclear medicine by the American Board of Radiology. He has been in practice in Roanoke, Virginia, USA, for 18 years and is co-founder of Molecular Imaging and Therapy Consultants of Virginia, LLC.

[1] **Schinmeister, et al.** Sensitivity in Detecting Osseous Lesions Depends on Anatomic Localization: Planar Bone Scintigraphy Versus ^{18}F FDG PET. *J Nucl Med* 1999. 40:1623-1629.

FLUDEOXYGLUCOSE F 18- fludeoxyglucose f-18 injection, solution
PETNET Solutions, Inc.

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 F18 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 F18 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 to7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose F18 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 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: 1/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fludeoxyglucose F18 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 F18 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 F 18 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 F18 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 F18 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 F18 Injection from its container.
- Inspect Fludeoxyglucose F18 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 30mL and 50mL 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.

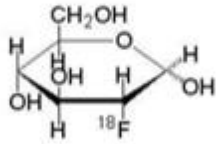
8.4 Pediatric Use

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 C6H11^{18}FO5 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 F 18

Radiation/Emission	% Per Disintegration	Mean Energy
Positron(β+)	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 (1.35×10^{-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 F 18

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 substrate, 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. [F 18]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[F 18]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 2deoxy-2-chloro-6-phospho-D-glucose (ClDG-6-phosphate) and 2-deoxy-2-chloro-6phospho-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. l-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.

Manufactured by:	PETNET Solutions Inc. 810 Innovation Drive Knoxville, TN 37932
Distributed by:	PETNET Solutions Inc. 810 Innovation Drive Knoxville, TN 37932

SODIUM FLUORIDE F 18- sodium fluoride f-18 injection, solution
PETNET Solutions, Inc.

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 PETNET Solutions, Inc. at 877-473-8638 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.

Revised: 1/2016

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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
Breasts		0.0028	0.0061	0.0097	0.015	0.030
GI	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 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.

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 F18 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 no-carrier-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 F18 decays by positron (β+) 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 (β+)	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

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 from 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 minutes	0.500
220 minutes	0.250
440 minutes	0.060
12 hours	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.

Manufactured by:

PETNET Solutions Inc.
810 Innovation Drive
Knoxville, TN 37932

Distributed by:

PETNET Solutions Inc.
810 Innovation Drive
Knoxville, TN 37932

AMMONIA N 13- ammonia n-13 injection
PETNET Solutions, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Ammonia N 13 Injection safely and effectively. See full prescribing information for Ammonia N 13 Injection.
Ammonia N 13 Injection for intravenous use
Initial U.S. Approval: 2007

INDICATIONS AND USAGE

Ammonia N 13 Injection is a radioactive diagnostic agent for Positron Emission Tomography (PET) indicated for diagnostic PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease (1).

DOSAGE AND ADMINISTRATION

Rest Imaging Study (2.1):
• Aseptically withdraw Ammonia N 13 Injection from its container and administer 10 mCi – 20 mCi (0.368 GBq – 0.736 GBq) as a bolus through a catheter inserted into a large peripheral vein.
• Start imaging 3 minutes after the injection and acquire images for a total of 10 minutes – 20 minutes.

Stress Imaging Study (2.2):
• If a rest imaging study is performed, begin the stress imaging study 40 minutes or more after the first Ammonia N13 injection to allow sufficient isotope decay.
• Administer a pharmacologic stress-inducing drug in accordance with its labeling.
• Aseptically withdraw Ammonia N 13 Injection from its container and administer 10 mCi – 20 mCi (0.368 GBq – 0.736 GBq) of Ammonia N 13 Injection as a bolus at 8 minutes after the administration of the pharmacologic stress-inducing drug.
• Start imaging 3 minutes after the Ammonia N 13 Injection and acquire images for a total of 10 minutes – 20 minutes.

Patient Preparation (2.3):
• To increase renal clearance of radioactivity and to minimize radiation dose to the bladder, hydrate the patient before the procedure and encourage voiding as soon as each image acquisition is completed and as often as possible thereafter for at least one hour.

DOSAGE FORMS AND STRENGTHS

Glass vial containing 0.138 GBq/mL – 1.387 GBq/mL (3.75 mCi/mL –37.5 mCi/mL) of Ammonia N 13 Injection in aqueous 0.9 % sodium chloride solution (approximately 7 mL volume) (3).

