## Chapter 1  Normal Distribution of FDG

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Normal Distribution of FDG

Today, more than 95% of PET procedures worldwide are performed with F-18 fluoro-deoxyglucose (FDG). This situation is dependent at first by practical reasons: Fluorine 18 is one of the four most important positron emitters, easily produced by "standard" cyclotrons, with the capability to radiolabel relevant biological molecules. Because of the favorable half-life (110 minutes) with respect to shorter-lived C-11, N-13 and O-15, Fluorine-18 is the only one in this series that can be distributed also to PET centers without cyclotrons. Therefore, it can be used in a wider geographic area covering, in more developed countries, all the national territory.

From a chemical point of view, Fluorine is a halogen allowing a very stable binding that does not affect the functional part of the molecule. But the real "absolute" value of F-18 is derived by its capability to radiolabel deoxy-glucose producing FDG; i.e., the glucose's tracer. Glucose is an essential compound for living organisms, being the most important carbon supplier in energy producing metabolic processes depending largely on its availability.

Pathophysiology of Glucose and FDG's Biodistribution

For a correct reading of PET-FDG images, based on the interpretation of all molecular involved events, we have to first analyze the normal glucose distribution, starting from the knowledge of its pathophysiological behavior. Devoting to more extensive and/or specialized publications a deeper analysis of FDG as a "molecular tracer" of glucose transporters (six isoforms: GLUT 1 to GLUT 5 and GLUT 7 have been identified so far), it is important to remember that the glucose uptake in human cells can take place through two mechanisms: facilitated diffusion and active transport.

The first one is a carrier-mediated transport, therefore characterized by saturation (and influenced by insulin, increasing its rate up to 20-fold). It means that a competitive inhibition of transport can occur in the presence of a second ligand that binds to the same carrier. This explains the strong interference on FDG uptake determined by diabetes and, more in general, by variations in glucose and insulin levels in the blood. For these reasons, to standardize the analysis of FDG distribution it is crucial to define a fasting time (at least 4–6 hours), a serum glucose range and, in diabetes, the timing after insulin injection. Although chronic hyperglycemia is less disturbing with respect to the acute variety, PET scans are preferably performed with serum glucose levels in the range of 70–110 ng/dl. It is better to avoid examinations in patients with glucose levels higher than 200 ng/dl or in the presence of hyperinsulinemia, both of which reduce diagnostic accuracy because of their strong interference on biodistribution.

Being less diffuse, glucose's active transport, occurring against an electrochemical gradient, functions only in certain special epithelial cells specifically adapted for active absorption, such as those present in gastrointestinal membranes or through the renal tubules.

FDG “Trapping”

The biochemical fates of glucose start with phosphorylation, immediately after its entrance in cells. The phosphorylation, both for glucose and FDG, is promoted by hexokinase in the large majority of cells, being dependent by glucokinase in the liver. After this first step, glucose-6-phosphate progresses in its metabolic fate, after a dephosphorylation mediated by glucose-6-phosphatase, undergoing glycolysis (and/or to the storage of glycogen and/or to lipids or proteins conversion). Conversely, FDG-6-phosphate is not further metabolized in the glycolytic pathway, remaining “intracellularly trapped”, because of the lack of significant amounts of FDG-6-phosphatase to reverse the phosphorylation. This is a “major advantage” for PET-FDG imaging: while the radiolabeled “native” glucose has a metabolism that is too fast to easily permit a PET study, the “trapped” FDG can reliably “in vivo” trace glucose concentration, reflecting the glucose metabolism in the whole organism, except for kidneys.

At this level, while normal individuals do not excrete glucose through the urinary system, an intense FDG uptake is observed in kidneys, ureters and bladders. In fact, whereas normal glucose is freely filtered by glomeruli and rapidly reabsorbed by the nephron, FDG is poorly reabsorbed after filtration, being excreted in a large amount in the urine. Other F-18 labeled radiochemical forms, derived from FDG’s catabolism, can further explain radioactivity in the urinary system.

It has to be pointed out that, in individuals with normal renal function, 50% of the radioactivity reaches the bladder at two hours. This is a major advantage in re-
ducing radiation dosimetry because of the consequent low effective half-life. Conversely, to define a major contraindication, it has to be remembered that FDG cross the placenta, being distributed mainly in fetal brains and excreted by fetal kidneys. Breastfeeding is contraindicated before 10 hours after i.v. injection of FDG.

Physiological and Para-Physiological Distribution of FDG

Devoting the knowledge of more precise rules and technical issues to national and/or international protocols, we will briefly describe here the standard procedure as a premise to the normal whole body FDG pattern.

