SIEMENS

White Paper

Management of Epilepsy with Neurology Analysis

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Answers for life.

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Introduction to Epilepsy

Epilepsy is a brain disorder in which a person has repeated seizures over time, resulting from abnormal, excessive or hypersynchronous neuronal activity in the brain, mainly in the gray matter. Approximately 1-2% of the worldwide population is affected by epilepsy. The diagnosis of epilepsy is typically made based on the description of the seizure and is usually controlled but not cured with medication. However, 20-30% of patients with epilepsy do not respond to treatment even with the best available medication. In patients with epilepsy that is refractory to drug therapy, surgery may be considered with the main aim of controlling seizures and, thus, improving the quality of life. Once a patient is considered for surgery, precise localization of epileptogenic zone is needed before surgery to minimize the side effects of the operation.[1,2]

Epilepsy surgery requires a multi-disciplinary approach where the pre-surgical evaluation and workup includes many different elements: patient and seizure history, semiology of the seizure, neurological examination, electroencephalogram (EEG), long-term video-EEG monitoring (in difficult cases), neuropsychological evaluation, and structural and functional neuroimaging such as magnetic resonance imaging (MRI), positron emission tomography (PET) and single-photon emission computed tomography (SPECT).

Although not used in the primary diagnosis or evaluation of epilepsy, radionuclide imaging such as PET and SPECT is very useful for the management of patients with medically refractory partial epilepsy. Partial epilepsy only affects one limited area of the brain, in contrast to primary generalized epilepsy that involves both sides of the brain at once. PET and SPECT are particularly useful in the non-invasive pre-surgical localization of intractable epileptogenic focus in patients with medically refractory partial temporal or extra-temporal lobe epilepsy and to assess whether surgery is an option. This is because the pathophysiological changes associated with epilepsy consist of an abnormal metabolism and perfusion in cerebral activity that can be observed with PET and SPECT imaging.[2,3]

Radionuclide imaging (PET and/or SPECT) may be particularly useful if MR imaging findings are inconclusive or show multi-focal lesions of which only one or two lesions are suspected to be epileptogenic, or if EEG recordings are ambiguous or conflicting with the structural imaging readings. In difficult cases where the epileptogenic lesion may be medial and correlated with generalized epileptiform activity on the EEG because of secondary bilateral synchrony, PET or SPECT imaging may allow for surgical treatment in a patient who might otherwise not have been considered for surgery. They can

Fludeoxyglucose F18 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 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:** 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 on pages 15-17.

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

also be helpful in identifying other pathology by assessing the presence of potential secondary epileptic foci (in which case surgery is not an option), evaluating the functional integrity of the rest of the brain and maybe even providing information on the possible development of the disease and the neurocognitive and behavioral abnormalities frequently observed in epileptic patients. It could also provide useful prognostic information in these patients.[2,3]

Positron Emission Tomography (PET)

PET imaging with ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F FDG*) reveals alterations in cerebral metabolism related to the synaptic and neuronal activity of the brain tissue.[4] An interictal ^{18}F FDG PET scan acquired when the brain is in a normal state (i.e., period between seizures) is very valuable and typically shows reduced metabolism, that is, hypometabolism of glucose in the epileptogenic region. This hypometabolism can result from a variety of mechanisms, including neuronal loss, diaschisis, or reduction in synaptic density.

^{18}F FDG PET usually shows a large area of hypometabolism often extending beyond the epileptogenic region. Therefore, ^{18}F FDG PET is not typically suitable for precisely determining the surgical region. It can, however, be used for lateralization and general localization of the epileptic focus, which is useful in making a hypothesis about subdural electrode placement. ^{18}F FDG PET is also useful in evaluating the function of the rest of the brain, as postsurgical neurocognitive outcome will depend on the integrity of the remaining non-resected cortex.

Interictal scans are easy to perform, as they can be acquired at any time during normal brain state. They can be acquired despite the slow uptake time of ^{18}F FDG tracer; however, it is due to the slow ^{18}F FDG uptake that ictal PET imaging is not possible. Interictal ^{18}F FDG PET has a good sensitivity in detection of the epileptic brain region in cases of temporal lobe epilepsy, but less in localizing the epileptogenic zone in frontal lobe epilepsy.

Clinical Example: Interictal PET

Figure 1 shows an example of interictal ^{18}F FDG PET scan. This 24-year-old male patient has treatment-resistant focal epilepsy and was evaluated as a candidate for surgery. The scan shows a major reduction of metabolism all over the left temporal lobe together with a minor reduction in parts of the frontal and parietal lobes on the same side.

Single Photon Emission Computed Tomography (SPECT)

SPECT imaging is used to provide information about alterations in cerebral perfusion, i.e., cerebral blood flow.[5] The most common radiotracers used are ^{99m}Tc ethyl cysteine dimer and ^{99m}Tc hexamethylpropyleneamine oxime (^{99m}Tc HMPAO).

Alterations in blood flow depend on the electrical status of the brain. In the ictal state, i.e., during a seizure, the cerebral blood flow changes rapidly over time, depending on the type of seizure and its mode of propagation. Therefore, early injection of the radiotracer during the seizure is important to capture blood flow changes in the epileptic zone. Ictal SPECT studies are obtained by injecting an appropriate radioisotope within seconds of a seizure onset to measure cerebral perfusion. The tracers are lipophilic substances that easily cross the blood brain barrier and remain trapped. So the cerebral blood flow is represented by a "frozen" image weighted primarily towards the first 30-60 seconds after injection.

During the ictal phase, blood flow in the epileptic region can increase significantly and can be seen as an area of hyperperfusion on ictal SPECT. True ictal SPECT, i.e., an image for which the tracer has been injected immediately after the onset of the seizure, shows perfusion at that specific time. Knowledge of the exact time of injection, duration, semiology and EEG, including video EEG, of the seizure is important for correct interpretation of the SPECT image. Delayed injection of radiotracer may show a variable pattern of blood flow changes in the epileptic zone as the seizure evolves, as well as a variation in the mode and pattern of seizure propagation.

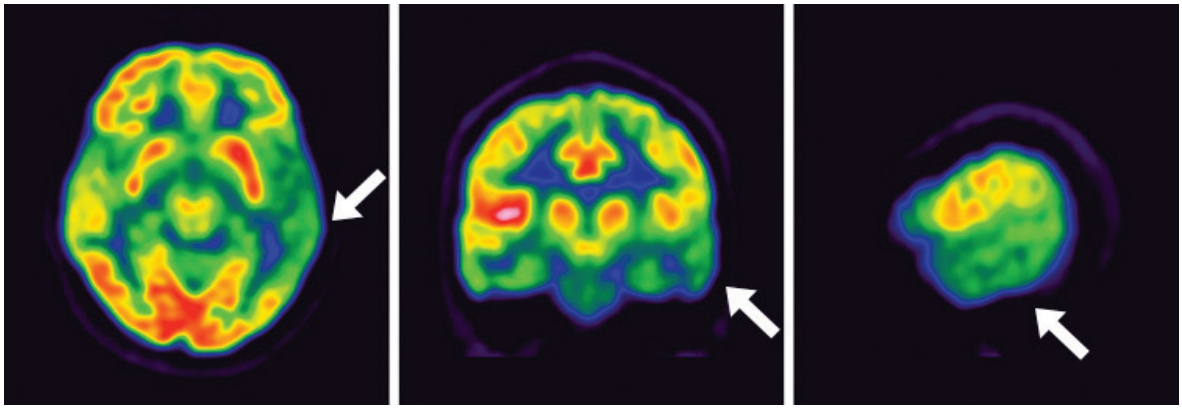

Figure 1: Clinical example: an interictal ^{18}F FDG PET scan showing lower glucose metabolism in the left temporal lobe (arrow). *Data courtesy of Friedrich Alexander University, Erlangen, Germany.*

**Indications and usage, important safety information and dosage forms and strengths can be found on page 1 of this paper. Prescribing information can be found on pages 15-17.*

Interictal SPECT on the other hand, shows the baseline perfusion pattern, thus showing normal or even reduced perfusion (i.e., hypoperfusion) in the epileptogenic region. However, sensitivity of interictal SPECT alone is low (compared to FDG PET). Ictal SPECT is more sensitive, as well as more specific. Therefore, often interictal SPECT scans are only performed to compare them to ictal SPECT scans.[2]

Clinical Example: Ictal and Interictal SPECT
Figure 2 shows an example of ictal and interictal SPECT using ^{99m}Tc ECD acquired from a 17-year-old female patient with epileptic seizures that had been treatment-resistant for about 3 years. She was considered for surgery due to the progression of the disease. The interictal scan shows minor hypoperfusion in right parietal lobe (and right temporal mesial lobe not shown in Figure 2), and the ictal scan shows a hyperperfusion in the right parietal lobe consistent with the interictal scan findings. An MR was also acquired and findings correlated with SPECT findings.

