White paper

Harmonizing SUV with EQ•PET

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Introduction

F 18 fludeoxyglucose (^{18}F FDG) PET/CT has become an invaluable tool in the initial staging and treatment monitoring of a wide array of oncological indications. Various therapy response guidelines have been developed using ^{18}F FDG PET measurements to assess changes in tumoral radiotracer uptake to determine disease burden at baseline and evaluate treatment response (e.g. EORTC, PERCIST, Deauville). Consistent measurement of radiotracer uptake is, thus, essential to not only ensure that disease is properly characterized at initial diagnosis and following therapy, but also to facilitate accurate comparison of studies.

The standardized uptake value (SUV) is a semi-quantitative surrogate of tissue metabolism, which provides an estimate of disease burden on PET/CT imaging. SUV measures, however, are prone to variability due to a number of factors.[1-3]

Fludeoxyglucose F 18 5-10mCi as an IV injection

Indications and usage

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

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

Important safety information

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

Dosage forms and strengths

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

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

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

Patient-related factors include serum blood glucose, patient weight, body habitus, and respiratory or bulk motion. Technical factors include calibration inaccuracies, radiotracer extravasation at injection, and improper assaying of residual syringe activity. Combining these sources of variation with differences between PET scanners and reconstruction algorithms may lead to a significant cumulative SUV error.

EQ•PET has been developed as a PET measurement harmonization tool, which minimizes the sources of variation due to scanner type and reconstruction protocol. The technology has been implemented as a feature within *syngo*®.MM Oncology. There are two primary use cases for EQ•PET:

1. Cross-scanner response assessment for patients imaged with different PET/CT systems. Examples include a mid-treatment scanner upgrade or large institutions with multiple PET/CT systems. Here, harmonization will typically be performed to the older generation PET/CT system.

2. Multicenter clinical trials, which require strict alignment of acquisition protocol and quantitative performance of scanners. Here, harmonization is performed either to a specific PET/CT scanner or a reference standard.

The EANM Research Ltd. (EARL) was established, in part, to enhance the comparability of data acquired by molecular imaging and to facilitate multicenter research projects.[4-7] EARL has published criteria for an ^{18}F FDG-PET/CT accreditation program. These criteria include a range for acceptable NEMA phantom recovery curves based on a broad set of acquisitions on modern PET/CT scanners. The recovery curve is a plot of the image activity measurement within each sphere in the NEMA phantom, normalized to the true activity, versus the respective diameter of each sphere.

In both EQ•PET and EARL, harmonization is achieved by applying a spatial filter, optimized with a NEMA phantom measurement for a particular scanner and reconstruction protocol, to the PET image. The spatial filter is selected to harmonize measurements to either a particular scanner and reconstruction protocol or to a pre-defined standard such as the EARL criteria. The EQ•PET workflow is summarized in Figure 1.

