Imaging of Osteomyelitis with FDG PET-MR

Cristina Mitea[1]; Tineke van de Weijer[1]; Lieke van de Meer[1]; Linda Jacobi[1]; Daan Loeffen[1]; Dennis Hulsen[2,3]; Jan Geurts[3]; Rik Moonen[1]

[1]Department of Radiology and Nuclear Medicine, Maastricht University Medical Centre Maastricht, The Netherlands
[2]MICT Department, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, The Netherlands
[3]Department of Orthopaedic Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands

Introduction

Osteomyelitis is an inflammatory process accompanied by bone destruction, and is caused by microorganism infection. The infection can be limited to a single portion of the bone or can involve several compartments such as marrow, cortex, periosteum and the surrounding soft tissue. Osteomyelitis can be (1) spread locally from a focal source of infection, (2) secondary to vascular insufficiency, or (3) caused by hematogenous spread of the microorganism from a different source.

For osteomyelitis in the extremities, the most common pathogen is Staphylococcus aureus. In skull-base osteomyelitis (SBO) it is Pseudomonas aeruginosa (50–90% of cases) [1]. Osteomyelitis of the skull base most often occurs as a complication of otitis externa, and can be categorized within the first category of focal infections. However, it is perceived as a special case due to the severe complications that can arise, given the location. The bacterial infection causes bone erosions, and uses fascial planes and venous sinuses for distant tissue invasion. It then can progress and spread to the surrounding osseous and soft tissues via the skull base.

Clinical presentation

Patients can present with a variety of symptoms, ranging from an open wound exposing fractured bone, or an indolent draining fistula, to no skin lesion but local swelling and bone pain. In the acute phase after surgery, infection can usually easily be recognized by clinical examination (fever, redness, swelling, wound leakage, pain and disability of the affected body part). In the later phases there can be clear signs of disease (fistula, purulent discharge), but often signs are subtler (slightly elevated temperature of the skin, diffuse pain) or not present at all, and then diagnosis may be very difficult.

Typical symptoms of patients with skull base osteomyelitis are: itching, otalgia, and/or otorrhea. Through possible bone erosions the infection can spread to the surrounding osseous and soft tissues, causing cranial nerve palsy and intracranial involvement.

Diagnosis

A great variety of imaging techniques can be used in diagnosing osteomyelitis [2].

Conventional radiological film (X-ray) is one of the most used techniques for the evaluation of osteomyelitis, mainly because it is cheap and fast. Plain film can show secondary signs of infection, for example edema of the soft tissue, bone destruction, and periosteal reaction. However, in general 30 to 50% of bone mineral content must be compromised to produce noticeable changes on plain radiographs, so this approach has low sensitivity in early diagnosis of osteomyelitis (sensitivity 63% and specificity 87% evaluated for diabetic foot osteomyelitis [3]).

Ultrasound is useful for evaluating the soft tissues and joints next to the infected bone. It can visualize soft tissue abscesses, cellulitis, subperiosteal collections, and joint effusion collections, which are seen in acute infections. However, it is less effective in evaluating bone erosions.

CT and MRI have far better resolution than conventional X-ray film or ultrasound, and provide information about destruction of the bone cortex, involvement of the medulla, periosteal reaction, and articular and soft tissue involvement. CT is superior to MRI in depicting bony margins and cortical erosions, and identifying sequestration [4]. CT imaging also has excellent spatial resolution for evaluating peripheral bone. It can be used to detect small foci of gas and areas of cortical erosion and destruction.

However, conventional CT imaging has limited value in early osteomyelitis. Its overall sensitivity and specificity is low, even for chronic osteomyelitis – reported to be 67% and 50%, respectively [5]. Another limitation is that single-energy CT imaging does not confidently detect bone marrow edema. While dual-energy CT imaging may be more effective, it is not available in most centers. Another problem was image degradation by streak artifacts when metallic implants are present, but this has been largely solved with the introduction of metal artifact reduction techniques.

MRI is superior to CT in delineating soft tissue involvement, including muscular structures, synovial and bone marrow involvement; and is superior even to dual-energy

CT imaging in bone marrow edema detection. For this reason, MRI is considered of value in diagnosing osteomyelitis [6]. It has a reported sensitivity of 70–90% and gives an excellent anatomic delineation of the infected or edematous area and the surrounding soft tissue [5, 7]; although specificity is relatively low (40–80%), and the images can lead to overestimated severity and extent of infection [5, 6].