Clinical Analysis and its Limitations
Interictal PET Analysis
Clinical visual examination remains the standard in reading and interpreting ^{18}F FDG PET imaging. This interpretation involves comparing hemispheric asymmetry. However, tough cases having regions with subtle hypometabolism may be difficult to assess visually.

Various methods for data analysis can be helpful. Statistical parametric mapping (SPM) is a voxel-based approach for identifying regions that are significantly different from normal controls. This method has been used as a research tool and can allow for detection of subtle pathological regions. It works by comparing the individual patient to a normal database and highlighting regions with unusual variations.[6] This analysis method may be beneficial in questionable and ambiguous cases.[7]

Ictal and Interictal SPECT Analysis
SPECT scans are typically performed using a protocol which defines an ictal scan followed by an interictal scan a few days later. This is because the interictal scan is only used as baseline in addition to the ictal scan. The key role of interictal SPECT is to support in the evaluation of ictal SPECT visually and also quantitatively. The interictal scan is especially helpful in cases where the hyperperfusion in ictal SPECT images may be mild and sometimes difficult to distinguish from the surrounding normal brain on visual examination.

Thus, a well-established technique exists to facilitate the localization of the epileptic foci–the subtraction of interictal from ictal scan. The oldest technique is the classical Subtraction Ictal SPECT co-registered to MRI (SISCOM) method[8,9], where the difference image produced by subtraction of the interictal scan from the ictal scan is superimposed on the anatomical MR image. The difference image obtained shows variations between the ictal and interictal scans and can be sometimes difficult to assess because it might contain distracting information due to the amount of non-significant variations and non-disease-related activations. However, SISCOM does not propose any processing on the difference image to facilitate its interpretation.

Other methods compare the ictal SPECT to normal controls (for example, using SPM)[10] in a similar way to the analysis of interictal PET. Comparison of ictal and interictal pairs to pairs of normal controls has also been investigated.[11]

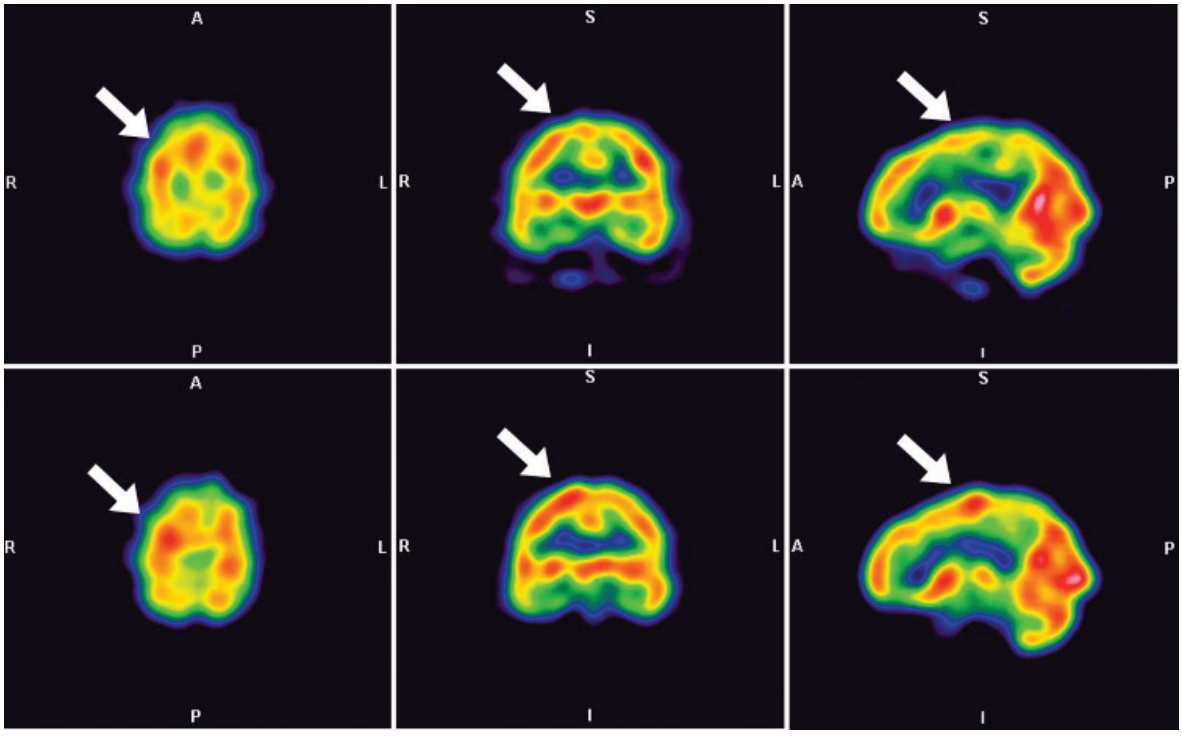

Figure 2: Clinical example: a 17-year-old female patient with right parietal epileptic focus (arrow). On the top: interictal SPECT scan with hypoperfused focus. On the bottom: ictal SPECT scan with hyperperfused focus correlated with interictal finding. *Data courtesy of Friedrich Alexander University, Erlangen, Germany.*

Neurology Analysis Workflows

Database Comparison and Subtraction are two Neurology Analysis tasks within *syngo*.via MI Neurology Workflow that can help the clinician analyze and assess PET and SPECT scans with supporting anatomical scans (MR or CT) for epilepsy, as well as other neurological disorders.

Database Comparison

Database Comparison is a software solution that enables the user to compare a PET or SPECT scan of an individual patient to a database of images of the same radiotracer composed of scans from confirmed normal controls. Comparison to a database is a commonly used technique,[12] and provides information that can be useful in the assessment of brain scans. Once a clinical visual assessment is made of the brain scan and a diagnosis is proposed, Database Comparison can be used to confirm the first impression from the visual read by providing regional quantification of deviation from normal tracer uptake.

Preparation and Analysis

Database Comparison workflow calculates and displays voxel-wise comparison statistics, highlighting regions in the patient scan where tracer uptake is different from that in the normal population used to build the selected database. It is possible to use Database Comparison to analyze ^{18}F FDG PET and/or ^{99m}Tc ECD/^{99m}Tc HMPAO SPECT images of epilepsy patients by comparing the particular scan to a normal database of an appropriate age group for the appropriate tracer. Young normal databases for ^{18}F FDG PET and ^{99m}Tc ECD SPECT are available. In addition, it is possible for users to create their own databases.