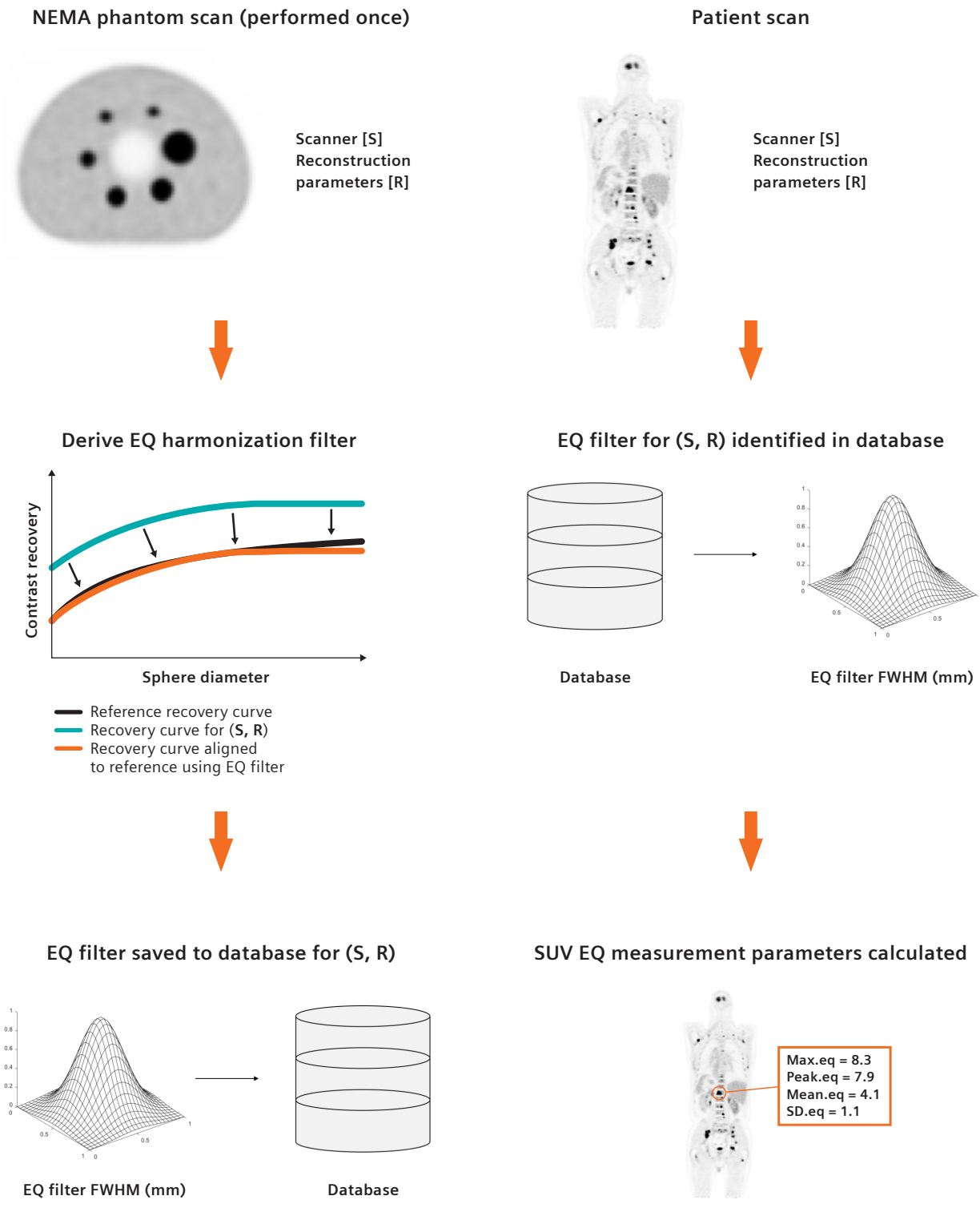


Figure 1. Summary of the EQ•PET procedure. A NEMA phantom is prepared and scanned according to the EARL criteria (this only needs to be done once per scanner). Progressive filtering is applied until optimal alignment is reached with a target scanner or reference recovery curve. The resulting EQ filter is saved in a database, where it is uniquely assigned based on scanner model, reconstruction method, convolution kernel, rows, columns, pixel spacing, and slice thickness. For any subsequent patient scans the appropriate EQ filter is loaded from the database and used to calculated harmonized EQ measurement parameters for SUV.

With EARL, the harmonization is achieved via a separate reconstruction with additional post filtering, while with EQ•PET, the filtering is applied locally in the background, saving both reconstruction and interpretation time (Figure 2). The EQ•PET and EARL approaches have been shown to produce similar results.[8]