Nuclear medicine imaging techniques are useful in evaluating specific physiological mechanisms of osteomyelitis. Three-phase bone scintigraphy is an imaging technique using bone-seeking tracers. It can visualize perfusion and bone formation reacting to destructive changes in osteomyelitis. Detection of osteomyelitis is highly sensitive (90%) and also highly specific (about 90%) in bones not affected by other conditions. In post-traumatic patients and after surgery, specificity is lower (circa 35%), as post-operative effects can increase perfusion and induce reactive bone changes [7].

Labeled leukocyte imaging is based on the recruitment of leukocytes by infections. The leukocytes will accumulate at the site of infection and can be visualized with SPECT-CT imaging. This technique has high sensitivity (94–95%) and specificity (89–100%) in expert hands, but it is time demanding for the patient, and not available in all nuclear medicine departments [8].

Pathologies with increased glucose metabolism, including osteomyelitis, can be visualized with ^{18}F-FDG PET-CT/MRI. FDG is a positron-emitting glucose analog, which is taken up by cells. Most malignant tumors as well as inflammatory processes have relatively high metabolic activity, meaning they take up more of the FDG. Detecting this with PET-CT has excellent sensitivity for infections, normally reaching or exceeding 95%, with high specificities above 87%. In spondylitis and spondylodiscitis, FDG PET-CT provides both a high sensitivity and a high specificity [9]. The CT component in hybrid PET-CT helps to differentiate between the different causes of FDG accumulation, including malignancy and trauma.

Recently, hybrid PET-MRI has become commercially available. It combines accurate functional imaging (PET) with high-resolution anatomical information (MRI), and shows promise in improving sensitivity and specificity in musculoskeletal infections, as these conditions require high soft-tissue contrast and resolution for accurate diagnosis. MRI is superior to CT imaging for soft tissue detail and resolution. Furthermore, MRI can visualize thrombosis and intracranial spread in SBO, which CT imaging cannot. Last, radiation burden for the patient is lower in PET-MRI imaging than in PET-CT, especially important in longitudinal follow-up. This technique cannot be used in patients with MRI-incompatible implants such as some defibrillators and pacemakers. Prostheses and osteosynthetic materials may cause artifacts on the MRI, but metal-artifact correction sequences may open PET-MRI for such patients.

Osteomyelitis in the extremities

Scan protocol:
After injection of ^{18}F-FDG (dosage 2 MBq/kg), patients rest for 45 minutes before the start of the PET-MRI scan. The arm or leg is stabilized with a vacuum pillow. A PET-compatible flexible surface coil (a single body matrix coil or flex coil, depending on the size and desired field of view) is placed on top. Multiple bed positions may be required, e.g., for a femur, and the PET acquisition time is 15 minutes per bed position. MRI is acquired simultaneously, including Dixon attenuation correction (soft tissue, fat, air, lung, bone) and a dedicated protocol such as the example in Table 1. Acquisitions are typically made in two anatomical planes, based on the anatomical location of the suspected lesion.

	TR/TE (ms)	FA (°)	FOV (mm)	Slices	Voxel size (mm)	TA (min)
T1 TSE bilateral	876/10	160	500 x 500 x 153.6	35	1.0 x 1.0 x 4.0	2:25
T1 TSE*	700/13	120	250 x 250 x 239	40	0.5 x 0.5 x 5.0	5:01 (bp)
T2 TSE FatSat*	6160/70	150	250 x 250 x 239	40	0.4 x 0.4 x 5.0	4:26 (bp)
DWI RESOLVE*	7110/ TE1: 53 TE2: 79	–	250 x 250 x 250.8	35	2.2 x 2.2 x 6.0	5:43 (bp)
T1 TSE STIR	5000/29	130	500 x 500 x 167.2	35	1.6 x 1.6 x 4.0	5:12
PD TSE FatSat	2500/20	150	500 x 250 x 193.2	44	0.8 x 0.8 x 4.0	3:22
Postcontrast T1 TSE FatSat cor	750/10	160	500 x 500 x 153.6	35	0.5 x 0.5 x 4.0	3:06
Postcontrast T1 TSE FatSat tra	750/13	120	250 x 250 x 239	40	0.5 x 0.5 x 5.0	5:23 (bp)

Table 1: MRI protocol for osteomyelitis of the femur.
**Scans during PET acquisition. bp: per bed position*

In a pilot study, 5 patients were scanned both by PET-CT and subsequently by PET-MRI, to assess the validity and quality of PET-MRI scans. Details can be found in the paper of Hulsen et al. [10].