The patient is i.v. injected, after fasting for at least 4–6 hours, but while well-hydrated. During the injection and the following uptake phase preceding the scan, the individual has to be at rest in a quiet room, comfortable and relaxed. In particular, he has to try to avoid such actions as chewing, eating, running and any other exercise and/or sensory activation affecting FDG distribution, mainly increasing muscular or regional cerebral uptake. Since it is impossible to avoid swallowing, it has to be remembered, mainly for patients undergoing a PET scan for head and neck tumors, the effect on the FDG’s uptake in the vocal cords when talking.

Under standard conditions the highest FDG activity is seen at the cerebral level (mainly in gray matter), since the brain is the only organ exclusively using glucose as a carburant. At fast, cardiac uptake (left ventricle) is variable, but most frequently mild and homogeneous. Occasionally, a difficult analysis can be determined by a high blood pool activity at the level of the great vessels, mainly in mediastinum. While liver and spleen show low-grade diffuse activity, variable uptake is seen in the gastrointestinal system, sometimes creating difficulties in the analysis and problems in differential diagnosis. This activity can be related both to smooth muscle uptake as well as to the intra-luminal content. Low and/or absent concentration is observed at the level of bone marrow. Similarly, no activity is seen at the level of normal lymph nodes, but after FDG’s extravasation at the injection site, determining high focal uptake in the draining regional glands. Moderate activity can be seen in tonsils, salivary glands, myelohyoid muscles and, in young patients, in the thymus, adenoidal tissue and testicles. No uptake is normally seen at the level of lungs, since a slight activity in posterior and inferior segments is sometimes present. The skeletal muscle’s uptake, being low at rest, increases as a specific response to stress and/or exercise in the involved muscular cells. An increased uptake can be determined by many conditions such as hyperventilation, hiccuping, torticollis and intense eye movement, as a result of involuntary tensions. The muscular uptake is generally bilateral and symmetric. Conversely, an apparent unilateral pathological concentration can be observed contralaterally to a nerve palsy. The urinary excretion, determining a high normal background at the renal and vesicle level, can create difficulties in evaluating FDG’s pathological uptake mainly in kidneys and prostates. Small areas of ureteric stasis may simulate lymphadenopathy. The presence of anomalous locations of kidneys and ureters has to be known so as to avoid mistakes in PET images interpretation. Thyroid uptake can be occasionally observed in clinically normal patients, being more frequently caused by thyroiditis or hyperthyroidism. In premenopausal women (and/or in women taking estrogens) breast tissue often demonstrates moderate symmetrical FDG concentration. Intense uptake is presented by breastfeeding mothers. A faint-to-moderate uterine uptake can be observed during menstruation. In adipose tissue a typical symmetric intense uptake can be determined by active brown fat, mainly in winter months in patients with a lower body mass index.

Since the lesion’s detectability in nuclear medicine is dependent on lesion/background ratio, it is evident that major difficulties in PET-FDG are present at the cerebral level and/or in the abdominal-pelvic territory, where activities deriving from the gastrointestinal and urinary emunctories can disturb.

Nevertheless, many physiological and para-physiological uptakes can be easily distinguished by the morphostructural information obtained by CT. To avoid problems, some authors also suggest the administration of muscle relaxants, cleansing bowel preparations and the placement of a Foley’s catheter. However, because of difficulties in standardizing these procedures and of the impossibility of reliably avoiding possible pitfalls, a “keep it simple” strategy is more frequently adopted.

Pathophysiology of FDG Uptake in Cancer (and Benign Diseases)

Cancer cells are generally characterized by an increased glucose metabolism with respect to normal cells. In
particular, malignancy is frequently associated with the appearance of new phenotypes with a higher expression of glucose transporters, an increasing rate of cell proliferation, protein and DNA synthesis, and anarchic neo-angiogenesis. All these conditions determine a significant increase of glucose’s uptake, to provide the fuel necessary to answer new requests for energy, produced mainly through anaerobic glycolysis. FDG uptake and bio-distribution in tumors is therefore influenced by many parameters, such as increased glucose turnover, expression of glucose transporters and hexokinase activity, being also dependent (through non-specific mechanisms, independent of the neoplastic transformation) on the increased number of cell divisions. Devoting a deeper analysis of molecular mechanisms to wider and/or specialized publications, and not being interesting for the purposes of this Atlas to discuss pathophysiological premises to clinical indications in cardiology and neurology, we define here some general behaviors and provide suggestions helpful in the analysis of PET-FDG images in oncology and other benign diseases to be taken into account for differential diagnosis:

A. FDG Uptake in Tumors
- The large majority of malignant tumors show an increased FDG uptake.
- FDG’s uptake is influenced by the “biological malignancy”, i.e. by issues such as growth rate, hypoxia, histopathology concerning both the histotype and grading. Intense uptake is more frequently observed in lymphoma, melanoma, colorectal, esophageal and head/neck cancer, NSCLC, sarcoma and, more in general, in high grade tumors.
- A minority of tumors can present low or absent FDG uptake. This pattern is mainly dependent on differentiation, as evidenced by the absence of FDG uptake in the large majority of lesions in patients with well-differentiated thyroid carcinoma or neuroendocrine tumors (NET). Low and/or absent FDG uptake is also frequently seen in low-grade hepatocarcinoma, also because of the presence of a higher glucose-6-phosphatase activity resulting in a low FDG uptake, in tumors characterized by a low growth rate, as in prostate cancer, in tumors characterized by functional features as the mucinous production, or by a particular tumor morphology, as can be observed in primary ovarian cancer, frequently consisting of large cystic portions.

B. FDG Uptake as Prognostic Indicator
- In tumors with a higher prevalence of normally not concentrating lesions, such as NET, thyroid or liver carcinomas, FDG concentration defines a worse prognosis with respect to patients not showing uptake.
- Similarly, in a very large majority of tumors, including in a single category all the patients bearing the same histotype, a higher uptake indicates a worse fate.

In fact, it has been demonstrated that FDG uptake in cancer tissue is determined, among other factors, by tumor proliferation rates, aggressiveness and rate of neo-angiogenesis. This relationship, however, is non-linear, mainly in rapidly growing tumors, since it is dependent on many parameters, including the various percentages of anaerobic metabolism and the presence of necrosis.

C. FDG Uptake as Recurrence Identifier
- Recurrent disease, because of the loss of differentiated features, is in general characterized by a higher FDG uptake with respect to the primary tumor.
- There is no FDG uptake in the absence of viable cancer cells and therefore in necrosis and/or fibrosis.
- In cancer patients, when a FDG uptake is observed at diagnosis and/or at the pre-therapeutic control, a negative PET scan at follow up can reliably exclude recurrence with respect to post-therapeutic fibrosis and/or necrosis.
- The opposite, however, is never true; i.e., FDG uptake is not necessarily determined by recurrence, because of possible false positive results (see below).

D. FDG Uptake as Guide to Biopsy and/or to Define the Target in Radiotherapy
- In inhomogeneous tumors, FDG uptake is higher in the most malignant part of the lesion, being lower in the most differentiated components and absent in necrotic or fibrotic areas.
- PET-FDG can guide a biopsy to the most malignant part of the tumor.
- For the same reason, PET-FDG allows a better definition of the “biological target” in radiotherapy. PET-CT images can serve to design a tailored therapeutic plan, giving a higher dosage to the most malignant part of the tumor, and reducing radiation to normal tissues.
E. FDG Uptake Variation as a Marker of Response to Therapy

- Glucose uptake rapidly decreases after an effective therapeutic action, remaining unchanged and/or increasing in non-responders. Therefore, FDG’s uptake can be an early marker of the therapeutic response in tumors with respect to the information allowed by CT, US and MRI detecting late variations on size and structure; moreover, it is less reliably connected to the therapeutic efficacy. This FDG advantage has already been demonstrated in many patients subjected to chemotherapy. A wider and deeper experience on the possible clinical usefulness in oncology, including all histotypes, better defining timing of evaluation and capability to also predict the response to radiotherapy, is under evaluation.

F. False Positive Results Due to FDG Uptake in Benign Diseases

- The highest percentage of benign lesions do not present FDG uptake, and are therefore distinguishable from malignant ones in the large majority of cases.
- A minority of benign lesions can show FDG uptake, generally with a lower entity with respect to malignant tumors.
- FDG accumulates in activated white cells and macrophages. Therefore, it can be concentrated at the level of active inflammatory processes either infectious or non-infectious.
- The presence of false positive results can create problems in diagnosis (and staging), but is less critical in re-staging and at follow up.
- It is necessary to be very careful in utilizing PET-FDG for a primary diagnosis, mainly in patients with a high prevalence of inflammatory or granulomatous conditions (tuberculosis, sarcoidosis, etc.).
- FDG uptake can be present at the level of the wound healing (in general up to 6 months), in the inflammatory reaction after radiotherapy, in associated benign lymphadenopathy or infections, in lung atelectasis and pleural effusion and in reactive thymus hyperplasia (sometimes appearing in young patients after chemotherapy). Dubious images can also be due to pathological conditions such as gastritis, gastroesophageal reflux, diverticulitis, inflammatory bowel disease, abscess, hiatal hernia and benign uterine fibroids. The uptake determined by benign healing fractures or arthropathies can be critical to avoiding possible mistakes in diagnosing bone metastases. A diffuse increase at the level of bone marrow (and/or of spleen) can be observed after the administration of granulocyte colony stimulating factor.