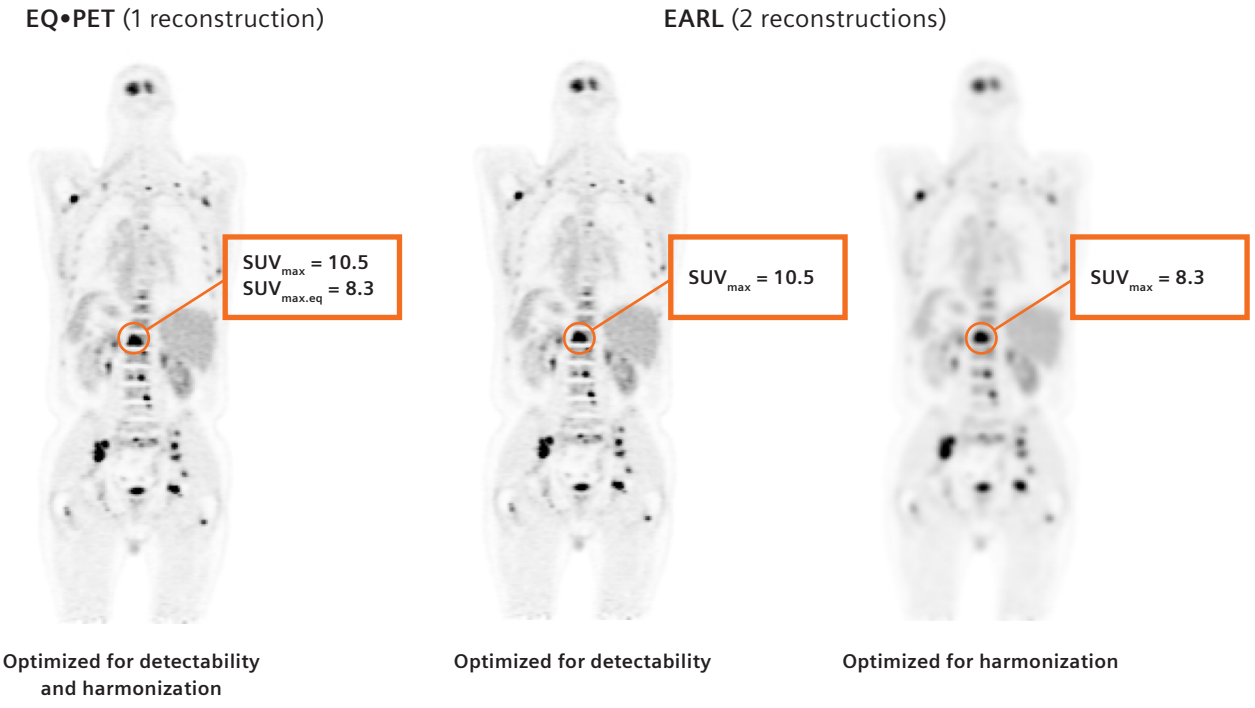


Figure 2. EQ•PET technology produces similar results as EARL harmonization, but with a single reconstruction, thus sparing both reconstruction and interpretation time.

EQ•PET has been validated in a prospective multicenter study on 517 patients, where the impact of reconstruction, specifically point spread function (PSF) modelling, was assessed.[9] PSF improves lesion detectability but also results in markedly higher SUV measurements compared to algorithms without PSF. 1,380 tumor lesions were measured from non-small cell lung cancer (NSCLC), non-Hodgkin lymphoma, and metastatic melanoma patient groups. Figure 3 shows the harmonization efficacy of EQ•PET using Bland-Altman plots of PSF (and PSF+TOF) versus ordered subsets expectation maximization (OSEM) for SUV_{max}. The bias and ±1.96 standard deviation range of 1.46±0.6 without EQ•PET (Figure 3a) is reduced to 1.02±0.14 with EQ•PET (Figure 3b).

A wealth of further evidence has been published in support of EARL harmonization and is summarized in Table 1. The technique is shown to be robust to various potential confounding factors and applicable for any type of solid tumor. PET response assessment criteria are improved and parameters, such as metabolic tumor burden and tissue heterogeneity metrics are shown to be more consistent with EARL harmonization.

Most of the studies in Table 1 are based on reconstructing images without and with PSF to represent an older and newer generation scanner, respectively. The effectiveness of EQ•PET when successively scanning the same patient on PET/CT scanners from two different vendors is demonstrated in two articles.[22,23] Furthermore, the application of EQ•PET has been shown to improve the prediction of 2-year outcome in a dual-scanner retrospective study.[24] These results are based on 95 PET pairs (pre- and post-treatment) performed on 2 scanners from different vendors in 73 oncological patients. Results show that, compared to the non-harmonized metabolic response classification, the use of EQ•PET provides a metabolic response classification, which better predicts the final clinical response assessment and the prognosis.

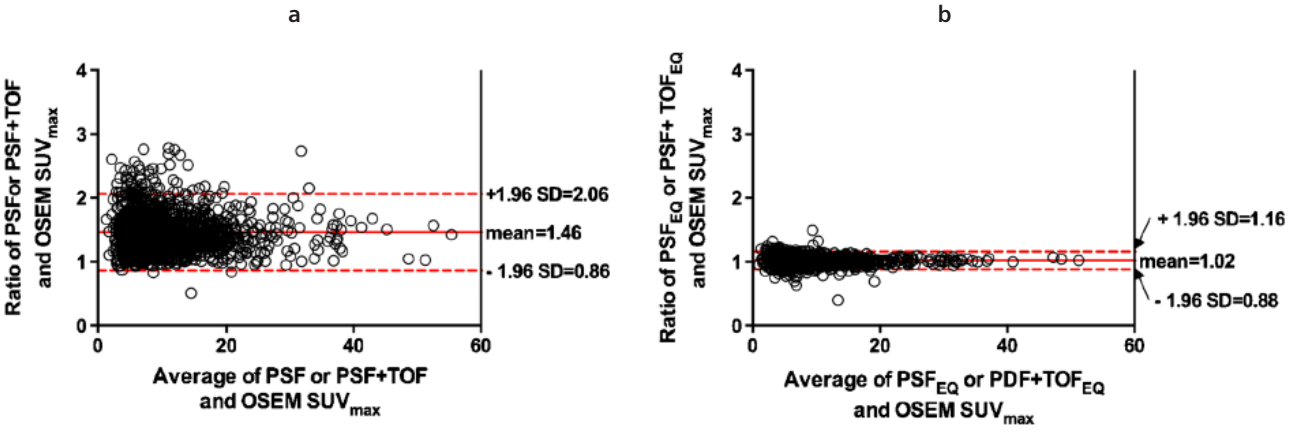


Figure 3. Bland-Altman plots showing the relationship of PSF (or PSF+TOF) and OSEM reconstructions without (a) and with (b) EQ•PET for 1380 tumor lesions. The SUV harmonization due to EQ•PET is evident by the reduced bias and range of the data points.[9] Reproduced under the terms of the Creative Commons CC BY license.