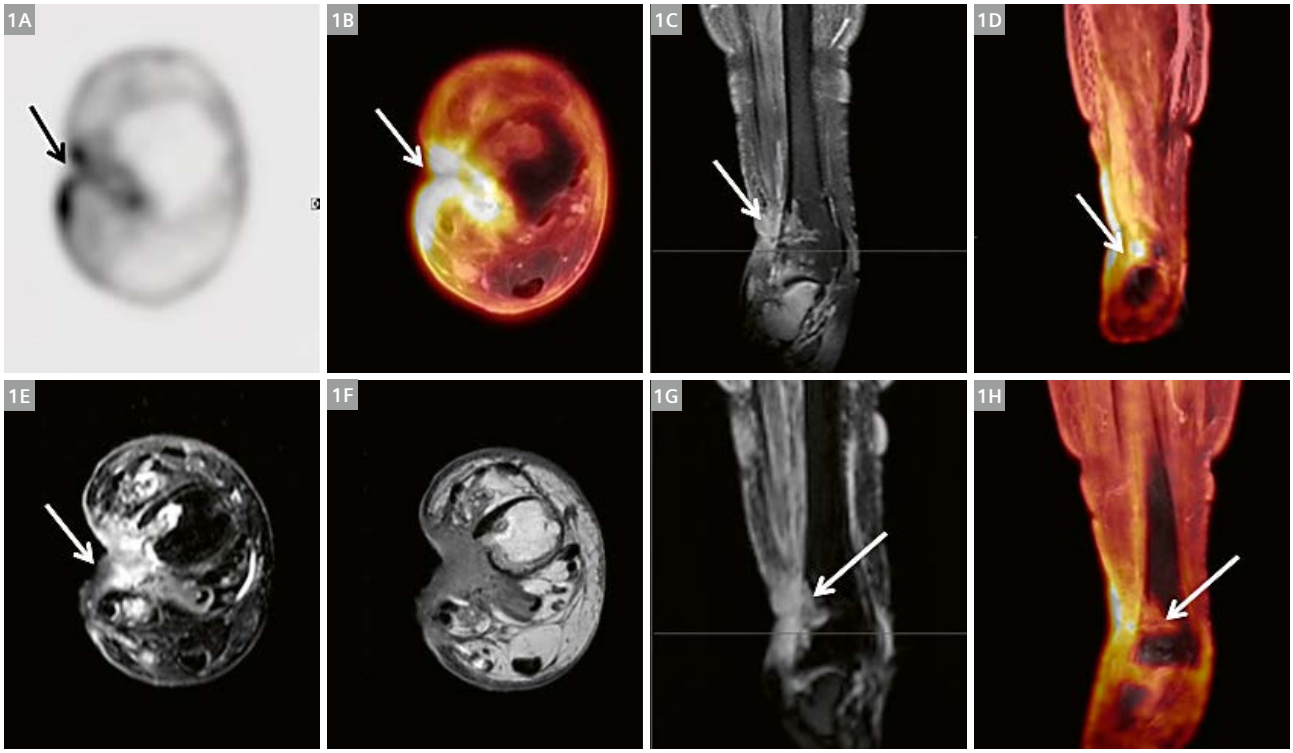
Osteomyelitis diagnoses based on PET-MR and PET-CT images were identical for all the patients included in this study, but for one patient the PET-CT failed to detect a fistula which was diagnosed on the PET-MRI.

The regions with high signal detected by MRI, and with increased FDG accumulation by PET, were mostly congruent, except for adjacent segment bone marrow. Based on MRI only, it was impossible to differentiate between reactive edema and bone marrow infection. This led to an overestimation of the infection extent by MRI as compared with PET. By including PET information it was possible to distinguish between reactive and infective edema. This will help an operating surgeon to determine the extent of the necessary debridement.

