PET/CT detection of $^{18}$F FDG-avid radioiodine negative recurrence in a patient with operated thyroid carcinoma with elevated serum thyroglobulin

By Dr. Samart Rajchadara, MD and Dr. Ananya Ruangma, PhD
Data courtesy of Bangkok General Hospital, Bangkok, Thailand

**History**

A 38-year-old female presented with a left breast mass, which initially proved to be benign following an examination and aspiration biopsy. However, during the clinical examination, a nodule in the right lobe of the thyroid was palpated. An ultrasonography of the thyroid was therefore performed and revealed 3 calcified nodules in the right lobe of the thyroid along with a small cystic nodule at the upper pole of the right lobe. The ultrasonography also demonstrated enlarged lymph nodes at the superior aspect of both jugular chains. A fine needle aspiration biopsy of the right thyroid nodules was performed under ultrasound guidance and a cytology revealed papillary thyroid carcinoma coexisting with nodular goiter.

In view of the diagnosis of papillary thyroid carcinoma, the patient underwent a near total thyroidectomy. A histopathology of the surgical specimen confirmed the diagnosis of encapsulated papillary microcarcinoma of the right lobe without capsular or vascular invasion. Due to high serum thyroglobulin (Tg), the patient was referred for high-dose radiiodine therapy for ablation of residual thyroid, where 100 mCi of $^{131}$I was administered. A post-therapy $^{131}$I whole-body scintigraphy (Figure 1) showed expected high $^{131}$I uptake of the residual thyroid in the neck but had no clearly defined iodine-avid metastases. The radiiodine uptake in the stomach and bowels were within physiological limits.

Data courtesy of Bangkok General Hospital, Bangkok, Thailand.
Six months post-¹³¹I large dose therapy, the patient underwent a follow-up Tg and ¹³¹I whole-body planar scan. The whole-body radiiodine scan (Figure 2) did not show ¹³¹I uptake in the neck, thus suggesting that the post-surgery residual thyroid tissue was ablated. There were no other functioning metastases and the colonic uptake of the tracer was within physiological limits.

Although the follow-up ¹³¹I whole-body scan was negative, the Tg was high, which suggested the possibility of radiiodine negative metastases or recurrence. Since radiiodine negative thyroid carcinoma recurrences are often poorly differentiated and ¹⁸F FDG-avid, the patient underwent a ¹⁸F FDG PET/CT scan.

The study was performed on a Biograph mCT Flow™ with FlowMotion™. Ninety minutes following an IV injection of 10 mCi of ¹⁸F FDG, the PET/CT study was performed with a whole-body contrast CT (120 kV, 222 eff mAs). Thereafter, the PET acquisition used continuous bed motion with a uniform table speed of 1 mm/sec as well as ultraHD•PET (time-of-flight with point-spread function (PSF) reconstruction). The reconstructed PET, contrast CT, and fused PET/CT images were evaluated for clinical reporting.

Findings

The ¹⁸F FDG PET/CT scan (Figures 3 and 4) revealed ¹⁸F FDG-avid recurrent thyroid carcinoma lesions in the neck, which were found within the lower thyroid bed adjacent to, anterior to, and lateral to the trachea. Hypermetabolic upper cervical lymph node metastases on both sides of the neck were also clearly delineated and especially prominent in the

Data courtesy of Bangkok General Hospital, Bangkok, Thailand.
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 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 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 ethanol as 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
high resolution PET reconstruction of the head and neck region.

In view of the diagnosis of $^{18}$F FDG-avid radioiodine negative recurrent disease in the neck and the bilateral lymph node metastases, the patient underwent further surgery to remove the recurrent lesion and the lymph nodes in the neck.

A histopathology of the resected recurrent nodules (Figure 5) and upper cervical lymph node metastases removed from along the internal jugular vein demonstrated presence of papillary thyroid carcinoma.

**Comments**

Differentiated thyroid carcinoma is usually treated by total thyroidectomy and radioactive iodine ablation therapy and during follow-up. An elevated Tg concentration is a sensitive marker indicating persistent or recurrent disease and is usually associated with positive $^{131}$I whole-body scan findings. Some patients, however, have metastases that do not concentrate $^{131}$I (even when it is given in therapeutic doses). Metastases that are unable to concentrate $^{131}$I are usually poorly differentiated with an impaired ability to trap iodine and are often more aggressive clinically. $^{18}$F FDG PET/CT has demonstrated high sensitivity for detection of thyroglobulin positive, radioiodine negative, recurrent or metastatic thyroid carcinoma. In a study, $^{18}$F FDG PET was performed in 37 patients with thyroid carcinoma post total thyroidectomy who showed elevated Tg with negative $^{131}$I whole-body scans. $^{18}$F FDG PET was positive in 76% (28/37) of these patients and accurately localized 89% of the lesions. A change in management secondary to PET was predominantly surgical resection of recurrent lesions or external radiation therapy in a smaller group.