Table 1. EARL harmonization provides more consistent clinical measurements and is shown to be robust to a wide variety of physical and acquisition parameters. Note that not all related functionality is available for EQ•PET in *syngo*.MM Oncology.

	Parameter	Details
Clinical measurements 	PERCIST and EORTC evaluation	Reconstruction algorithm-dependent variability in PERCIST and EORTC classification is a significant issue but can be overcome by harmonizing SUVs.[10,11]
	Deauville criteria	PSF reconstruction has been shown to increase the tumor-to-liver ratio by 31%. With harmonization this is reduced to 6%.[12] The role of reconstruction parameters on Deauville scoring is still a topic of debate.[13-16]
	Metabolically active tumor volume (MATV)	Use of EARL-compliant images compared to PSF leads to significantly higher ($p<0.0001$) dice coefficients and concordance indices for tumor volumes.[17]
	Tissue heterogeneity	Significant differences ($p<0.05$) in select 1st, 2nd, and 3rd order heterogeneity metrics are found between OSEM and PSF images. These differences were not significant after applying EARL harmonization.[18]
Physical parameters 	Patient body mass index (BMI)	No significant difference ($p<0.05$) between BMI types <25, 25≤BMI<30, ≥30.[19]
	Lesion size	SUV_{max} and SUV_{peak} PSF/OSEM ratio less than 1.05 for 195 lesions assessed in quartiles from 2.4-98.9 mm,[19] and for 1167 lesions assessed by <10 mm, 10-20 mm, >20 mm.[9]
	Lesion anatomical location	SUV_{max} and SUV_{peak} PSF/OSEM ratio less than 1.05 for 1380 lesions in bone, digestive tract, liver, lung, lymph node, pleura, peritoneum, and soft tissue,[9] as well as 195 lesions in lung, thoracic nodes, visceral and bone.[19]
	Tumor-to-background ratio	Harmonization produces similar recovery curve alignment for both PSF and OSEM at a range of clinically relevant tumor-to-background ratios (3:1, 5:1, 10:1, ∞:1).[20] Effect of TOF+PSF consistently removed for tumor-to-background ratios of <10, 5-10, >10.[10]
Acquisition parameters 	Radial offset from FOV center	SUV_{max} and SUV_{peak} PSF/OSEM ratio less than 1.05 for radial offset <75 mm and >75 mm.[9]
	Emission scan duration	No significant difference ($p<0.05$) between 160 and 220 second scan durations.[19]
	Resolution modeling and time of flight	Harmonizing PET/CT systems with TOF and PSF technologies from different vendors is shown to be feasible.[21,22]

Performing EQ•PET harmonization

EQ•PET filter parameters are derived using a NEMA phantom prepared and scanned according to the EARL guidelines.[25] SUV_{max} measurements are made on the 6 phantom spheres to repeatedly derive recovery curves while iterating through a range of EQ filter values. The EQ filter is a 3D Gaussian spatial filter defined by its full width at half maximum (FWHM) in millimeters. An estimate of the difference between a filtered recovery curve and the reference recovery curve is used to define the optimal EQ filter, which corresponds to the best spatial alignment between the recovery curves. The phantom scan only needs to be performed once for each scanner at a clinical site, and a unique EQ filter should be calculated for each reconstruction protocol in clinical use at the site. If harmonization is being performed to another scanner (typically of an older generation), then the NEMA phantom also needs to be scanned on the target scanner to define the target recovery curve. The procedure to derive the optimal EQ•PET filter is summarized in Figure 4 below, and a more detailed description can be found upon request.