Database comparison workflow involves several steps for the comparison to be as robust as possible. First, the user must select an appropriate database for comparison. Then, automatic rigid registration is performed to align any related anatomical images such as MR or CT that are loaded to facilitate correlation of findings. Automatic non-linear registration (for ^{18}F FDG) or affine registration (for ^{99m}Tc ECD/^{99m}Tc HMPAO) is then performed to align the subject image to the database that is in the standard Montreal Neurological Institute (MNI) space,[15] as used by other packages such as SPM.[16]

These two registration steps can be visually assessed and adjusted by the user, if needed. Smoothing of the functional image is also performed to account for differences in brain anatomy and physiology (e.g., gyri position), as well as intensity normalization to eliminate global uptake differences between the patient functional image and the database. These steps are performed for the purpose of processing only and are internal properties of the database selected. For more details, consult the Database Comparison white paper.[13]

Once these steps are completed, comparison to the database is possible and provides statistics in two forms: voxel-based statistics displayed as an image volume; and region of interest (ROI) statistics.

Both types of statistics are calculated by comparing, at each voxel, the corresponding mean value estimated for the normal population to the value from the subject, and dividing by the corresponding voxel-based standard deviation value estimated from the normal population as specified in Equation 1.

$$\text{Statistics Image} = \frac{\text{Patient Image} - \text{Mean}_{\text{population}}}{\text{Standard Deviation}_{\text{population}}}$$

Equation 1: Calculation of statistics from estimated population mean, standard deviation and subject value.

Figure 3 provides a summary of the Database Comparison workflow.

The statistics computed for the subject image provide a measure indicating how much the subject's uptake deviates from uptake at the corresponding position in the normal database population. A larger statistic (in terms of absolute value) indicates a larger deviation (which may be higher or lower) from the normal population.[13]

Findings of Database Comparison should be compared to the initial visual impressions and any discrepancies require further investigation. For example, direct comparison between the original data and the Database Comparison, and comparison to diagnostic MR or CT (e.g., malformations or tumors). Any findings from the Database Comparison without correlation to the uptake images should be treated with care.

Database Comparison also provides statistics for regions of interest (ROIs), by first computing the population mean value for a particular ROI for each of the normal subjects in the database, and then computing the mean and standard deviation of those mean values. The ROI statistics are then obtained from those values and the mean uptake within the same ROI for the individual patient.[13]

Clinical Example: Interictal PET

Figure 4 shows the interictal ^{18}F FDG PET example described previously. The first row shows the uptake image and the second row shows the statistics compared to the ^{18}F FDG Biograph™ mCT and Biograph TruePoint database for younger subjects with whole-brain intensity normalization (FDG4A).[13] The variations colored in blue show the regions with hypometabolism compared to the normal database, highlighting the regions that could be epileptic lesions.

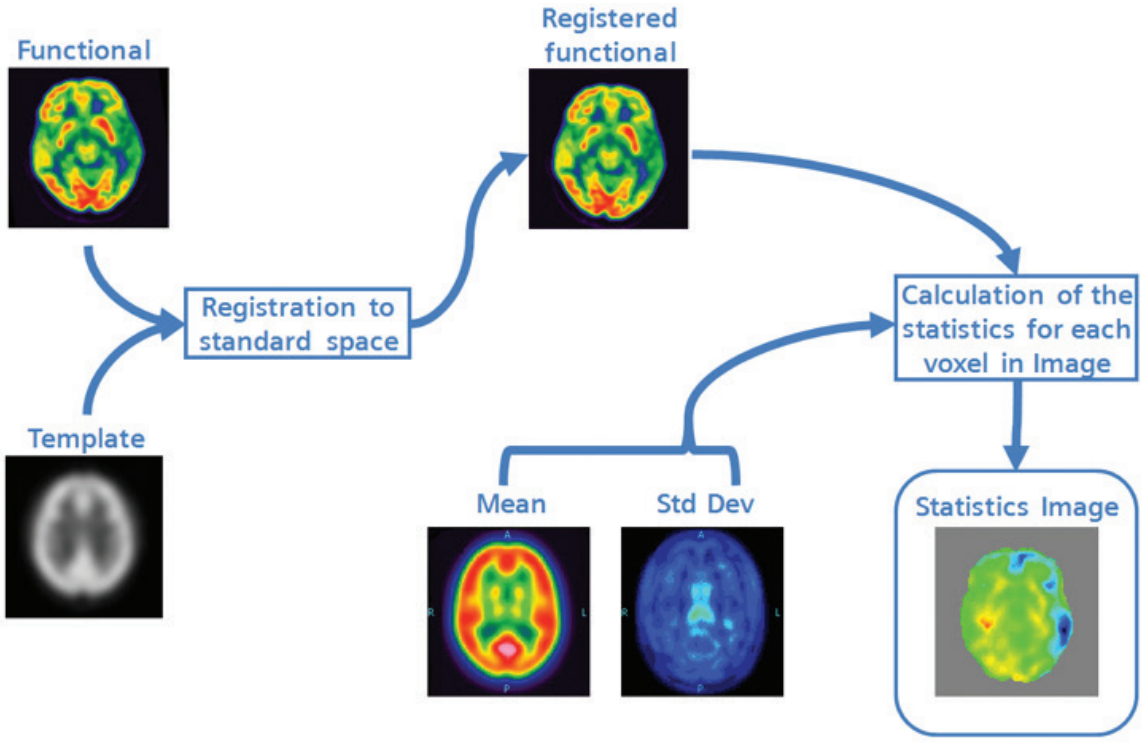

Figure 3: Standard database comparison workflow in Neurology Analysis. Once the PET or SPECT is aligned with the template, the statistics for each voxel are calculated using the mean and standard deviation of a selected database.

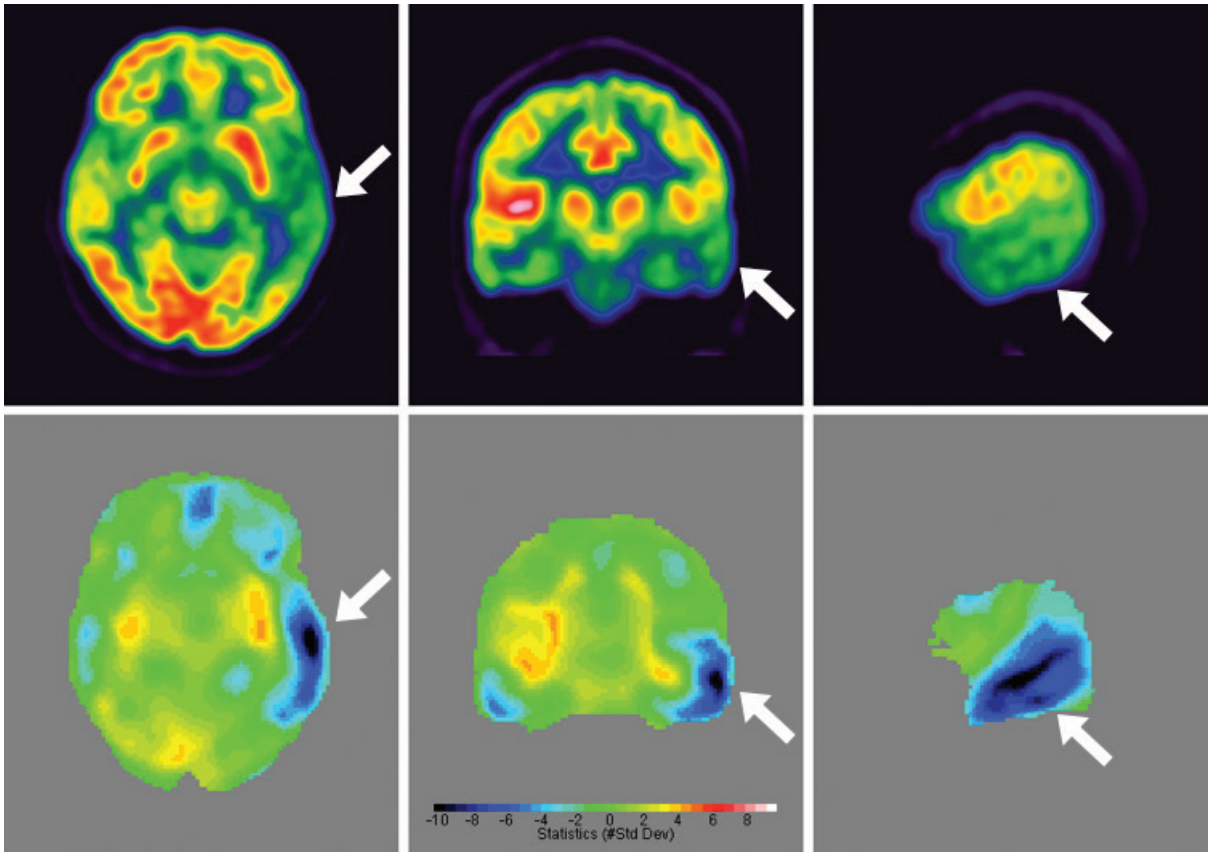

Figure 4: Clinical example of interictal ^{18}F FDG PET scan. The first row shows the uptake of FDG metabolism and the second row shows the statistics image.
Data courtesy of Friedrich Alexander University, Erlangen, Germany.