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Ammonia N 13 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).

ADVERSE REACTIONS

No adverse reactions have been reported for Ammonia N 13 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting system (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

- It is not known whether this drug is excreted in human milk. Alternatives to breastfeeding (e.g. using stored breast milk or infant formula) should be used for 2 hours (>10 half-lives of radioactive decay for N 13 isotope) after administration of Ammonia N 13 Injection (8.3).
- The safety and effectiveness of Ammonia N 13 Injection has been established in pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION.

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ammonia N 13 Injection is indicated for diagnostic Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.

2 DOSAGE AND ADMINISTRATION

2.1 Rest Imaging Study

- Aseptically withdraw Ammonia N 13 Injection from its container and administer 10 mCi – 20 mCi (0.368 GBq – 0.736 GBq) as a bolus through a catheter inserted into a large peripheral vein.
- Start imaging 3 minutes after the injection and acquire images for a total of 10 minutes – 20 minutes.

2.2 Stress Imaging Study

- If a rest imaging study is performed, begin the stress imaging study 40 minutes or more after the first Ammonia N 13 injection to allow sufficient isotope decay.
- Administer a pharmacologic stress-inducing drug in accordance with its labeling.
- Aseptically withdraw Ammonia N 13 Injection from its container and administer 10 mCi – 20 mCi (0.368 GBq – 0.736 GBq) of Ammonia N 13 Injection as a bolus at 8 minutes after the administration of the pharmacologic stress-inducing drug.
- Start imaging 3 minutes after the Ammonia N 13 Injection and acquire images for a total of 10 minutes – 20 minutes.

2.3 Patient Preparation

To increase renal clearance of radioactivity and to minimize radiation dose to the bladder, ensure that the patient is well hydrated before the procedure and encourage voiding as soon as a study is completed and as often as possible thereafter for at least one hour.

2.4 Radiation Dosimetry

The converted radiation absorbed doses in rem/mCi are shown in Table 1. These estimates are calculated from the Task Group of Committee 2 of the International Commission on Radiation Protection.[1]

Table 1: N 13 Absorbed Radiation Dose Per Unit Activity (rem/mCi) for Adults and Pediatric Groups.

Organ	Adult	15 - year old	10 - year old	5 - year old	1 - year old
Adrenals	0.0085	0.0096	0.016	0.025	0.048
Bladder wall	0.030	0.037	0.056	0.089	0.17
Bone surfaces	0.0059	0.0070	0.011	0.019	0.037
Brain	0.016	0.016	0.017	0.019	0.027
Breast	0.0067	0.0067	0.010	0.017	0.033
Stomach wall	0.0063	0.0078	0.012	0.019	0.037
Small intestine	0.0067	0.0081	00013	0.021	0.041
*ULI	0.0067	0.0078	0.013	0.021	0.037
**LLI	0.0070	0.0078	0.013	0.020	0.037
Heart	0.0078	0.0096	0.015	0.023	0.041
Kidneys	0.017	0.021	0.031	0.048	0.089
Liver	0.015	0.018	0.029	0.044	0.085
Lungs	0.0093	0.011	0.018	0.029	0.056
Ovaries	0.0063	0.0085	0.014	0.021	0.041
Pancreas	0.0070	0.0085	0.014	0.021	0.041
Red marrow	0.0063	0.0078	0.012	0.020	0.037
Spleen	0.0093	0.011	0.019	0.030	0.056
Testes	0.0067	0.0070	0.011	0.018	0.035
Thyroid	0.0063	0.0081	0.013	0.021	0.041
Uterus	0.0070	0.0089	0.014	0.023	0.041
Other tissues	0.0059	0.0070	0.011	0.018	0.035

*Upper large intestine, **Lower large intestine

2.5 Drug Handling

- Inspect Ammonia N 13 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.

- Do not administer Ammonia N 13 Injection containing particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Wear waterproof gloves and effective shielding when handling Ammonia N 13 Injection.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Ammonia N 13 Injection. The contents of each vial are sterile and non-pyrogenic.
- 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.
- Before administration of Ammonia N 13 Injection, assay the dose in a properly calibrated dose calibrator.

3 DOSAGE FORMS AND STRENGTHS

Glass vial (30 mL) containing 0.138 GBq/mL – 1.387 GBq/mL (3.75 mCi/mL – 37.5 mCi/mL) of Ammonia N 13 Injection in aqueous 0.9 % sodium chloride solution (approximately 7 mL volume) that is suitable for intravenous administration.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

Ammonia N 13 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 *[see Dosage and Administration (2.4)]*.