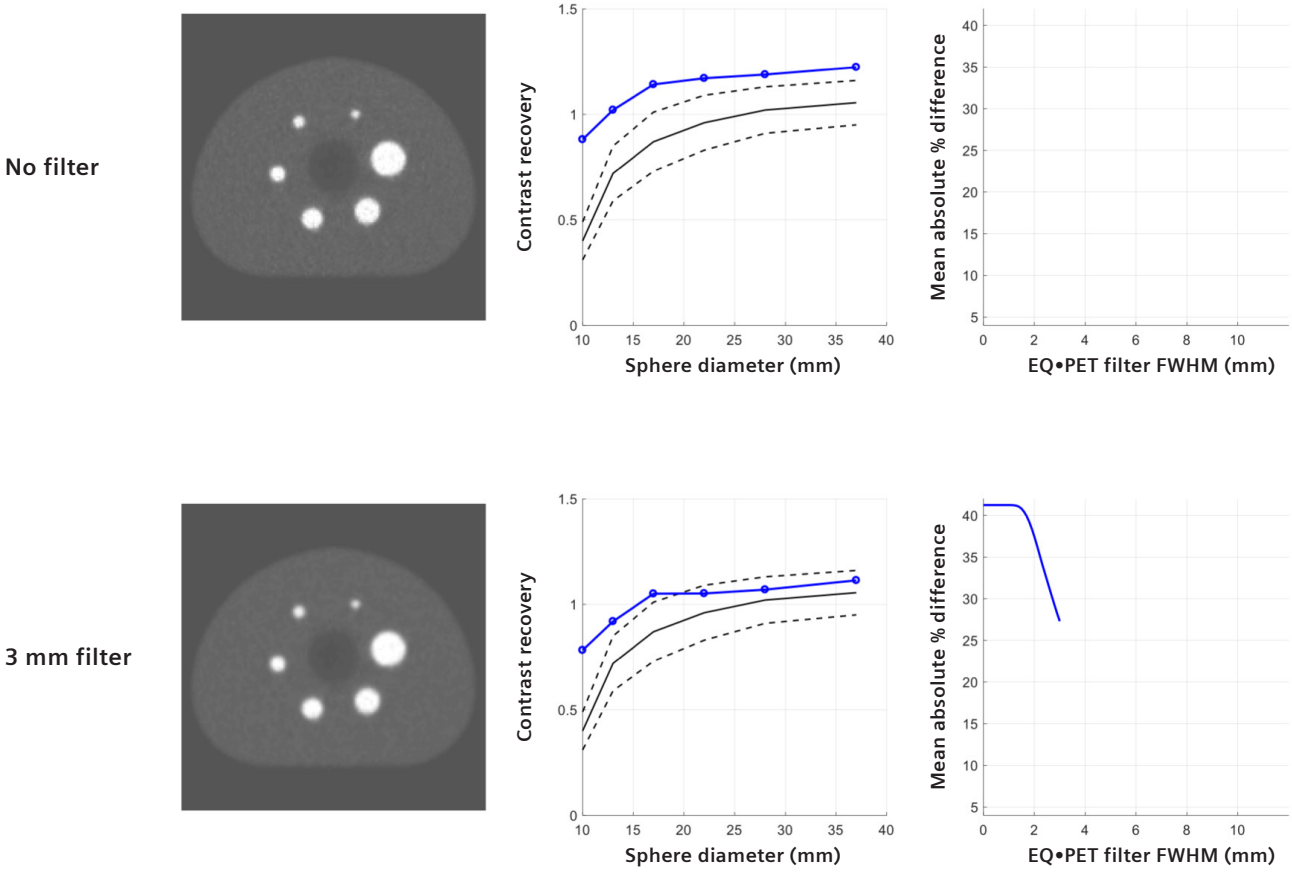
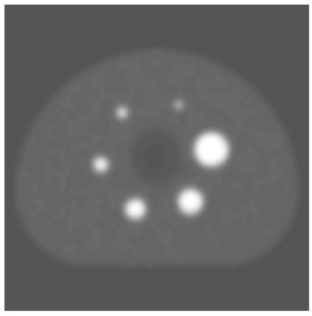
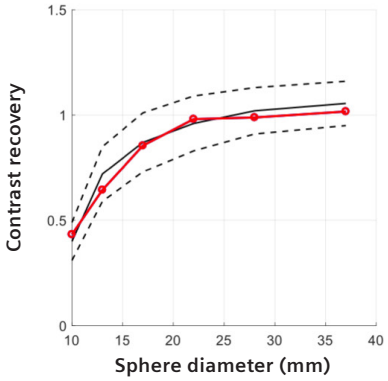


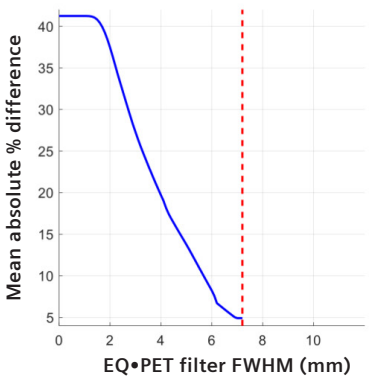
Figure 4. EQ•PET filter optimization showing the effect of increased spatial filtering on the phantom image and contrast recovery curve. The points on the contrast recovery curve are pulled downwards as the filter size increases, with the effect being more pronounced for smaller spheres. The EARL limits are plotted in black. The best alignment with the mean EARL curve is shown in red and corresponds to an optimal EQ filter size of 7.2 mm. Left to right: NEMA phantom image, contrast recovery curves, and mean absolute percent difference with the EARL standard. Top to bottom: filter full width at half maximum (FWHM) sizes 0 mm, 3 mm, 7.2 mm and 12 mm.

Figure 4 (cont.)