Clinical Example: Ictal and interictal SPECT

Figure 5 shows the ictal ^{99m}Tc ECD SPECT scan described previously and the statistics image when compared with the ^{99m}Tc ECD database for younger subjects unsmoothed with whole-brain intensity normalization (ECD3C).[13] The variations colored in red show the regions with hyperperfusion compared to the normal database, indicating regions that could be epileptogenic.

When comparing the interictal ^{99m}Tc ECD scan to the same database, there appears to be only non-significant hypoperfusion at the location of the questionable focus; therefore, in this case, the interictal SPECT alone cannot be considered as diagnostic.

Database Comparison workflow also offers the possibility to view the statistics in stereotactic surface projection (SSP) view.[14] However, the SSP statistics view is less interesting for epilepsy cases when the epileptic focus is located deeper in the brain.

Subtraction

Subtraction workflow is a software solution that enables the user to subtract an interictal from an ictal SPECT scan of a patient; the difference image obtained shows positive and negative variations. Positive high variations in the difference image may help the identification of ROIs that may represent epileptic lesions. In addition, subtraction workflow lists ROIs that are positive regions on the difference image and that have, at the same time, a local increase in the ictal scan.

Preparation and Analysis

Subtraction workflow for the analysis of ictal and interictal SPECT scans involves several steps for the analysis to be as robust as possible. First, automatic rigid registration is performed to align any related anatomical images such as MR or CT to facilitate the correlation of findings. Second, automatic affine registration is performed to align the subject image to standard space, from which the rigid transformation is extracted and applied to the scans so that the scans can be visually assessed in a standard orientation. Third, the ictal and interictal scans are aligned rigidly to enable subtraction. All registration steps can be visually assessed and adjusted by the user if needed. Once the ictal image is aligned to the interictal image, the ictal image needs to be resampled to match the interictal scan dimensions and space.

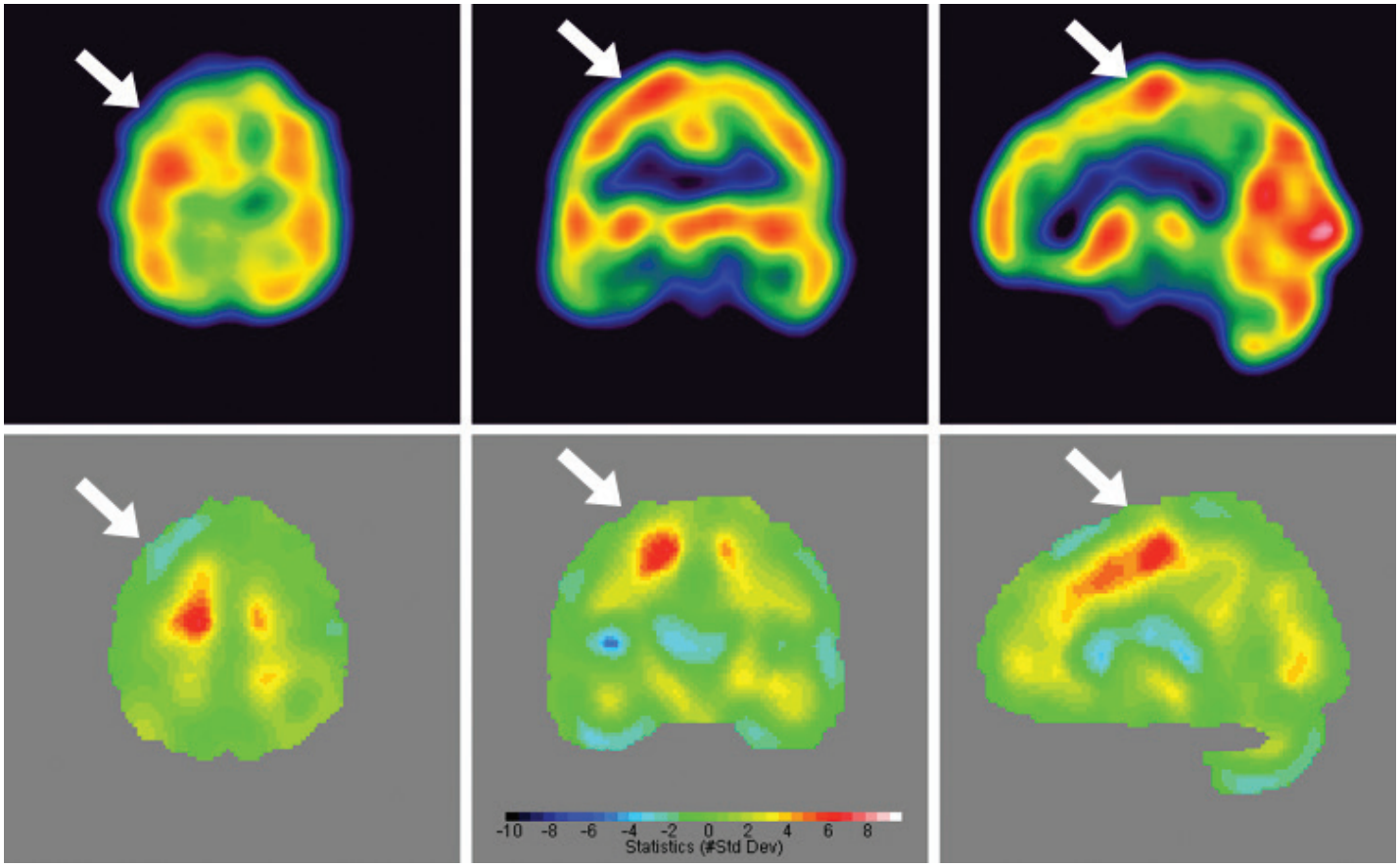

Figure 5: Clinical example of the ictal ^{99m}Tc ECD SPECT scan. The first row shows the uptake of the perfusion scan and the second row shows the statistics image. *Data courtesy of Friedrich Alexander University, Erlangen, Germany.*

Intensity normalization is applied prior to subtraction, where the ictal and interictal images are each divided by the mean value computed inside the brain of the corresponding image, as shown in Equation 2, where $Mean_{IctalBrain}$ and $Mean_{InterictalBrain}$ are the mean intensities of the ictal and interictal images within the brain region.

Gaussian smoothing of ictal and interictal scans can be performed prior to the subtraction if desirable. This will produce a smoothed difference image that could be better suited for the analysis of potential foci by reducing noise. Gaussian smoothing can be applied with different full width half max (FWHM) up to 18 mm.

Once the difference image is computed using Equation 2, it is normalized so that it represents a normalized difference image. This is done so that the reader is able to interpret the difference image in a more standardized manner, as its values can be read as numbers of standard deviations. The difference image is normalized according to Equation 3, where the $Mean_{DifferenceImage}$ and $StandardDeviation_{DifferenceImage}$ are the mean and standard deviation of the difference image in brain region only.