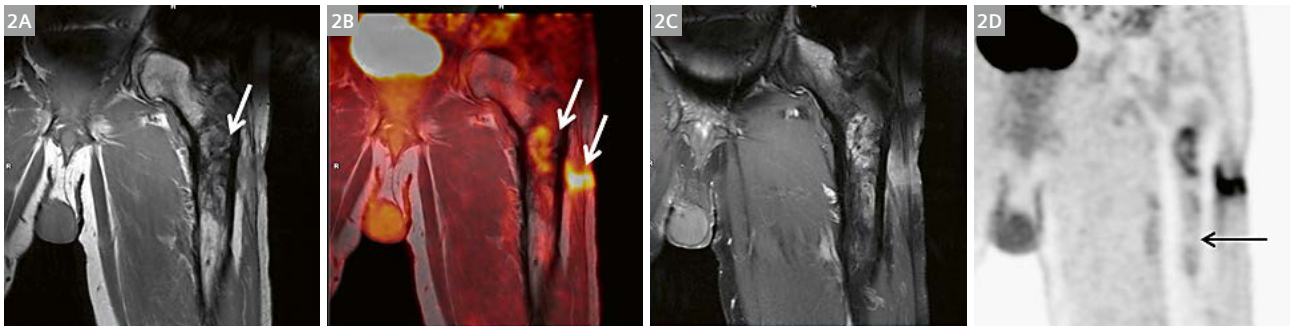
For the PET, the ratio of SUV max measured with PET-MRI to that measured with PET-CT was close to 1 (range 0.6–1.3).

Examples of FDG PET-MRI evaluations of patients diagnosed with osteomyelitis are shown in Figures 1 and 2. These two cases illustrate the strengths of PET-MRI, as additional information on soft tissue defects can be appreciated. Also, the extent of bone marrow infection in the PET images is clearly more limited than the extent of reactive bone marrow edema shown in the MRI. The combination of PET and MRI gives a convincing picture of the infection. In Figure 2, the MRI shows a fistula, which is of utmost importance for adequate treatment of the osteomyelitis.

FDG PET-MRI is of added value not only in the extremities, but also for the spine. Here, FDG PET-MRI has been studied in spondylodiscitis patients showing a sensitivity of 100% and specificity of 88.2% [11].



1 65-year-old woman with a skin lesion on the lateral malleolus of the right ankle. **(1A)** PET; **(1B)** FDG PET-MRI overlay; **(1C)** T1 FS; **(1D)** FDG PET-MRI overlay; **(1E)** T1 FS after gadolinium; **(1F)** T1 STIR; **(1G)** T2 FS; **(1H)** FDG PET-MRI overlay. The arrows show soft tissue defects with increased FDG accumulation on the lateral malleolus and extension in the distal tibia.



2 64-year-old man with a history of a femur fracture presents with pain in the left leg and wound leakage. He was diagnosed with an osteomyelitis with positive Staphylococcus aureus cultures.
(2A) T1; **(2B)** FDG PET-MRI overlay; **(2C)** T1 FS; **(2D)** PET. White arrows denote area of high FDG uptake, in both the bone marrow and an area in the soft tissue adjacent to the bone. Here a clear fistula was found in MRI. The black arrow denotes an area of moderate FDG uptake, with high signal intensity on the T2-weighted images, which was explained by reactive bone marrow.

Skull base osteomyelitis

One of the indications for an FDG PET-MRI in our center is skull base osteomyelitis (SBO). The scan is performed at initial diagnosis and for therapy evaluation, in most cases after 3 months of antibiotic therapy.

Scan protocol:
After injection of ^{18}F-FDG (dosage 2 MBq/kg), patients rest for 45 minutes before the start of the PET-MRI scan. In order to prevent motion artifacts, inflatable pillows are placed inside the head coil on both sides of the head. The PET acquisition time is 20 minutes and MRI is simultaneously acquired, with Dixon attenuation correction (soft tissue, fat, air, lung, bone) and the dedicated protocol in Table 2.

We use a combination of PET-MRI (sequences are described in Table 2) and a separate high-resolution CT scan. The CT scan is mainly added to evaluate cortical erosions, and does not have any added value in evaluating an active infection.

We studied 21 patients with SBO that were followed during and after treatment with PET-MRI and CT imaging. For three of these patients the diagnosis of SBO was made on the basis of the PET-MRI. One patient had thrombosis of the cavernous sinus as a complication, which was detected in the MRI but missed on the CT scan.