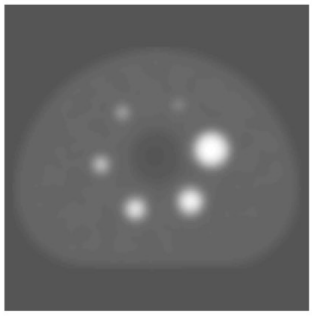
7.2 mm filter

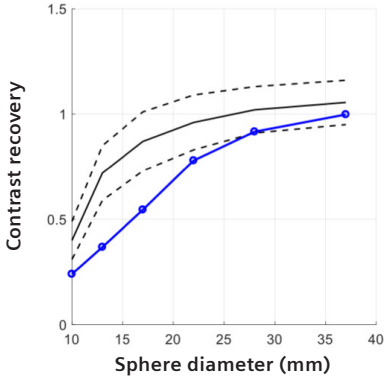


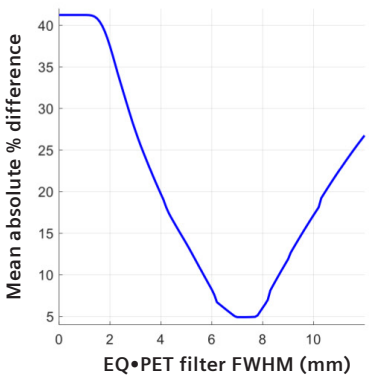




12 mm filter







Clinical example

This is a pre- and post-therapy clinical scenario exemplifying how EQ•PET allows SUV comparisons between different imaging systems.

In August of 2014, a 71-year old male with a significant smoking history underwent CT imaging of the chest as a work-up for an episode of hemoptysis. The diagnostic scan revealed a right apical pulmonary mass. Subsequent imaging with ^{18}F FDG PET/CT was performed later that month on a Siemens Biograph™ mCT (Scanner 1, Figure 5). The scan demonstrated hypermetabolic activity localizing to the large right pulmonary mass (SUV_{max} 23.0) that was previously seen on diagnostic chest CT.

Overall the findings were consistent with neoplastic disease, warranting biopsy for confirmation. The patient underwent biopsy of the right lung mass, with pathology revealing adenocarcinoma of the lung. Clinical management of this patient entailed radiation therapy followed by several rounds of chemotherapy. A month following the last round of chemotherapy, the patient was scheduled for a post-therapy ^{18}F FDG PET/CT scan to evaluate response to therapy. This scan, however, was performed on an imaging system from another vendor (Scanner 2, Figure 6). This scan also showed hypermetabolic activity in the right pulmonary mass, this time exhibiting an SUV_{max} of 14.3.

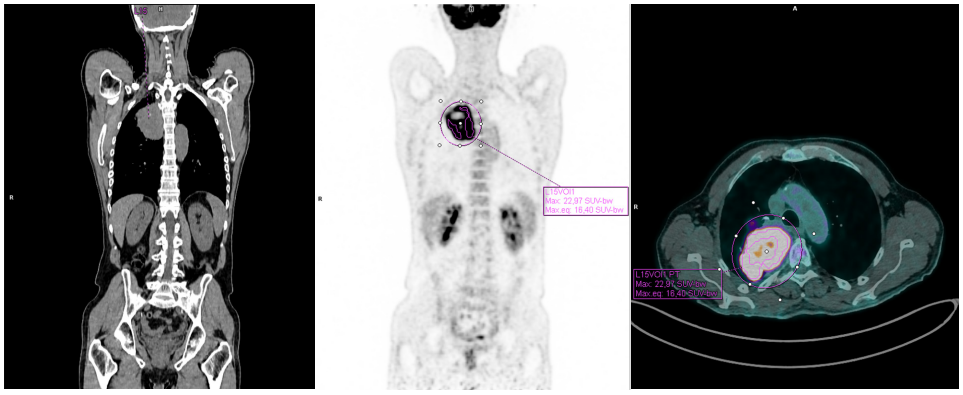


Figure 5. Pre-therapy ^{18}F FDG PET/CT performed on scanner 1 demonstrating a large, hypermetabolic right apical pulmonary mass, SUV_{max} 23.0.

Dr. Maria Vittoria Mattoli, Nuclear Medicine Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

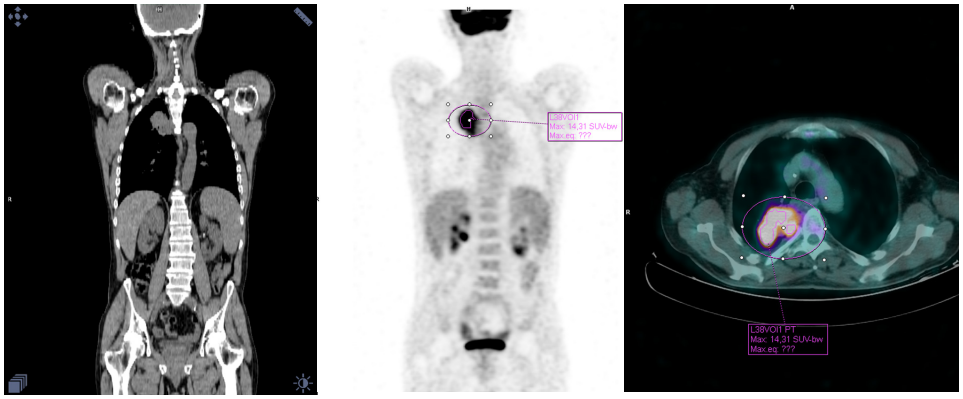


Figure 6. Post-therapy ^{18}F FDG PET/CT performed on scanner 2, demonstrating the slightly smaller hypermetabolic right apical pulmonary mass with a measured SUV_{max} of 14.3.