Although the majority of recurrent or metastatic thyroid carcinoma lesions with high Tg are also radioiodine-avid (and thus successfully treatable with a high dose of $^{131}$I therapy), a small percentage show low iodine uptake but high $^{18}$F FDG uptake. In 49 post-thyroidectomy cancer patients who had persistently elevated serum Tg following initial radioiodine ablation, Salvatore et al. performed $^{18}$F FDG PET/CT immediately prior to empirical high dose $^{131}$I therapy. In 9 of the 9 patients (18%), $^{18}$F FDG PET/CT was positive while $^{131}$I whole-body planar imaging was negative. Conversely, in a similar percentage of patients, $^{18}$F FDG PET/CT was negative and $^{131}$I whole-body planar imaging was positive. Following an empirical high-dose $^{131}$I radioiodine therapy, Tg levels remained unchanged or increased in a larger number of patients with positive $^{18}$F FDG PET/CT scans compared to those with negative $^{18}$F FDG PET/CT scans. The patients with positive PET/CT (76%) did not have a significant decrease in Tg following empirical radioiodine ablation, although ablation results were superior in patients who were FDG negative and radioiodine positive.

**Conclusion**

In the present case, a histopathology following an initial surgery revealed papillary microcarcinoma without capsular or vascular invasion and thus was suggestive of a good prognosis. However, very high Tg following thyroidectomy was an indication of a potentially aggressive tumor, which led to the decision for high-dose radioiodine ablation therapy. Although a follow-up diagnostic $^{131}$I whole-body scan showed no evidence of residual thyroid or metastases, persistently increasing Tg raised the suspicion of poorly differentiated non-iodine-avid
recurrence, which was confirmed with an FDG PET/CT scan. High-resolution reconstructions of the PET/CT enabled sharp high contrast delineation of bilateral upper cervical lymph node metastases with low level of FDG uptake, which indicated nodal spread. The PET/CT appearance of multiple paratracheal recurrent thyroid carcinoma nodules with hypermetabolic upper cervical lymph nodes on both sides of the neck and the possibility of multiple neck nodal micrometastases led to surgical excision of recurrent nodules as well as bilateral lymph nodal resection. A histopathology subsequently confirmed presence of papillary thyroid carcinoma within recurrent nodules and some lymph nodes.

Empirical high-dose $^{131}$I therapy in patients who are Tg positive but $^{131}$I diagnostic whole-body scan negative have shown mixed results with 63% of patients achieving a decrease in Tg following therapy and post-high-dose $^{131}$I therapy scans, thus demonstrating recurrence or metastases in 62% of patients. Studies have also shown the efficacy of tyrosine kinase inhibitors, such as Lenvatinib, in radioactive iodine refractory metastatic thyroid cancer. Although clear delineation of $^{18}$F FDG-avid metastases (which do not show radioiodine avidity in the present situation) make a clear case for surgical excision, close Tg follow-up is an absolute necessity.

Examination protocol

Scanner: Biograph mCT Flow

<table>
<thead>
<tr>
<th>PET</th>
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<tbody>
<tr>
<td>Injected dose</td>
<td>10 mCi (370 MBq) $^{18}$F FDG injection</td>
</tr>
<tr>
<td>Scan delay</td>
<td>90 minute post-injection delay</td>
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<tr>
<td>Acquisition</td>
<td>FlowMotion acquisition 1 mm/sec ultraHD•PET</td>
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</table>

<table>
<thead>
<tr>
<th>CT</th>
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</thead>
<tbody>
<tr>
<td>Tube voltage</td>
<td>120 kV</td>
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<tr>
<td>Tube current</td>
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<tr>
<td>Slice thickness</td>
<td>3 mm</td>
</tr>
</tbody>
</table>

$^{*}$The full prescribing information can be found at the conclusion of this publication.