Figure 6 depicts the standard subtraction workflow described in this section, resulting in the normalized difference image. Note that the normalized difference image computed in subtraction is different from that computed in Database Comparison. In subtraction, the normalized difference image is computed based on the mean and standard deviation inside the brain only of the difference image itself, whereas in Database Comparison, the voxels of a patient scan are compared to the mean and standard deviation of a database using a voxel-based comparison.

$$\text{Difference Image} = \frac{\text{Ictal Image}}{\text{Mean}_{\text{IctalBrain}}} - \frac{\text{Interictal Image}}{\text{Mean}_{\text{InterictalBrain}}}$$

Equation 2: Calculation of the difference image. The ictal and interictal images are normalized to mean values in the brain and then subtracted.

$$\text{Normalized Difference Image} = \frac{\text{Difference Image} - \text{Mean}_{\text{DifferenceImage}}}{\text{Standard Deviation}_{\text{DifferenceImage}}}$$

Equation 3: Normalization of the difference image, so that the values correspond to number of standard deviation from the mean.

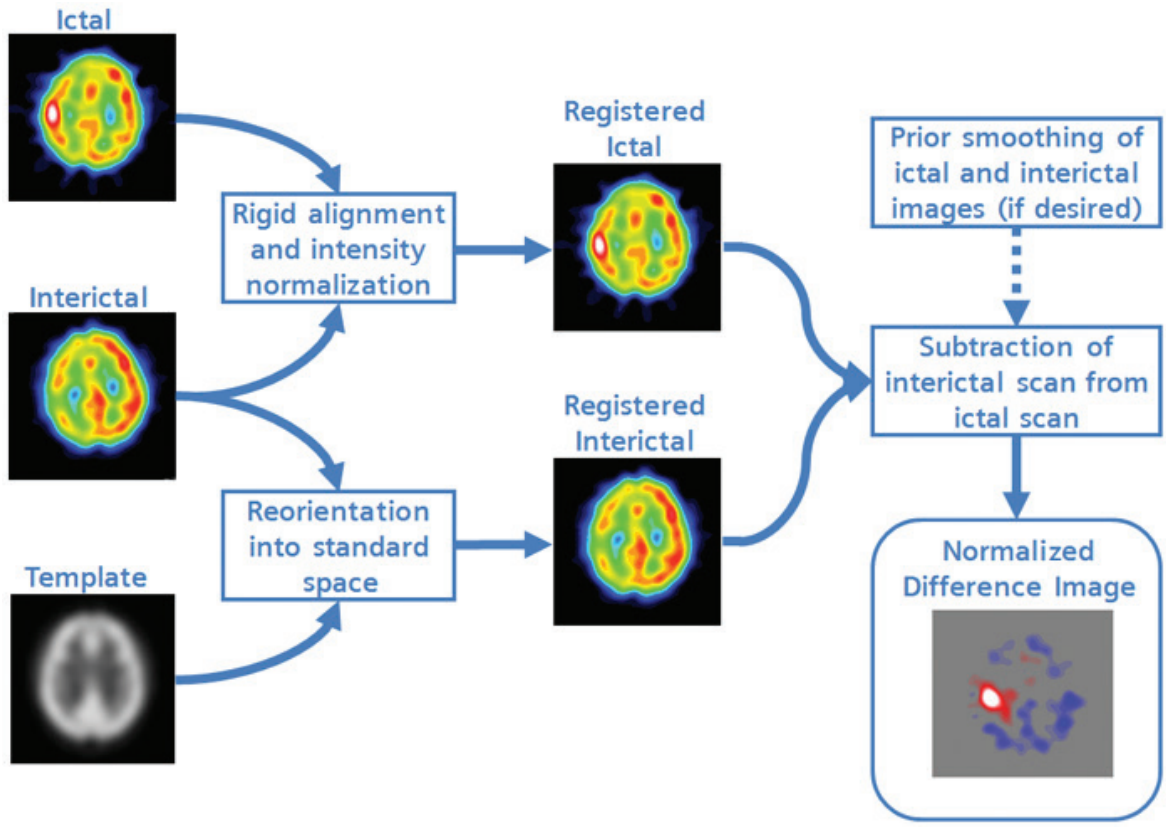

Figure 6: Standard subtraction workflow in Neurology Analysis. Once the ictal and interictal images are aligned and intensity normalized, the subtraction is performed and the normalized difference image is calculated (with or without prior Gaussian smoothing of ictal and interictal image).

Filtering and Regions of Interest

The steps described in the previous section and shown in Figure 6 constitute the base of the standard subtraction workflow. The difference image, obtained after subtraction of the interictal from the ictal scan, will show variations where positive high variations are of interest and may help the identification of regions that may be epileptogenic. Since an epileptic focus has high perfusion in the ictal scan compared to the interictal scan, the difference image is expected to highlight the epileptogenic regions. However, the difference image might contain distracting information, i.e., too many regions with high variation between the ictal and interictal image that might not be relevant.

Subtraction offers a sophisticated filtering to help the user identify the most relevant variations in the difference image. When many variations are seen in the difference image, the filtering will automatically identify regions of interest (ROIs) that have important perfusion uptake in the ictal image and list them in a table. The aim of filtering is to facilitate interpretation, by highlighting relevant information in the difference image, and reduce the amount of distracting information.

The filtering identifies ROIs with the greatest variations in the difference image that are, at the same time, significant in the ictal scan. That is, identifying all regions above a Filtering threshold in the difference image, and retaining only the regions that have a local maximum in the ictal scan. Since the normalized difference image described in Equation 3 is used, it is possible to threshold this normalized difference image with a threshold equal to a number of standard deviation (NBSTD), typically, a NBSTD equal to 2 is used in literature.[5] Figure 7 shows a summary of the filtering. It is possible to change this threshold and control the amount of useful information in the difference image. The list of ROIs is ordered by the maximum value in the difference image, i.e., the number of standard deviations.