It is known that in MRI the abnormal bone marrow signal can still be present a relatively long time after remission. On the other hand, the PET will more rapidly reveal decreased inflammation, which results in lower FDG accumulation. However, spatial resolution of PET is

	TR/TE (ms)	FA (°)	FOV (mm)	Slices	Voxel size (mm)	TA (min)
T2 TSE (T2_tse_tra_512)	6000/100	150	220 x 220 x 69.3	28	0.4 x 0.4 x 5.0	2:26
T1 TSE	550/9.5	150	220 x 220 x 153.5	18	0.2 x 0.2 x 3.0	6:25
T2 TSE FatSat	4000/89	150	180 x 180 x 76.4	32	0.2 x 0.2 x 2.0	4:18
T2 3D SPACE	1400/158	120	210 x 210 x 28	–	0.2 x 0.2 x 0.5	4:21
T1 FLASH	250/2.48	70	220 x 220 x 170	31	0.7 x 0.7 x 5.0	2:10
DWI RESOLVE	5000/ TE1: 72 TE2: 122	–	220 x 220 x 118.4	27	1.0 x 1.0 x 4.0	3:17
Postcontrast T1 MPRAGE*	1800/2.73 TI: 900	9	240 x 210 x 172.8	–	0.9 x 0.9 x 0.9	5:54
Postcontrast T1 TSE FatSat*	550/9.5	150	220 x 220 x 69.3	18	0.2 x 0.2 x 3.0	6:25

Table 2: Skull-base osteomyelitis MRI protocol (Biograph mMR)
**Contrast injection and postcontrast scans were performed after PET acquisition*

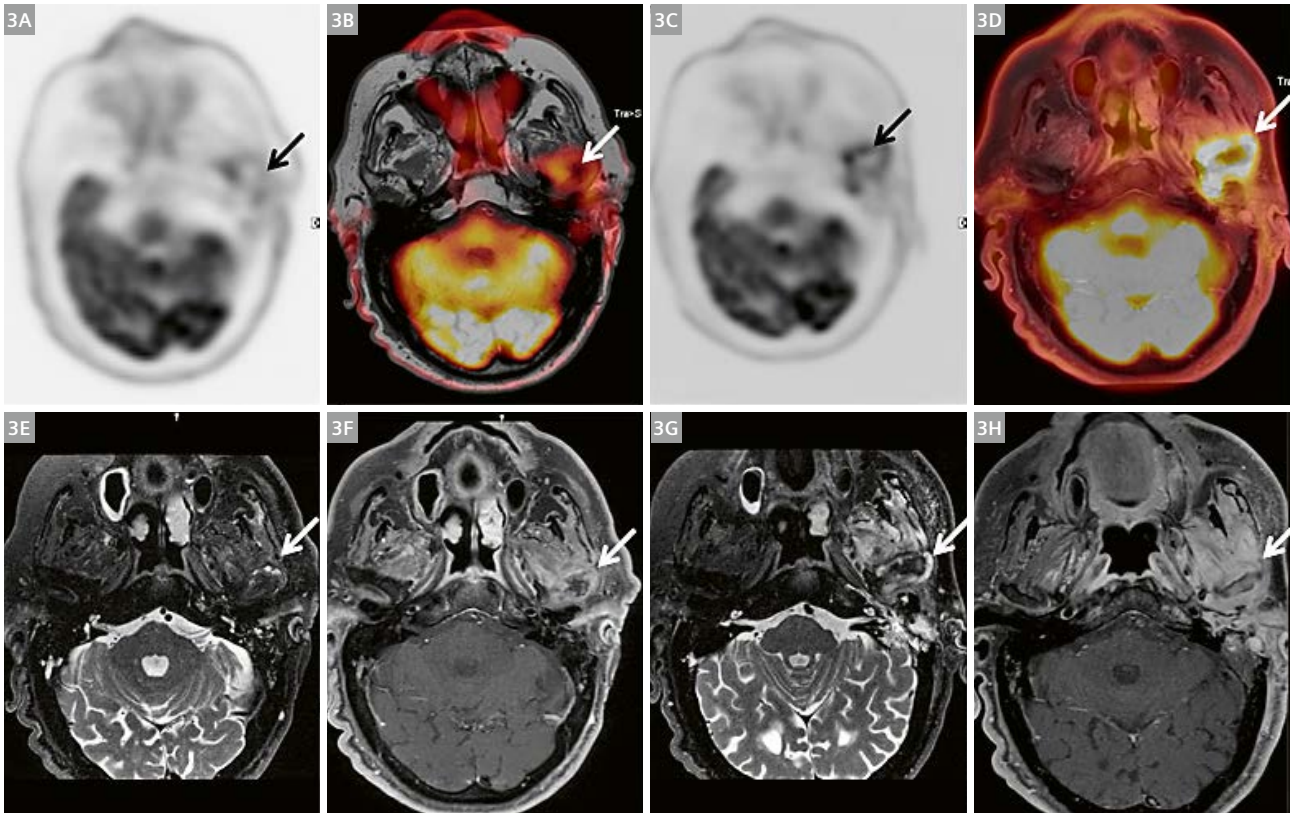
relatively low, so correlation is needed with MRI anatomical information. For these reasons a hybrid PET-MRI is preferred for disease monitoring.