G. Usefulness of FDG in Benign Diseases

- Without discussing here the clinical usefulness in cardiology and in neuropsychiatry, and putting in evidence that false positive results in oncology occurs in only a very low percentage of the PET results, it has to be pointed out that, although it may have possible negative effects on specificity in patients with cancer, FDG uptake can also determine useful clinical indications in benign diseases.
- For example, PET-FDG is a first line procedure in the diagnosis of fever of unknown origin (FUO), because of the need for the highest sensitivity to detect occult lesions, not negatively counterbalanced by a reduced specificity. Other useful information can be obtained in defining the activity in many inflammatory diseases, to detect activated atherosclerotic plaques in great vessels, to determine the presence of a reaction in the area surrounding prosthetic devices, and in autoimmune diseases, etc.

H. Differential Diagnosis Using PET-FDG in Oncology

- Role of quantitation. To increase information acquired through visual analysis, quantitative and/or semi-quantitative methods can be utilized. This evaluation is outside the scope of our publication. Although precise and rigorous quantitative procedures have been proposed, the only one used today in the clinical routine is the so-called SUV.
- Standardized uptake value (SUV). This is a semi-quantitative method, defining the FDG uptake’s entity based on a ratio approximately referring the lesion value to the whole body activity. It is affected by many parameters, such as serum glucose level, body weight and compartmental glucose distribution. For these reasons it can not be considered an absolutely reliable method. Nevertheless, it can have a useful clinical role, complementary with visual analysis, mainly for determining temporal variations in the same patient, and therefore the effect of a therapy. SUV has also been proposed for helping differential diagnosis in solitary pulmonary nodules through the definition of an uptake threshold (for lesions higher than 1 cm, cancer is more probable in the presence of a SUV higher than 2.5).
Case 1  Normal Distribution of FDG

- Grey Matter Uptake
- Kidney Excretion
- Bone Marrow Uptake
- Bladder Excretion
Myocardial uptake is quite unpredictable, as related to several factors, probably the most important being fasting.
Cricoarytenoid muscles

**Teaching point**

Muscles usually do not avidly uptake FDG, assuming that fasting has been respected and that intense contraction has not occurred during the uptake period (especially during the first 20 minutes after FDG injection). However, it may be difficult to prevent patients from talking and swallowing, therefore some uptake in the head and neck muscle has to be expected.
To avoid muscle uptake it is mandatory to have the patient at rest for at least 20 minutes after injection; also administration of myorelaxant has been suggested. With the use of PET-CT fused images it is usually possible to distinguish muscle uptake from pathologic findings.
Case 5  Lingual Tonsils

Mild Uptake At Insertion Of Genioglossus Muscle

Ligual Tonsil
Teaching point

Salivary glands and lymphatic tissue can show a variable degree of FDG uptake; this has to be taken into particular account in diseases affecting these organs.
Teaching point

Usually physiologic uptake in the salivary glands is symmetric, but not necessarily in all cases and glands. Again, PET-CT fusion images are extremely helpful to establish the site of uptake.
Case 8  Great Vessels

Blood Pool Activity of Great Vessels
Case 9  Pulmonary Hilum

Teaching point
Non-specific uptake at both lung hila can be observed quite frequently, maybe related with aspecific inflammation. It has to be taken into particular consideration in order to avoid a wrong report: it is usually not intense and symmetrical.
Aspecific Nipple Uptake
Teaching point

Breast and nipples frequently show a faint uptake. It should be considered physiological, given that no focal area of intense uptake is observed.
Teaching point

As FDG is excreted through the urinary pathway, intense tracer concentration can be observed in the kidney pelvis, ureters and bladder.
Case 14  Bowel

Aspecific bowel FDG uptake.

Teaching point

FDG uptake is frequently observed at bowel level; again the use of PET-CT fused images is important to correctly identify the site of uptake.
Aspecific bowel FDG uptake.

Teaching point

The degree of FDG uptake at bowel level is almost unpredictable, and a quite intense uptake can be seen, especially at cecal and sigma level. The use of PET-CT fused images is important to correctly identify the site of uptake, and in cases of focal intense uptake, referring the patient for further evaluation has to be suggested.
Case 16  
Testis

Teaching point

The testis almost always show a faint FDG uptake; in young patients the degree of uptake can be more relevant.
Case 17  Blood Vessels

Teaching point

Blood vessels may show faint uptake. It should be considered physiological, especially in older patients.
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