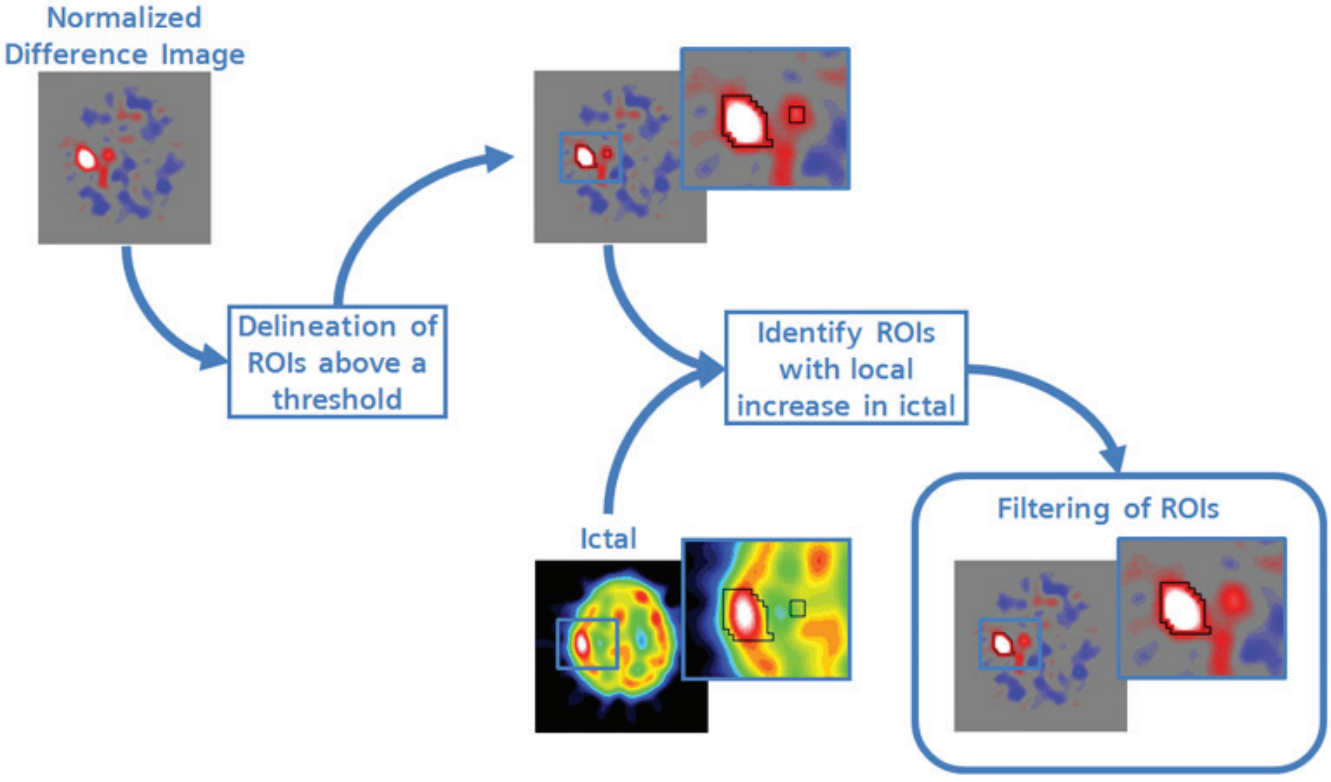

Figure 7: Filtering is achieved by propagating the ROIs delineated on the difference image into the ictal image and keeping the ROIs that have a local maximum only.

Filtering Performance

The performance of the filtering for the automatic selection of ROIs was evaluated on 38 clinical epilepsy cases (Department of Nuclear Medicine, Poliklinik der Friedrich-Alexander-Universität, Erlangen, Germany) and the results compared with the clinical findings and reports available. Experiments compared the automatically identified ROIs to the clinically identified foci (there is only one identified focus per scan). Eight of the cases (21.1%) had questionable foci, i.e., the SPECT scans were not clinically conclusive, amounting in 30 cases with identified clinically-significant foci.

Three different variants of the automatic selection of ROIs were analyzed for each case. ROIs were produced by the filtering: 1) without smoothing the SPECT scans prior to subtraction, 2) Gaussian smoothing of SPECT scans with FWHM of 6 mm, and 3) Gaussian smoothing of SPECT scans with FWHM of 12 mm. In practice, it is up to the user to decide how much smoothing to apply prior to subtraction. Figure 8, Figure 9 and Figure 10 summarize the results of the filtering to select the list of ROIs.

Figure 8 shows the number of ROIs before and after filtering for different amounts of Gaussian smoothing of SPECT scans. The blue bars show the number of delineated ROIs on the normalized difference image with a NBSTD = 2, and the red bars show the number of ROIs remaining after filtering, i.e., after propagation of the ROIs to the ictal images and eliminating ROIs that are not significant (i.e., not containing a local maxima). The filtering significantly reduced the number of ROIs (reduction of approx. 75%). Without prior smoothing, the filtering was able to delineate smaller ROIs; it, however, produced a higher number of regions that were not clinically relevant (mean number of ROIs of 5.1). With Gaussian smoothing with FWHM 6 mm, the number of ROIs was reduced, and with FWHM of 12 mm the number of ROIs was reduced even further (with mean of number of ROIs equal to 4.1 and 2.8 respectively).

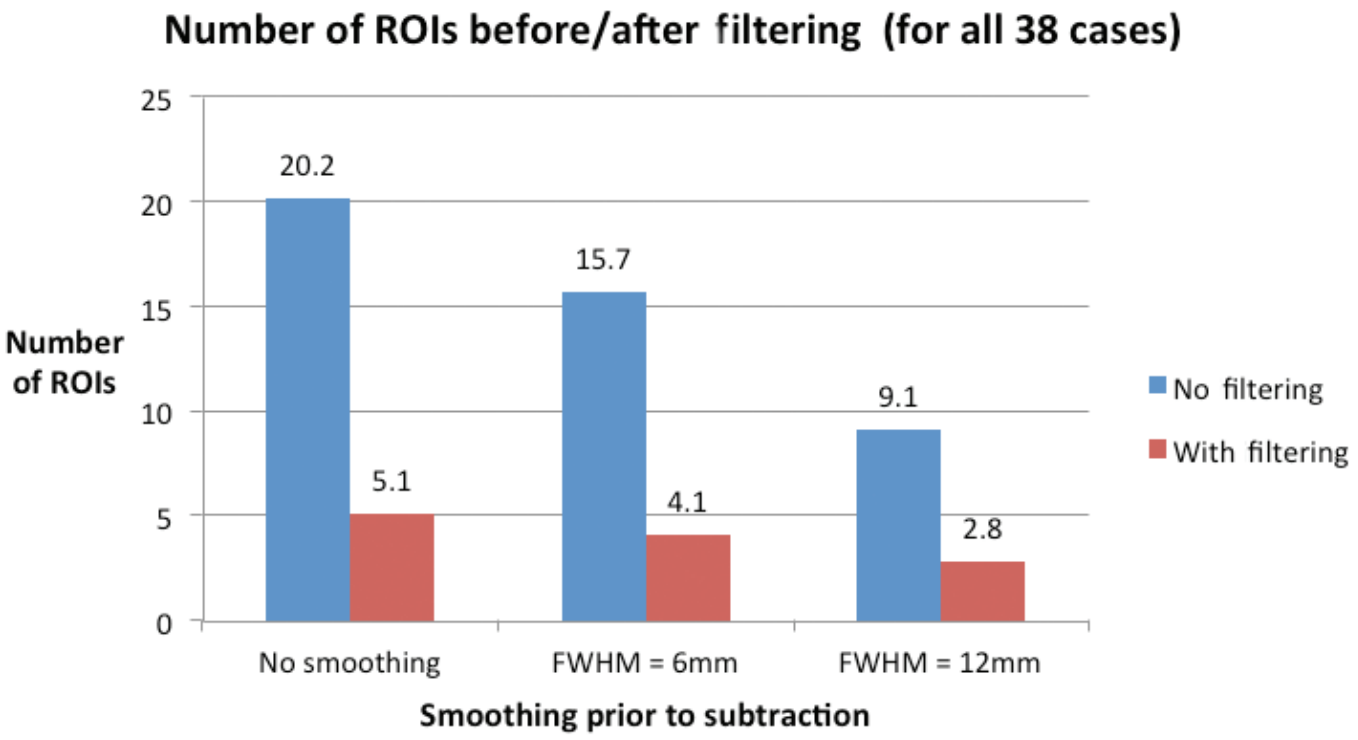

Figure 8: Number of ROIs delineated on difference image as well as number of ROIs after filtering with no smoothing and with smoothing using FWHM of 6 mm and 12 mm.

Figure 9 shows the number of cases where the clinically-significant focus is ordered 1st, 2nd, 3rd, etc. in the ROIs list obtained with filtering; that is, the order of the ROI corresponding to the clinically-significant focus. Note that the order of the list of ROIs produced with filtering is based on the maximal value within the ROI in the difference image. The figure shows the number of cases with the specified order produced with filtering using different amounts of smoothing: no smoothing, Gaussian smoothing with FWHM of 6 mm and FWHM of 12 mm.

It is interesting to note that all 30 clinically-significant foci and two additional questionable foci (with order 3 and 9, not shown in figure) were identified when no smoothing was applied prior to subtraction. However, the number of cases where the clinically-significant focus was identified as the first in the list of ROIs increased with Gaussian smoothing: 15, 16 and 19 cases were identified as first without smoothing, with smoothing with FWHM of 6 mm and with FWHM of 12 mm, respectively. It is also worth noting that four foci were not identified with a Gaussian smoothing with FWHM of 12 mm but were identified without prior smoothing; and only one was not identified with smoothing with FWHM of 6 mm compared to without.