6 ADVERSE REACTIONS

No adverse reactions have been reported for Ammonia N 13 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 Ammonia N 13 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 Ammonia N 13 Injection. It is also not known whether Ammonia N 13 Injection can cause fetal harm when administered to a pregnant woman or can

affect reproduction capacity. Ammonia N 13 Injection should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for radiation exposure to nursing infants from Ammonia N 13 Injection, use alternative infant nutrition sources (e.g. stored breast milk or infant formula) for 2 hours (>10 half-lives of radioactive decay for N 13 isotope) after administration of the drug or avoid use of the drug, taking into account the importance of the drug to the mother.

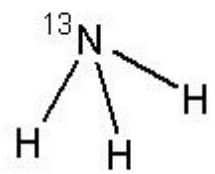
8.4 Pediatric Use

The safety and effectiveness of Ammonia N 13 Injection has been established in pediatric patients based on known metabolism of ammonia, radiation dosimetry in the pediatric population, and clinical studies in adults *[see Dosage and Administration (2.4)]*.

11 DESCRIPTION

11.1 Chemical Characteristics

Ammonia N 13 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient, [^{13}N] ammonia, has the molecular formula of $^{13}NH_3$ with a molecular weight of 16.02, and has the following chemical structure:



Ammonia N 13 Injection is provided as a ready to use sterile, pyrogen-free, clear and colorless solution. Each mL of the solution contains between 0.138 GBq to 1.387 GBq (3.75 mCi to 37.5 mCi) of [^{13}N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 to 7.5. The recommended dose of radioactivity (10 mCi – 20 mCi) is associated with a theoretical mass dose of 0.5 picomoles – 1.0 picomoles (8.47 picograms – 16.94 picograms) of ammonia.

11.2 Physical Characteristics

Nitrogen N13 decays by emitting positron to Carbon C13 (stable) and has a physical half-life of 9.96 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 Nitrogen 13

Radiation/Emission	% Per Disintegration	Energy

Positron(β+)	100	1190 keV (Max.)
Gamma(±)*	200	511 keV

*Produced by positron annihilation

The specific gamma ray constant (point source air kerma coefficient) for nitrogen N13 is 5.9 R/hr/mCi (1.39 x 10-6 Gy/hr/kBq) at 1 cm. The half-value layer (HVL) of lead (Pb) for 511 keV photons is 4 mm. Selected coefficients of attenuation are listed in Table 3 as a function of lead shield thickness. For example, the use of 39 mm thickness of lead will attenuate the external radiation by a factor of about 1000.

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

Shield Thickness (Pb) mm	Coefficient of Attenuation
4	0.5
8	0.25
13	0.1
26	0.01
39	0.001
52	0.0001

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

Table 4: Physical Decay Chart for Nitrogen N 13

Minutes	Fraction Remaining
0*	1.000
5	0.706
10	0.499
15	0.352
20	0.249
25	0.176
30	0.124

*Calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ammonia N 13 Injection is a radiolabeled analog of ammonia that is distributed to all organs of the body after intravenous administration. It is extracted from the blood in the coronary capillaries into the myocardial cells where it is metabolized to glutamine N 13 and retained in the cells. The presence of ammonia N 13 and glutamine N 13 in the myocardium allows for PET imaging of the myocardium.

12.2 Pharmacodynamics

Following intravenous injection, ammonia N 13 enters the myocardium through the coronary arteries. The PET technique measures myocardial blood flow based on the assumption of a three-compartmental

disposition of intravenous ammonia N 13 in the myocardium. In this model, the value of the rate constant, which represents the delivery of blood to myocardium, and the fraction of ammonia N 13 extracted into the myocardial cells, is a measure of myocardial blood flow. Optimal PET imaging of the myocardium is generally achieved between 10 minutes to 20 minutes after administration.

12.3 Pharmacokinetics

Following intravenous injection, Ammonia N 13 Injection is cleared from the blood with a biologic half-life of about 2.84 minutes (effective half-life of about 2.21 minutes). In the myocardium, its biologic half-life has been estimated to be less than 2 minutes (effective half-life less than 1.67 minutes).