Dr. Maria Vittoria Mattoli, Nuclear Medicine Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

To accurately determine therapeutic response, it is critical that SUV_{max} values consistently reflect the metabolic activity in the lesion of concern. In this case, by comparing the values from each scanner without harmonization, it appears that there was 37.8% decrease in metabolic activity in the pulmonary mass. According to both the EORTC and PERCIST metabolic response criteria, this degree of decrease constitutes a significant change in metabolic activity, and thus, is considered a partial metabolic response to therapy. An 8-mm-Gaussian filter was applied for the scanner 1 protocol to bring the recovery coefficients down to within the EARL harmonization standard. The recovery curve for scanner 2 fell within the EARL limits; so no filter was applied. After applying EQ•PET to the pre-therapy scanner 1 images, the SUV_{max} of the right pulmonary mass was measured at 16.4; as opposed to 23.0 prior to EQ•PET harmonization. This represents an almost 30% difference in the SUV_{max} measurements pre- and post-application of the EQ filter, demonstrating how variable SUV results can be across different scanners and reconstruction parameters. When the EQ•PET-derived SUV_{max} from images on scanner 1 was compared with the post-therapy SUV_{max} from scanner 2, the change in metabolic activity between the pre- and post-therapy scan was only 12.7% (Figure 7). Therefore, the change in metabolic activity in the lesion was not considered significant, and the metabolic therapeutic response was more accurately characterized as one of stable metabolic disease instead of partial metabolic response. A two-year clinical follow-up showed progressive disease, confirming that the patient was a non-responder to the treatment. The use of EQ•PET thus provided a clinical assessment more consistent with patient outcome than without EQ•PET.