Thus, the real clinical focus has a higher and more significant order in the list of ROIs with increased smoothing, where the mean order is 1.8 and 1.4 with FWHM of 6 mm and with FWHM of 12 mm, respectively; in contrast to the mean order of 2.5 without prior smoothing.

Figure 10 shows the cumulative percentage of cases where the clinically-significant foci were correctly identified. It can be noted that, without smoothing, all 30 clinical foci were identified with an order of 6 or less (100%). In 15 of the cases (50%), the clinical focus was identified as the first one in the list. Out of the remaining eight cases that were considered non-diagnostic, the filtering identified questionable foci in two cases and none in the other six.

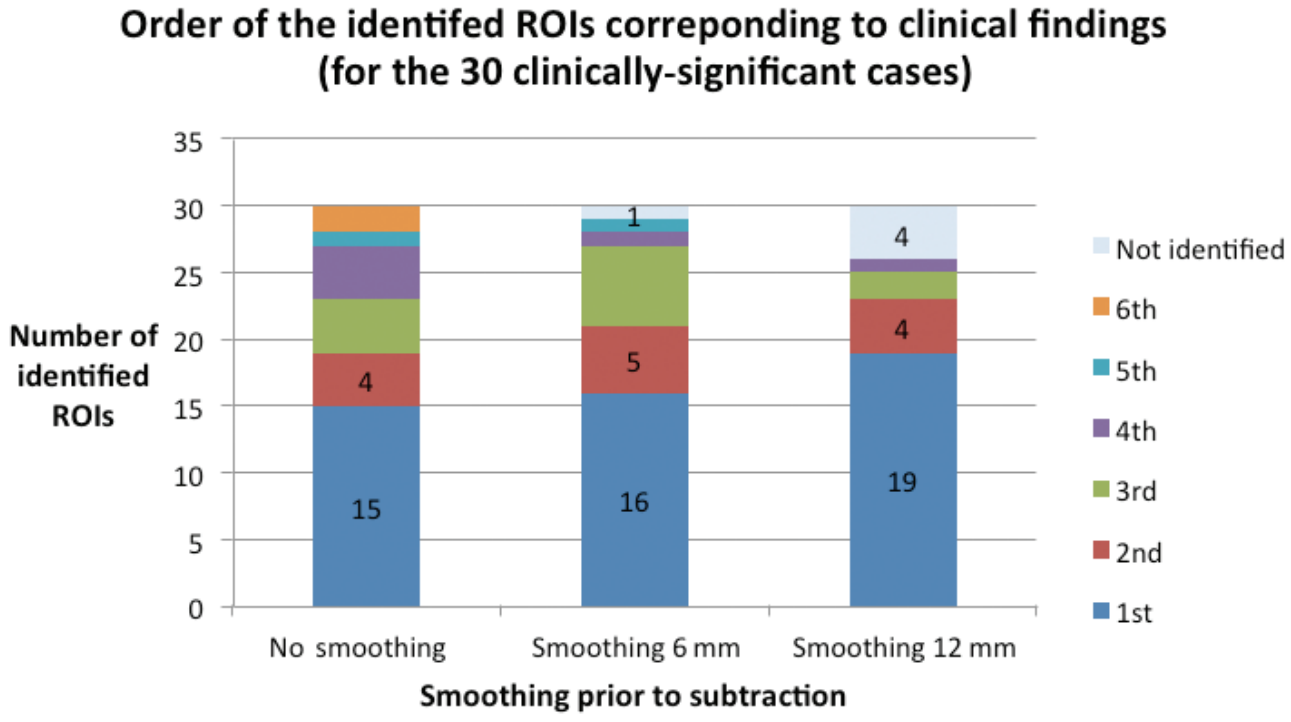

Figure 9: Number of cases where the clinically-significant focus was correctly identified as the 1st, 2nd, 3rd, etc. and not identified.

With Gaussian smoothing with FWHM of 6 mm, only one clinically-significant focus was not identified compared with no prior smoothing. This results in 29 clinical foci identified (96.7%), one clinical focus not identified and eight questionable foci not identified. In more than half of the cases (53.3%), the clinical focus was identified as the first one in the list.

Applying a Gaussian smoothing with FWHM of 12 mm, four clinically-significant foci were not identified compared with no prior smoothing, resulting in 26 clinical foci identified (86.67%) and four small clinically identified foci being missed. In approximately one third of the cases (63.30%), the clinical focus was identified as the first one in the list.

The results in Figure 10 show that, without prior smoothing, all clinically-significant foci were identified and, with smoothing, fewer ROIs were identified.

Clinical Example: ictal and interictal SPECT

Figure 11 shows the case described previously where, in addition to the interictal (left column) and ictal (middle column) scans, the difference image obtained with subtraction is shown. The ROIs with the highest variation (i.e., with maximum value on the difference image) obtained by the filtering are overlaid on the difference image as a contour in black, highlighting a candidate epileptic focus which corresponds with the one defined clinically.

Figure 12 shows the epileptic focus overlaid on the interictal, ictal, difference and MR images (left to right, top to bottom) for the same case.

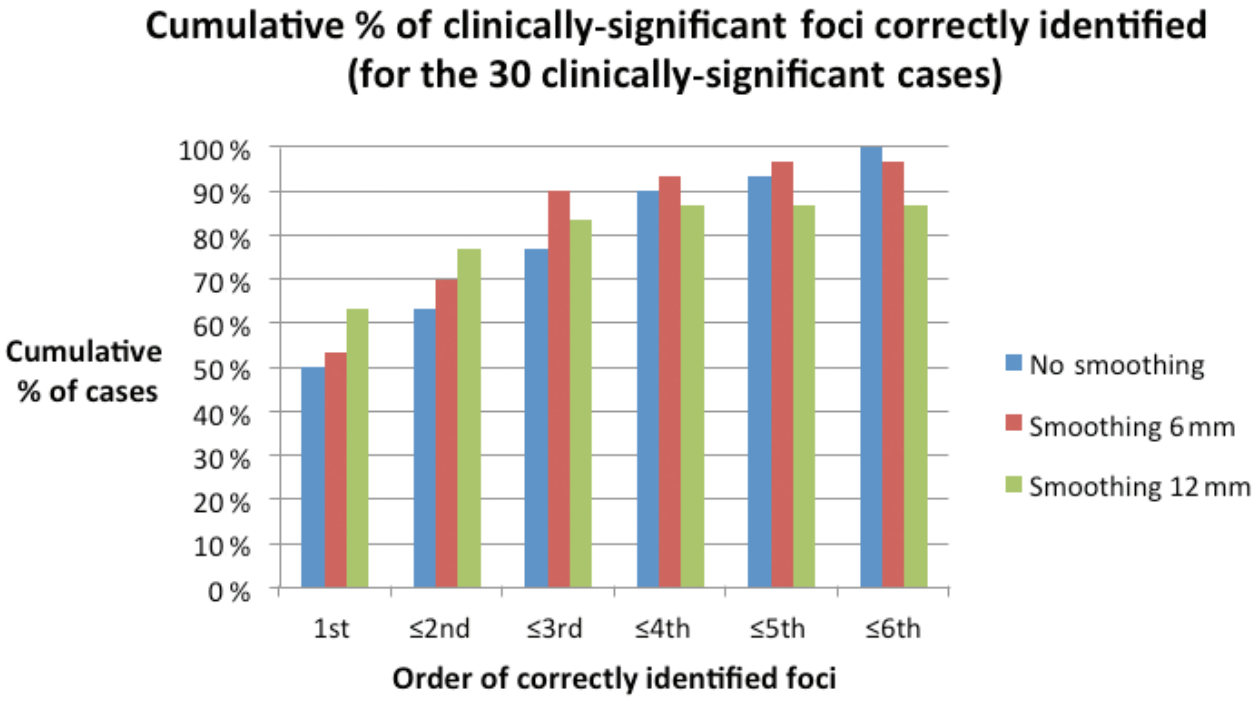

Figure 10: Cumulative percentage of cases where the clinically-significant focus was correctly identified according to its order.