References


The statements by Siemens customers described herein are based on results that were achieved in the customer’s unique setting. Since there is no “typical” hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.
Fludeoxyglucose F 18 Injection, USP

**INDICATIONS AND USAGE**

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

- **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.
- **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.
- **Neurology**: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

**DOSAGE AND ADMINISTRATION**

- **Recommended Dose for Adults**: The recommended dose for adults is 5 to 10 mCi (185 to 370 MBq) as an intravenous injection.
- **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 Specific Populations (8.4)].

- **Patient Preparation**

  - To minimize the radiation absorbed dose to the bladder, encourage adequate hydration.
  - Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [see Warnings and Precautions (5.2)].
  - 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 (2.3).

- **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 data and using dosimetry data published by the International Commission on Radiological Protection for Fludeoxyglucose 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>
<thead>
<tr>
<th>Organ</th>
<th>Newborn (3.4 kg)</th>
<th>1-year old (9.8 kg)</th>
<th>5-year old (19 kg)</th>
<th>10-year old (32 kg)</th>
<th>15-year old (57 kg)</th>
<th>Adult (70 kg)</th>
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<tbody>
<tr>
<td>Bladder wall</td>
<td>4.3</td>
<td>1.7</td>
<td>0.93</td>
<td>0.60</td>
<td>0.40</td>
<td>0.32</td>
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<td>Heart wall</td>
<td>2.4</td>
<td>1.2</td>
<td>0.70</td>
<td>0.44</td>
<td>0.29</td>
<td>0.22</td>
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<td>Pancreas</td>
<td>2.2</td>
<td>0.88</td>
<td>0.33</td>
<td>0.25</td>
<td>0.13</td>
<td>0.096</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.2</td>
<td>0.84</td>
<td>0.46</td>
<td>0.29</td>
<td>0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.96</td>
<td>0.38</td>
<td>0.20</td>
<td>0.13</td>
<td>0.092</td>
<td>0.064</td>
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<tr>
<td>Kidneys</td>
<td>0.81</td>
<td>0.34</td>
<td>0.19</td>
<td>0.13</td>
<td>0.089</td>
<td>0.074</td>
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<tr>
<td>Ovary</td>
<td>0.80</td>
<td>0.8</td>
<td>0.19</td>
<td>0.11</td>
<td>0.058</td>
<td>0.053</td>
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<tr>
<td>Uterus</td>
<td>0.79</td>
<td>0.35</td>
<td>0.19</td>
<td>0.12</td>
<td>0.076</td>
<td>0.062</td>
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<td>LL1 wall</td>
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<td>0.28</td>
<td>0.15</td>
<td>0.097</td>
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<tr>
<td>Liver</td>
<td>0.69</td>
<td>0.31</td>
<td>0.17</td>
<td>0.11</td>
<td>0.076</td>
<td>0.058</td>
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<td>Gallbladder wall</td>
<td>0.69</td>
<td>0.26</td>
<td>0.14</td>
<td>0.093</td>
<td>0.059</td>
<td>0.049</td>
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<tr>
<td>Small intestine</td>
<td>0.68</td>
<td>0.29</td>
<td>0.15</td>
<td>0.096</td>
<td>0.060</td>
<td>0.047</td>
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<tr>
<td>ULL wall **</td>
<td>0.67</td>
<td>0.27</td>
<td>0.15</td>
<td>0.090</td>
<td>0.057</td>
<td>0.046</td>
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<tr>
<td>Stomach wall</td>
<td>0.65</td>
<td>0.27</td>
<td>0.14</td>
<td>0.089</td>
<td>0.057</td>
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<tr>
<td>Adrenals</td>
<td>0.65</td>
<td>0.28</td>
<td>0.15</td>
<td>0.095</td>
<td>0.061</td>
<td>0.048</td>
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<tr>
<td>Testes</td>
<td>0.64</td>
<td>0.27</td>
<td>0.14</td>
<td>0.085</td>
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<tr>
<td>Red marrow</td>
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<td>0.26</td>
<td>0.14</td>
<td>0.089</td>
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<td>Thyroid</td>
<td>0.61</td>
<td>0.26</td>
<td>0.13</td>
<td>0.080</td>
<td>0.049</td>
<td>0.039</td>
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<tr>
<td>Muscle</td>
<td>0.58</td>
<td>0.25</td>
<td>0.13</td>
<td>0.078</td>
<td>0.049</td>
<td>0.039</td>
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<tr>
<td>Bone surface</td>
<td>0.57</td>
<td>0.24</td>
<td>0.12</td>
<td>0.079</td>
<td>0.052</td>
<td>0.041</td>
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<tr>
<td>Breast</td>
<td>0.54</td>
<td>0.22</td>
<td>0.11</td>
<td>0.068</td>
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<tr>
<td>Skin</td>
<td>0.49</td>
<td>0.20</td>
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<tr>
<td>Brain</td>
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<td>0.13</td>
<td>0.09</td>
<td>0.078</td>
<td>0.072</td>
<td>0.070</td>
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<tr>
<td>Other tissues</td>
<td>0.59</td>
<td>0.25</td>
<td>0.13</td>
<td>0.083</td>
<td>0.052</td>
<td>0.042</td>
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</table>