Examples of FDG PET-MRI evaluations of patients diagnosed with skull base osteomyelitis are shown in Figures 3 and 4. Here again the extent of the reactive edema and contrast enhancement on MRI is far greater than the region with active infection on FDG-PET. Furthermore, after treatment, clear remission in metabolic activity at the site of infection was observed, despite lingering edema and contrast enhancement on MRI. MRI helps to assess vascular structures and cortical erosions that cannot be depicted on PET alone. Nonetheless, a CT scan was performed to further evaluate the extent of bone destruction at the temporomandibular joint (TMJ).

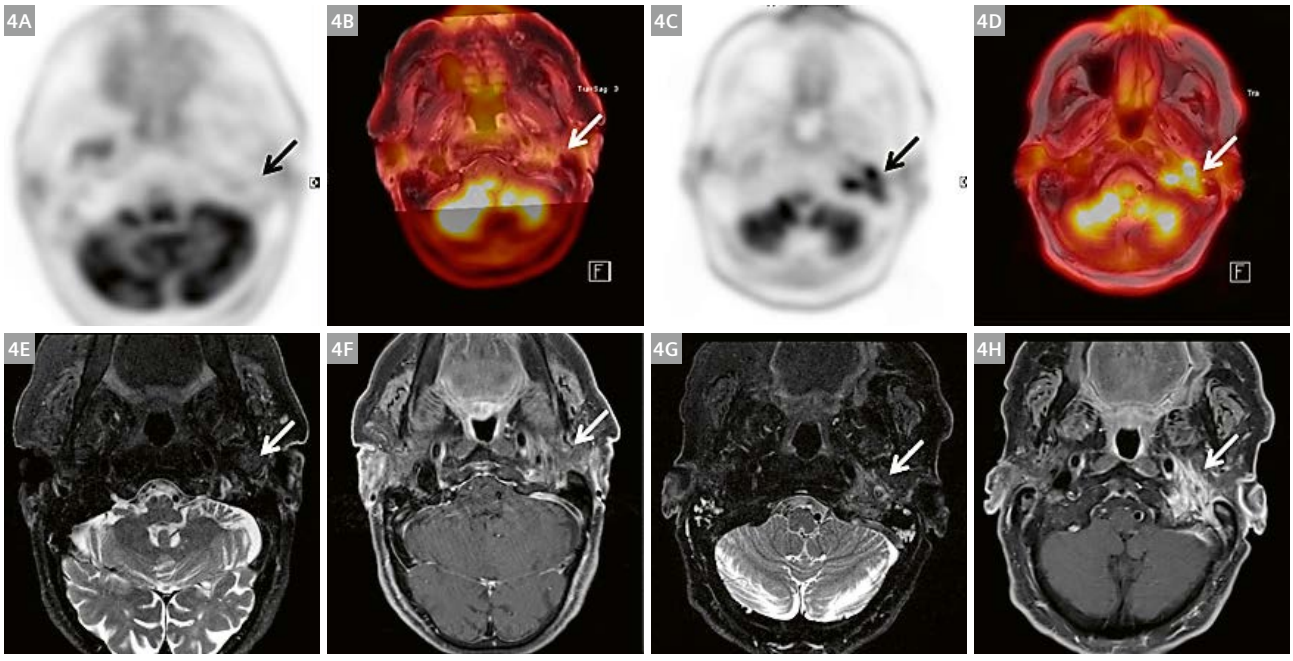
Conclusion

PET-MRI is a useful imaging modality for musculoskeletal infections such as osteomyelitis, as it couples the molecular and physiological information acquired from PET with the unparalleled soft tissue resolution of MRI to provide a superior level of anatomic and functional patient information.