The mass dose of Ammonia N 13 Injection is very small as compared to the normal range of ammonia in the blood (0.72 mg – 3.30 mg) in a healthy adult man *[see Description (11.1)]*.

Plasma protein binding of ammonia N 13 or its N 13 metabolites has not been studied.

Ammonia N 13 undergoes a five-enzyme step metabolism in the liver to yield urea N 13 (the main circulating metabolite). It is also metabolized to glutamine N 13 (the main metabolite in tissues) by glutamine synthesis in the skeletal muscles, liver, brain, myocardium, and other organs. Other metabolites of ammonia N 13 include small amounts of N 13 amino acid anions (acidic amino acids) in the forms of glutamate N 13 or aspartate N 13.

Ammonia N 13 is eliminated from the body by urinary excretion mainly as urea N 13.

The pharmacokinetics of Ammonia N 13 Injection have not been studied in renally impaired, hepatically impaired, or pediatric patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies have not been performed to evaluate the carcinogenic potential of Ammonia N 13 Injection. Genotoxicity assays and impairment of male and female fertility studies with Ammonia N 13 Injection have not been performed.

14 CLINICAL STUDIES

In a descriptive, prospective, blinded image interpretation study of adult patients with known or suspected coronary artery disease[2], myocardial perfusion deficits in stress and rest PET images obtained with Ammonia N 13 (N=111) or Rubidium 82 (N=82) were compared to changes in stenosis flow reserve (SFR) as determined by coronary angiography. The principal outcome of the study was the evaluation of PET defect severity relative to SFR.

PET perfusion defects at rest and stress for seven cardiac regions(anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were graded on a 0 to 5 scale defined as normal (0), possible (1), probable (2), mild (3), moderate (4), and severe (5) defects. Coronary angiograms were used to measure absolute and relative stenosis dimensions and to calculate stenosis flow reserve defined as the maximum value of flow at maximum coronary vasodilatation relative to rest flow under standardized hemodynamic conditions. SFR scores ranged from 0 (total occlusion) to 5 (normal).

With increasing impairment of flow reserve, the subjective PET defect severity increased. A PET defect score of 2 or higher was positively correlated with flow reserve impairment (SFR<3).

15 REFERENCES

1. Annals of the ICRP. Publication 53. Radiation dose to patients from radiopharmaceuticals. New

York: Pergamon Press, 1988.
2. Demer, L.L.K.L.Gould, R.A.Goldstein, R.L.Kirkeeide, N.A.Mullani, R.W. Smalling, A.Nishikawa, and M.E.Merhige. Assessment of coronary artery disease severity by PET: Comparison with quantitative arteriography in 193 patients. Circulation 1989; 79: 825-35.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ammonia N 13 Injection is packaged in 30 mL multiple dose glass vial containing between 1.11 GBq to 11.1 GBq (30 mCi to 300 mCi) of [^{13}N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% sodium chloride injection solution in approximately 7 mL volume. The recommended dose of radioactivity (10 mCi – 20 mCi) is associated with a theoretical mass dose of 0.5 picomoles – 1.0 picomoles (8.47 picograms – 16.94 picograms) of Ammonia.

Storage

Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F). Use the solution within 30 minutes of the End of Synthesis (EOS) calibration.

17 PATIENT COUNSELING INFORMATION

17.1 Pre-study Hydration

Instruct patients to drink plenty of water or other fluids (as tolerated) in the 4 hours before their PET study.

17.2 Post-study Voiding

Instruct patients to void after completion of each image acquisition session and as often as possible for one hour after the PET scan ends.

17.3 Post-study Breastfeeding Avoidance

Instruct nursing patients to substitute stored breast milk or infant formula for breast milk for 2 hours after administration of Ammonia N 13 Injection.

Manufactured and distributed by:

PETNET Solutions, Inc.
810 Innovation Drive
Knoxville, TN 37932

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Siemens Healthcare Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen
Germany
Telephone: +49 9131 84-0
siemens.com/healthcare

Global Business Line
Siemens Medical Solutions USA, Inc.
Molecular Imaging
2501 N. Barrington Road
Hoffman Estates, IL 60192
USA
Telephone: +1 847 304-7700
siemens.com/mi

Siemens Medical Solutions USA, Inc.
Molecular Imaging
810 Innovation Drive
Knoxville, TN 37932-2751
USA
Telephone: +1 865 218-2000
siemens.com/mi

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