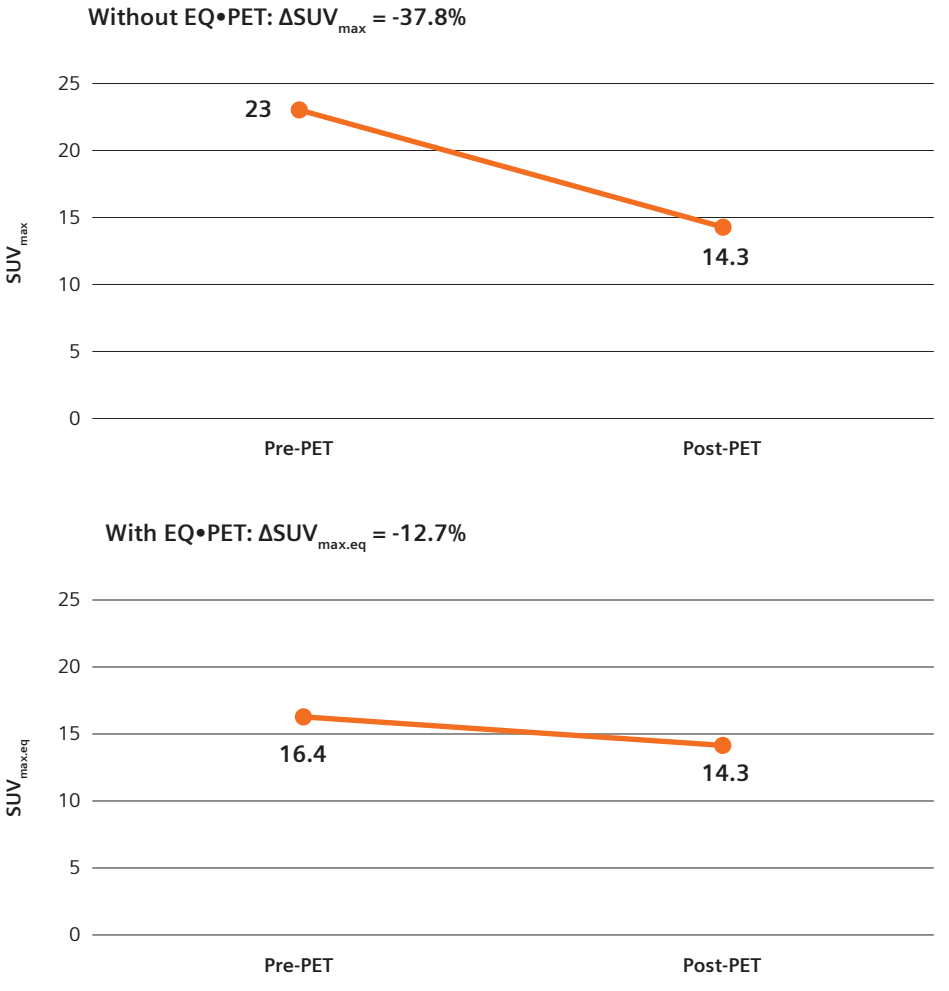


Figure 7. Pre- and post-therapy SUV_{max} measures without (a) and with (b) EQ•PET. Without EQ•PET, the pre-therapy SUV_{max} of the right lung mass measured 23. When compared to the post-therapy SUV_{max} of 14.3 on scanner 2, this resulted in a 37.8% decrease in metabolic activity, corresponding to a partial metabolic response. When EQ•PET is applied on scanner 1, the SUV_{max} is measured as 16.4, resulting in only a 12.7% change in metabolic activity, corresponding to stable metabolic disease. Two-year clinical follow-up showed progressive disease, confirming that the patient was a non-responder to the treatment.

Conclusion

EQ•PET is a software solution in *syngo*.MM Oncology, which minimizes sources of SUV variation due to scanner type and reconstruction protocol. It can be applied to harmonize measurements for patients imaged longitudinally on different PET/CT systems or to a reference standard in multicenter studies. The technology is mature in that it has been validated in a prospective multicenter study and demonstrated to improve PET response evaluation, providing results more consistent with patient outcome. Harmonization has been shown to be maintained in the presence of common SUV confounding factors. EQ•PET harmonization provides results consistent with EARL, but without an additional reconstruction, thus saving both computational and interpretation time.

About the authors

Bruce Spottiswoode holds a B.S. in Electrical Engineering and a Ph.D. in Biomedical Engineering. He started his career in the mining industry developing remote sensing electronics before entering the field of medical imaging focusing on multi-spectral X-ray technology. For five years, he served as director of the Cape Universities Brain Imaging Centre primarily conducting neuro MR research. In 2012, Bruce joined Siemens Healthineers as an MR scientist where he managed research collaborations, implemented product features, and developed prototypes for cardiovascular MR. He transitioned to Siemens Healthineers' molecular imaging business in 2016 as a senior staff scientist in the clinical applications research team, focusing on oncology and intelligent workflows, and now serves as director for clinical applications research. He is inventor of seven issued US patents, authored two book chapters, and contributed to 60 journal papers.

Dr. Damita Thomas is a board-certified nuclear medicine physician. She has a background in general surgery but found her niche in nuclear medicine, completing residency at the University of Iowa Hospitals and Clinics under former Society of Nuclear Medicine and Molecular Imaging (SNMMI) president Dr. Michael Graham. Upon graduation, she was the clinical research associate at Queen's Medical Center. Deciding that clinical medicine was her calling, she relocated to central Florida where she was a staff physician with MD Anderson Cancer Center Orlando and subsequently with Medical Center Radiology Group, where she currently provides molecular imaging interpretation for their nine hospitals/clinics, of one of the largest healthcare systems in central Florida.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

The recommended dose:

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Oncology

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

1.2 Cardiology

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

1.3 Neurology

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

2 DOSAGE AND ADMINISTRATION

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

2.1 Recommended Dose for Adults

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

2.2 Recommended Dose for Pediatric Patients

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

2.3 Patient Preparation

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

2.4 Radiation Dosimetry

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

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

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

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

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

2.5 Radiation Safety – Drug Handling

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

2.6 Drug Preparation and Administration

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

2.7 Imaging Guidelines

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

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

5.2 Blood Glucose Abnormalities

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

6 ADVERSE REACTIONS

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

8.3 Nursing Mothers

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

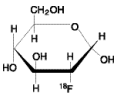
8.4 Pediatric Use

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

11 DESCRIPTION

11.1 Chemical Characteristics

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



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

11.2 Physical Characteristics

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

Table 2. Principal Radiation Emission Data for Fluorine F18

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

*Produced by positron annihilation

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

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

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

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

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

Table 4. Physical Decay Chart for Fluorine F18

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

*calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

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

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

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

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

12.3 Pharmacokinetics

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

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

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

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

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

Special Populations:

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Oncology

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

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

14.2 Cardiology

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

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

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

14.3 Neurology

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

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

15 REFERENCES

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2. Jones S.C., Alavi, A., Christman D., Montanez, I., Wolf, A.P., and Reivich M. "The radiation dosimetry of 2 [F-18] fluoro-2-deoxy-D-glucose in man," J Nucl Med, 1982; 23, 613-617.
3. Kocher, D.C. "Radioactive Decay Tables: A handbook of decay data for application to radiation dosimetry and radiological assessments," 1981, DOE/TIC-I 1026, 89.
4. ICRP Publication 53, Volume 18, No. I-4,1987, pages 75-76.

16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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