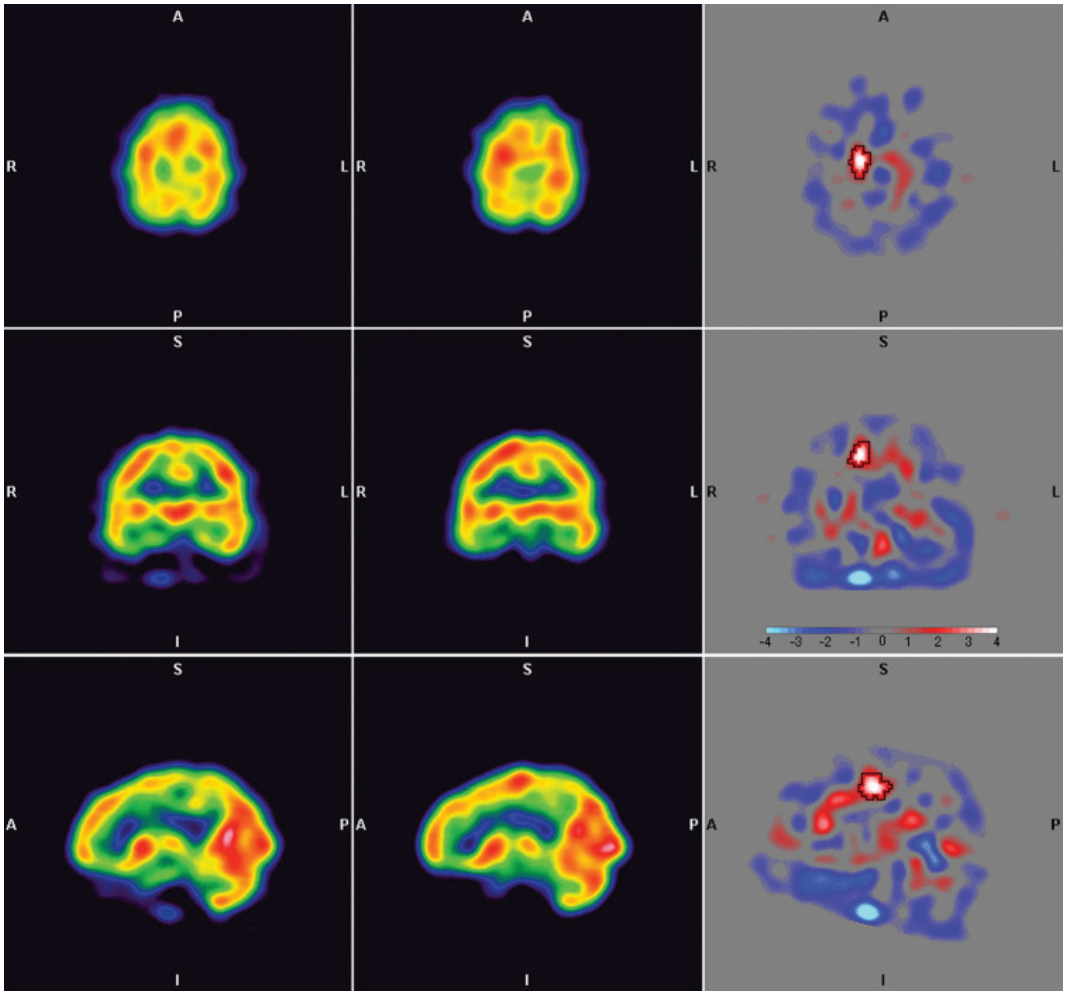

Figure 11: Clinical example of the ictal and interitcal ^{99m}Tc SPECT case. On the left: interictal SPECT scan. In the middle: ictal SPECT scan. On the right: difference image with the first ROI obtained with filtering, overlaid and corresponding with the clinically-defined epileptic focus. *Data courtesy of Friedrich Alexander University, Erlangen, Germany.*

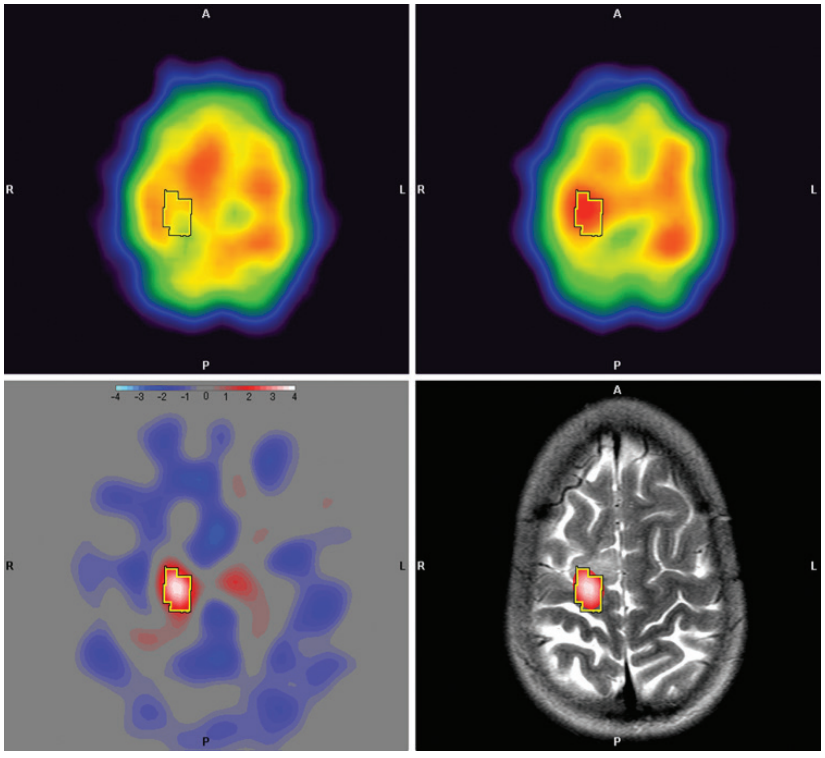

Figure 12: . Clinical example of interictal and ictal ^{99m}Tc SPECT case. The clinical epileptic focus is overlaid on the interictal, ictal, difference and MR images (left to right, top to bottom). *Data courtesy of Friedrich Alexander University, Erlangen, Germany.*

Conclusion

Neurology Analysis workflows provide the clinician with two workflows to help with the management of epilepsy. Database Comparison allows ictal and interictal SPECT or interictal PET scans to be compared with normal database and subtraction allows visualizing the difference image as well as selection ROIs that have increased perfusion in the ictal image. Together, these applications provide a comprehensive solution to facilitate the localization of the epileptogenic lesions.

About the Author

Dr. Kinda Anna Saddi received a B. Ing. in Computer Engineering from the University of Montreal in 2003, and then completed a joint PhD also in Computer Engineering with Biomedical Specialization at University of Montreal and with Siemens Corporate Research in Princeton, New Jersey, in 2008.

She has worked in medical imaging since 2003 and joined the Research and Clinical Collaboration team of Siemens Molecular Imaging in Oxford in 2008.

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15 **MNI: Montreal Neurological Institute and Hospital,** http://www.mni.mcgill.ca/

16 **SPM99 and SPM2:** Welcome Department of Imaging Neuroscience, Statistical Parametric Mapping software: http://www.fil.ion.ucl.ac.uk/spm/software/spm2/

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.

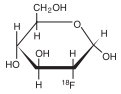
8.4 Pediatric Use

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 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 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

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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.
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16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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