Hybrid PET-MRI reduces image acquisition time and misregistration artifacts. Additionally, using PET-MRI over PET-CT gives better appreciation of soft tissue involvement. It will add information on possible complications such as fistulas for the osteomyelitis of the extremities, and cerebral involvement in SBO. Furthermore, PET-MRI will substantially reduce ionizing radiation exposure for the patient, especially in those who require longitudinal follow-up.



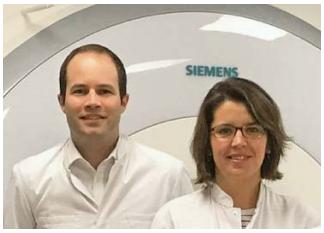
3 76-year-old diabetic patient with otalgia and otorrhea of the left ear. Cultures were positive for P. Aeruginosa. FDG PET-MRI was performed before (3C, D, G, and H) and after 3 months of antibiotic treatment (3A, B, E, and F). **(3A, C)** PET image; **(3B, D)** PET-MR overlay; **(3E, G)** MRI T2 FS; **(3F, H)** MRI T1 FS after gadolinium injection. Pre-treatment images show enhancement of the soft tissue of the middle ear and the mastoid cells, and enhancement of the os petrosum with bone erosion extending to the temporomandibular joint (TMJ). They also show infiltration of the soft tissue of the left infratemporal fossa, the masseter lodge, and the pterygoid and masseter muscles. Bone marrow edema is shown in the mandible and zygomatic arch at the left side.
The follow up images show decreased FDG accumulation around the TMJ compared with pre-treatment PET images. The MRI shows persistent edema in the mandible, and decreased enhancement around the TMJ and the surrounding muscles.



4 85-year-old patient with skull base osteomyelitis at the left side and paresis of the facial nerve. **(4A, C)** PET image; **(4B, D)** FDG PET-MRI overlay; **(4E, G)** T2 FS MRI; **(4F, H)** T1 FS after gadolinium injection MRI; 4A, B, E, and F follow-up after 3 months of antibiotic treatment. The arrows show contrast enhancement in the subtemporal soft tissue and around the styloid processes with engagement of the stylomastoid foramen. The follow-up scan shows decreased soft tissue enhancement and decreased FDG accumulation.

References

1 Grandis JR et al. The changing face of malignant (necrotising) external otitis: clinical, radiological and anatomic correlations. Lancet Infect Dis. 2004;4(1):34–39.
2 Pineda C et al. Imaging of osteomyelitis: current concepts. Infect Dis Clin North Am. 2006;20(4):789-825.
3 Nawaz A et al. Diagnostic Performance of FDG-PET, MRI, and Plain Film Radiography (PFR) for the Diagnosis of Osteomyelitis in the Diabetic Foot. Molecular Imaging and Biology. 2010;12(3):335–342.
4 Gold RH et al. Bacterial osteomyelitis: findings on plain radiography, CT, MR, and scintigraphy. American Journal of Roentgenology. 1991;157:365–370.
5 Termaat MF et al. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg Am. 2005;87-A(11):2464–2471.
6 Lee YJ et al. The imaging of osteomyelitis. Quant Imaging Med Surg. 2016;6(2): 184–198.
7 van der Bruggen, W. (2010). PET and SPECT in Osteomyelitis and Prosthetic Bone and Joint Infections: A Systematic Review. Seminars in Nuclear Medicine, 3–15.
8 Erba PA et al. Image acquisition and interpretation criteria for 99mTc-HMPAO-labelled white blood cell scintigraphy: results of a multicentre study. European Journal of Nuclear Medicine and Molecular Imaging. 2014;41(4):615–623.
9 Gratz S et al. 18F-FDG hybrid PET in patients with suspected spondylitis. European Journal of Nuclear Medicine and Molecular Imaging. 2002;29(4):516–524.
10 Hulsen DJW et al. Hybrid FDG-PET/MR imaging of chronic osteomyelitis: a prospective case series. European Journal of Hybrid Imaging. 2019;3: article number 7.
11 Fahner J et al. Use of Simultaneous 18F-FDG PET/MRI for the Detection of Spondylodiskitis. J Nucl Med. 2016;57(9):1396–1401.