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

- **Radiation risks**: Use smallest dose necessary for imaging (5.1).
- **Blood glucose abnormalities**: May cause suboptimal imaging (5.2).
- **Hyperglycemia reactions**: Have emergency resuscitation equipment and personnel immediately available (6).
- **Fludeoxyglucose F 18 Injection is administered to a woman who is pregnant.** Consider alternative diagnostics; use procedures to minimize radiation exposure. Calculate the final dose in a properly calibrated dose calibrator (2.4).

**ADVERSE REACTIONS**

- Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available (6).
- **Use in neonates**: 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.

**FULL PRESCRIBING INFORMATION: CONTENTS**

1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
3. CONTRAINDICATIONS
4. WARNINGS AND PRECAUTIONS
5. ADVERSE REACTIONS
6. DRUG INTERACTIONS
7. USE IN SPECIFIC POPULATIONS
8. FULL PRESCRIBING INFORMATION

---

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

- **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 in a properly calibrated dose calibrator before administration to the patient** [see Description (11.2)].

---

**1. INDICATIONS AND USAGE**

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

- **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.

---

**2. DOSAGE AND ADMINISTRATION**

**Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose in a properly calibrated dose calibrator before administration to the patient** [see Description (11.2)].

---

**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.
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.
- Radiopharmacists 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.
- Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
- Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

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 from the EOS.
- 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.

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 (2.3)].

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

8.3 Nursing Mothers

- It is not known whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in a pregnant woman; administer Fludeoxyglucose F 18 Injection only if clearly needed.

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 adults 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-[18F]fluoro-D-glucose has the molecular formula of C6H11O6F with a molecular weight of 181.26, and has the following chemical structure:

![Chemical Structure](image)

Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.400 mCi (20.0 to 200 mCi) of 2-deoxy-2-[18F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/v/ 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 simultaneously in opposite direction when the positron interacts with an electron (Table 2).

<table>
<thead>
<tr>
<th>Radiation/Emission</th>
<th>% Per Disintegration</th>
<th>Mean Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma (e+)</td>
<td>193.46</td>
<td>511.0 keV</td>
</tr>
</tbody>
</table>

*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-1 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 10^4 Gy/fkr/kg) 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%.

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

<table>
<thead>
<tr>
<th>Shield thickness (Pb) mm</th>
<th>Coefficient of attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
</tr>
<tr>
<td>8</td>
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<tr>
<td>52</td>
<td>0.0001</td>
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</table>

*Calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

- Fluoride 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 [18F]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 ‘jumped 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 phosphate 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 energetic requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycogen is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these condi-
Fludeoxyglucose F 18 Injection, USP

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 mCi ([18F]FDG) in the arterial blood level profile for Fludeoxyglucose F 18 decays 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 ["F"]FDG-6-phosphate at a rate proportional to the glucose utilization within that tissue. FDG-6-phosphate is presumably metabolized to 2-deoxy-2-["F"]fluoro-D-glucose (FDG, ["F"]FDG-6-phospho-D-mannose) (["F"]18F[FDG-6-phosphate]). Fludeoxyglucose F 18 Injection may contain some impurities (e.g., 2-deoxy-2-chloro-D-glucose (CDG)). Biodegradation and metabolism of CDG 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 (CDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (CDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, CDG, and CDM) 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 administered 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 renal-impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and avoid use in this patient population.

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. Clinical studies in animals indicate that Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (148/7) of the patients; in 34% (308/7) of the patients, Fludeoxyglucose F 18 Injection PET imaging 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 subphenoidal 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 diaphragmatic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

15 REFERENCES
4. IRCP Publication 53, Volume 18, No. 14,1987, pages 75-76.
5. HOW SUPPLIED/STORAGE AND DRUG HANDLING
Fludeoxyglucose F 18 Injection is a sterile, sodium-free, aqueous, multiple-dose, capped 30 mL and 50 mL glass vial containing between 0.740 to 7.40mCi/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-2-["F"]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 15-50°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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