Contact

Rik Moonen
Department of Radiology and Nuclear Medicine
Maastricht University Medical Centre
Maastricht
The Netherlands
rik.moonen@mumc.nl

Cristina Mitea
Department of Radiology and Nuclear Medicine
Maastricht University Medical Centre
Maastricht
The Netherlands
cristina.mitea@mumc.nl

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fludeoxyglucose F 18 Injection safely and effectively. See full prescribing information for Fludeoxyglucose F 18 Injection. Fludeoxyglucose F 18 Injection, USP For intravenous use Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

The recommended dose:

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Oncology

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

1.2 Cardiology

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

1.3 Neurology

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

2 DOSAGE AND ADMINISTRATION

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

2.1 Recommended Dose for Adults

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

2.2 Recommended Dose for Pediatric Patients

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

2.3 Patient Preparation

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

2.4 Radiation Dosimetry

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

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

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

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

[b] The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.

*LLI = lower large intestine; **ULI = upper large intestine

2.5 Radiation Safety – Drug Handling

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

2.6 Drug Preparation and Administration

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

2.7 Imaging Guidelines

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

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

5.2 Blood Glucose Abnormalities

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

6 ADVERSE REACTIONS

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

8.3 Nursing Mothers

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

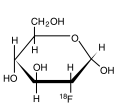
8.4 Pediatric Use

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

11 DESCRIPTION

11.1 Chemical Characteristics

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



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

11.2 Physical Characteristics

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

Table 2. Pricipal Radiation Emission Data for Fluorine F18		
Radiation/Emission	% Per Disintegration	Mean Energy
Positron (b+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

*Produced by positron annihilation

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

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

Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield thickness (Pb) mm	Coefficient of attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

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

Table 4. Physical Decay Chart for Fluorine F18	
Minutes	Fraction Remaining
0*	1.000
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250

*calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial sub strate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these conditions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging.

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

12.3 Pharmacokinetics

Distribution: In four healthy male volunteers, receiving an intravenous administration of 30 seconds in duration, the arterial blood level profile for Fludeoxyglucose F 18 decayed triexponentially. The effective half-life ranges of the three phases were 0.2 to 0.3 minutes, 10 to 13 minutes with a mean and standard deviation (STD) of 11.6 (±) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 4 min. Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

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

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

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

Special Populations: The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in renally-impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues. The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained [see Warnings and Precautions (5.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Oncology

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fludeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq. In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false-positive scans. The efficacy of Fludeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

14.2 Cardiology

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery. Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects). Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is more limited.

14.3 Neurology

In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185 to 370 MBq (5 to 10 mCi). The mean age was 16.4 years (range: 4 months to 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (14/87) of the patients; in 34% (30/87) of the patients, Fludeoxyglucose F 18 Injection PET images provided new findings. In 32% (27/87), imaging with Fludeoxyglucose F 18 Injection was inconclusive. The impact of these imaging findings on clinical outcomes is not known. Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL glass vial containing between 0.740 to 7.40 GBq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-2-[F 18] fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL.
The contents of each vial are sterile, pyrogen-free and preservative-free.
NDC 40028-511-30; 40028-511-50
Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.
Store the Fludeoxyglucose F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Store and dispose of Fludeoxyglucose F 18 Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.
The expiration date and time are provided on the container label. Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS time.

17 PATIENT COUNSELING INFORMATION

Instruct patients in procedures that increase renal clearance of radioactivity.
Encourage patients to:
- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.

Manufactured by: PETNET Solutions Inc. 810 Innovation Drive Knoxville, TN 37932
Distributed by: PETNET Solutions Inc.^ 810 Innovation Drive Knoxville, TN 37932^
PETNET Solutions
PN0002262 Rev. A
Marcg 1, 2011

Indications

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.

Important Safety Information

Radiation Risks: Radiationemitting products, including Fludeoxyglucose F18 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 healthcare 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 F18 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.
Fludeoxyglucose F^{18} injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732, USA.